Premorbid and Prodromal Functioning as Predictors at Onset of Psychosis:
A First-Episode Study

Ana Barajas Vélez

The work described in this thesis was performed at the Parc Sanitari Sant Joan de Déu of Sant Boi de Llobregat (Barcelona, Spain), at the Hospital Sant Joan de Déu of Esplugues de Llobregat (Barcelona, Spain) and at the Department of Clinical and Health Psychology of the Faculty of Psychology, Universitat Autònoma de Barcelona of Cerdanyola del Vallès (Barcelona, Spain).

It was financially supported by Fondo de Investigaciones Sanitarias (FIS PI05/1115) Instituto de Salud Carlos III (Spain), Centro de Investigación en Red de Salud Mental (CIBERSAM) (Spain), Caja Navarra (Spain) and Fundació Marató de TV3 (Catalonia, Spain). Moreover, two grants were awarded to the author of this thesis to carry out stays in several centers of reference for research in first-episode psychosis. One of them was at the Birmingham Early Intervention Service (EIS) of Birmingham and Solihull Mental Health NHS Foundation Trust (Birmingham, United Kingdom), and at the School of Psychology, University of Birmingham (Birmingham, United Kingdom), financed by Fondo de Investigación Sanitaria del Instituto Carlos III, Ministerio de Investigación e Innovación (Spain). Another was at the Department of Research of the Adolescent Psychiatry Unit, University Hospital Gregorio Marañón (Madrid, Spain), financed by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM).

Premorbid and Prodromal Functioning as Predictors at Onset of Psychosis:
A First-Episode Study

Doctoral Thesis

ANA BARAJAS VELEZ

Directors:

Prof. Dr. Jordi E. Obiols Llandrich

Dr. Susana Ochoa Güerre

Barcelona, December 2015

Doctorat en Psicopatologia de l'infant, l'adolescent i l'adult

Departament de Psicologia Clínica i de la Salut. Facultat de Psicologia

Universitat Autònoma de Barcelona

To my family

and especially David and Unai

In memory of Marta Barceló and Jaume Autonell

Acknowledgments

Hace 9 años, tal día como hoy, llamaba a la puerta del despacho del Prof. J.E. Obiols para informarme acerca de un programa de doctorado con la idea de continuar mis estudios de Psicología. Aquel día no era consciente de que estaba empezando una 'carrera de fondo', que iba a suponerme momentos de gran satisfacción, pero también otros de cierto sacrificio y esfuerzo. El desarrollo de esta tesis doctoral ha seguido un camino paralelo al desarrollo de otros acontecimientos vitales de gran importancia para mí. Esta tesis ha sido testigo de algunos cambios, por ejemplo, a nivel laboral con mi incorporación al mundo laboral en el área de la salud mental o, ya en la última etapa, a nivel personal con el nacimiento de Unai. Haciendo balance, todos estos años han supuesto un período de gran enriquecimiento no sólo a nivel intelectual sino también a nivel personal, puesto que me ha permitido conocer y compartir esta experiencia con personas de gran valía. Gracias por vuestro tiempo, conocimiento, comprensión, paciencia, amistad, entusiasmo y apoyo. Tras estos años tan intensos, y después de coger aliento en varias ocasiones para poder continuar en esta carrera de fondo, parece que ha llegado ese momento tan esperado, 'la meta'. En cierto modo, supone cerrar un capítulo para continuar avanzando. Es ahora cuando realmente siento la satisfacción del trabajo realizado, de los fines de semanas en casa y de las veces que he tenido que decir 'no puedo, tengo tesis'. No obstante, todo el esfuerzo realizado ha valido la pena, pues me ha permitido vivir experiencias que de otro modo no hubiera sido posible, cómo aproximarme a la mente humana y conocer de cerca algunas experiencias vitales de los **pacientes** y sus **familias**. A ellos quiero dedicar especialmente esta tesis doctoral, pues sin su colaboración y generosidad no hubiera sido posible realizar este trabajo que supone una pequeña contribución al entendimiento del desarrollo de los trastornos psicóticos.

A mis directores de tesis…

Jordi, gracias por estar siempre ahí, por la confianza depositada y por darme la oportunidad de iniciar mi carrera investigadora. Te agradezco que hayas aceptado dirigir esta tesis doctoral. Es un placer haber podido contar en este trabajo con alguien de tu nivel y experiencia profesional. Gracias por compartir una parte conmigo.

Susana, gracias por tantas y tantas cosas… pero sobretodo por tu apoyo y generosidad. Has sido y eres un referente para mí. Gracias por abrirme las puertas al mundo laboral, por compartir conmigo parte de tu experiencia profesional, por tu sentido común, por tu paciencia, por tener siempre un momento y, por supuesto,… por tu amistad.

To international researchers that have contributed in some way at the devolopment of this thesis…

I would like to thank the Birmingham Early Intervention Service (EIS) of the Birmingham and Solihull Mental Health NHS Foundation Trust, in particular its clinical director, Prof. **Max Birchwood**, for giving me the opportunity to conduct a training period with two of their clinical teams: Birmingham East and North (BEN) Team and Early Detection & Intervention (ED:IT) Team. I want to emphasize not only his professional quality and talent, which have been instrumental in my development as a researcher and which have served me as a guide and inspiration for the development of this thesis, but also for his kindness, time and support.

To **Chris Jackson**, who was my supervisor in research topics during the stay in the EIS of Birmingham, I thank you for your interest in my thesis and suggestions made concerning some of the articles. By the way, whenever you want please repeat your visit to Barcelona with your family; it was very nice!

To the BEN Team, especially **Mark Bernard**, for his patience, generosity and invaluable help in the day-to-day activities during the stay, as well as, for sharing moments of his family life.

To **Amanda Skeate** and her ED:IT team for their dedication, support and giving me the opportunity to share the daily clinical work in patients' follow-up.

Thanks to **Linda Mcarthy**, who was always available with a smile when sought.

Finally, for his great human qualities, the admiration that he engenders in me, and his selfless disposition I would like to thank Prof. **Heinz Häfner** for his advice during my training career as a researcher. Thank you for being my inspiration from the beginning of the thesis. It has been a real pleasure to count on your collaboration and I hope that it continues for a long time.

Al tribunal de la tesis doctoral…

Prof. **Vázquez-Barquero**, Dra. **Modinos**, Dr. **Penadés**, Dra. **Pousa** y Dra. **Ruíz**, gracias por mostrar interés en este trabajo de investigación y por formar parte del tribunal de esta tesis. Sin duda este trabajo de investigación adquiere mayor rigurosidad gracias a vuestra experiencia y prestigio.

A las distintas fuentes de financiación…

Gracias al **Fondo de Investigaciones Sanitarias** del **Instituto de Salud Carlos III**, al **Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM)**, a **Caja Navarra** y a la **Fundació Marató de TV3**, por apoyar este tipo de investigación y permitir que sea posible ampliar la evidencia científica en esta área de conocimiento.

A los profesionales de la Unitat de Docència, Recerca i Innovació del Parc Sanitari Sant Joan de Déu, y especialmente …

A **Judith Usall**, perquè has estat no només una gran mestra per mi, sinó també una gran consellera i amiga. Admiro els teus valors, la teva energia i l'entusiasme per les coses en les que realment creus.

A **Josep Maria Haro**, perquè has estat un referent des dels meus inicis en la recerca en salut mental, a qui sempre he tingut gran admiració per la seva capacitat de treball.

A **Aida Farreny**, **Victoria Villalta**, **Raquel Iniesta**, **Vanesa Carral**, **Ana Fernández**, **Marcelo Pezzimenti**, **David Suárez**, **Elena Romero**, **Janina Carlson**, **Alexandrina Foix**, **Jaume Autonell**, **Montserrat Fusté, Elena Rubio, Raquel López**,… (y una larga lista de compañeros/as con los que he compartido algún momento en mis primeros años como investigadora en el Parc Sanitari Sant Joan de Déu),… y muy especialmente a **Marta Barceló** (siempre en mi mente!), **Helena Huerta** (un gran descubrimiento!) y **Iris Baños** (compañera de batalla!).

Al grupo GENIPE del estudio de “Diferencias de género en primeros episodios psicóticos”, y en especial a **Trini Peláez**, **Maria Arteaga** y **Olga González**. Gracias por vuestro tesón y esfuerzo para sacar adelante uno de los artículos de esta tesis. Vuestra experiencia clínica ha sido de gran ayuda.

A los profesionales del servicio de Psiquiatría/Psicología del Hospital Infanto-Juvenil de Sant Joan de Déu y especialmente …

A **Bernardo Sánchez**, **Montserrat Dolz**, **Daniel Muñoz**, **Marta Pardo** y **Ana Torres**. Vosotros habéis sido testigos de mis primeros pasos en este mundo de la investigación y con vosotros me he formado. Gracias por esas sesiones clínicas con las que tanto he aprendido. Y gracias por vuestra colaboración e implicación en el proyecto y por hacer la investigación algo más fácil.

A los profesionales del Centre d’Higiene Mental Les Corts y especialmente …

A **Lluís Lalucat**, por compartir parte de su conocimiento y experiencia día tras día, lo que me ha permitido crecer como profesional. Gracias por apostar por la investigación y dar continuidad a mi trayectoria profesional en el campo de la psicosis. Gracias por hacer la vida laboral más sencilla!

A los profesionales del equipo de psicosis incipiente (PAE-TPI), **Maite San Emeterio**, **Maite Carbonero**, **Carolina Franco**, **Elena Sánchez**, **Amparo Escudero**, **Natalia Mantecón**, **Juanjo Gil**, **Mercè Teixidó**, **Elisenda Conesa**, **Irene Álvarez**, **Mª Antonia Argany**, **Judith Anglès**, **Isabel Cebrià**, **Elena González**, **Francisco Villegas**, **Ana Aznar**, **Raquel Rubio** y … al resto de profesionales que se han ido añadiendo al equipo posteriormente. Gracias por compartir vuestra práctica clínica y por lo que cada uno de vosotros me enseñáis en el día a día. Os agradezco vuestro apoyo en las tareas de investigación!

A los profesionales de la Unidad de Investigación y Docencia, **Àngels Ciutat**, **Rocío Casañas**, **Laia Mas**, **Gemma Boix**, **Noemí Riera**, **Rosa Muriente** y **Aida Valls**. Gracias por hacer más ameno el trabajo!

A aquellos que casi sin conocerlos se convirtieron en imprescindibles para el desarrollo de esta tesis, …

A **Alex**, por tu ayuda incondicional para ‘resucitar’ al Toshi. A **Ángel**, gracias por esas últimas sugerencias en la impresión de esta tesis.

A mis amigos, …

A **Sonia**, **Vanesa T.**, **Vanesa B.**, y **Patricia** … por los buenos momentos que hemos vivido desde las clases en la Escuela Oficial de Idiomas, y por los que quedan por venir. Y como no!, a los peques… **Pol**, **Jon**, **Thiago**, **Iker** y **Lucía**, que me hacen pensar … cómo pasa el tiempo!.

A **Rebeca**, **Puri, Isma, Pi, Lucio y Félix** … porque, de algún modo, habéis formado parte de este proyecto.

Y, por último, a mi familia, …

A mis tíos/as y primos/as, muy especialmente a **Pam** (por fin está aquí la teresina!!), a **Esetal** (queréis máaas??), a **Lolo** (mi suplente en el padel), a **Gemma** (la chica), y a **Ari** (la canguro).

Ups! … no sé si me dejo a alguien… Ah! sí, '**al cousin'**. Gracias, por la paz que me das, por las risas que nos echamos y porque con tu modo de ver la vida se ha hecho más fácil llegar hasta aquí. Por estar ahí incluso cuando no lo estás ... Mercy!. Ahora sí, … por muchos más de nuestros momentos!!

A mis cuñados, **Ainhoa** y **Steve** por la paciencia que tenéis conmigo cuando os pido alguna revisión del idioma. A mi cuñado **Ángel** por tener siempre una solución práctica en los momentos difíciles!

A mis sobrinos, **Aitor**, **Irati** y **Aitana**, que son la alegría de la familia. Espero poder ahora disfrutar más de vosotros!

A mis suegros, **Teo** y **Edel** que han sufrido junto con el resto de mi familia el largo camino hasta aquí. Gracias por vuestra paciencia, comprensión y por cuidarme tanto.

A mis hermanos/a, **Jose**, **Miguel** y **Choni**, habéis sido un referente para mí, no sólo a nivel personal, también profesional. Gracias por estar ahí siempre que os he necesitado. Ahora ya podremos volver a ser cuatro hermanos. Desde la Florida con cariño!!

A mis padres, **José P.** y **Alfonsa**, por vuestro apoyo incondicional durante todos estos años. Gracias por darme aliento en los momentos más difíciles y hacer posible que ahora pueda estar escribiendo estas letras.

A **David**, mercy por todo!, (ves como sí que estás en los agradecimientos ;). Una parte de este trabajo es tuyo, por todo el tiempo que nos ha robado. Ahora sí, puedo decirte que 'HE ACABADO LA TESIS'. Gracias por acompañarme en este largo camino, por entenderme, por hacerme la vida más sencilla, y por compartir conmigo tantos momentos. En ningún sitio mejor que contigo!

Y, por último, a mi peke, … **Unai**. Gracias por darme la energía que necesitaba para acabar este proyecto cuando supe que ibas a formar parte de nuestras vidas. Gracias por cada una de tus sonrisas!

A todos vosotros que me habéis acompañado en esta 'carrera de fondo', GRACIAS!

POR FIN … EL FIN

Abbreviations

ABC Study	The Age, Beginning and Course Schizophrenia Study
AMHS	Adult Mental Health Services
APA	American Psychiatric Association
APS	Attenuated Psychotic Symptoms
APSS	Adolescent Psychotic-Like Symptom Screener
ARMS	At-Risk Mental State
AS	Attention and Speech Impairment
AU	Auditory Uncertainty
BEN team	Birmingham East North team
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BPRS	Brief Psychiatric Rating Scale
BS	Basic Symptoms
BSABS	Boon Scale for the Assessment of Basic Symptoms
BSIP	Basel Screening Instrument for Psychosis
CAARMS	Comprehensive Assessment of At-Risk Mental States
CAMHS	Child and Adolescent Mental Health Services
CAPE-42	Community Assessment of Psychic Experiences
CBT	Cognitive Behavior Therapy
CER study	Cologne Early Recognition study
CHR	Clinical High-Risk
CHR+	Clinical High-Risk – positive
CHR-	Clinical High-Risk – negative
CIBERSAM	Centro de Investigación Biomédica en Red de Salud Mental
COPS	Criteria of Prodromal Syndromes
CUD	Cannabis Use Disorders
DISC-C	Diagnostic Interview Schedule for Children
DP	Deviant Perception
DSM	Diagnostic and Statistical Manual of mental disorders
DSM-III	3rd edition of the Diagnostic and Statistical Manual of mental disorders
DSM-IV	4th edition of the Diagnostic and Statistical Manual of mental disorders
DSM-IV-TR	4th edition of the Diagnostic and Statistical Manual of mental disorders – Text Revision
DSM-5	5th edition of the Diagnostic and Statistical Manual of mental disorders
DUI	Duration of Untreated Illness
DUP	Duration of Untreated Psychosis
DUPS	Dutch Prediction of Psychosis Study
EDEN project	A National Evaluation of Early Intervention for Psychosis Services: DUP, Service Engagement and Outcome. The National EDEN Project
ED:IT	Early Detection and Intervention Team
EIS	Early Intervention Service
EPOS	European Prediction of Psychosis Study
EPS	Elgin Prognostic Scale
ERIraos	Early Recognition Inventory for the restrospective assessment of the onset of schizophrenia
ERIraos-CL	Early Recognition Inventory for the restrospective assessment of the onset of schizophrenia – Checklist
ERIraos-SL	Early Recognition Inventory for the restrospective assessment of the onset of schizophrenia – Symptom List
ESI	Eppendorf schizophrenia inventory
FCQ	Frankfurt Complaint Questionnaire
FEP	First-Episode Psychosis
FIS	Fondo de Investigaciones Sanitarias
FR	Frankness-scale

GAF	Global Assessment of Functioning
hr	hazard risk
ICD-10	10th revision of the International Classification of Diseases
IQ	Intelligence Quotient
IR	Ideas of Reference
IRAOS	Interview for the Retrospective Assessment of the Onset and course of Schizophrenia and other psychosis
JCR	Journal Citation Reports
MHV Model	Multi-Hits Vulnerability Model
MPAS	Modified Premorbid Adjustment Scale
MRI	Magnetic Resonance Imaging
NAPLS	North American Prodrome Longitudinal Study
NARP	Non-affective Acute Remitting Psychosis
NHS	National Health Service
PA	Premorbid Adjustment
PAAS	Premorbid Asocial Adjustment Scale
PACE	Personal Assessment and Crisis Evaluation
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PAS-S	Premorbid Adjustment Scale – Spanish version
PDI	Peters Delusion Inventory
PLIKSi	Interview for psychosis-like symptoms
PQ	Prodromal Questionnaire
PQ-B	Prodromal Questionnaire – Brief
PQ-16	Prodromal Questionnaire – 16-item
PRIME	Prevention through Risk Identification, Management and Education
PROD-screen	Screen for PRODromal symptoms of psychosis
PSA	Premorbid Social Adjustment Scale
PS-revised	PRIME Screen – revised
QoL	Quality of Life
RETIC	Redes Temáticas de Investigación Cooperativa
R-DoC	Research Domain Criteria
SIPS	Structured Interview for Prodromal Symptoms
SCS	Social Competence Scale
SOPS	Scale of Prodromal Symptoms
SPI-A	Schizophrenia Prediction Instrument – Adult version
SPI-CY	Schizophrenia Prediction Instrument – Child and Youth version
SPQ	Schizotypal Personality Questionnaire
SPro	or Self-Screen-Prodrome
TV3	Televió de Catalunya
UCLA	University of California, Los Angeles
UHR	Ultra High Risk
Y-PARQ	Youth Psychosis At-Risk Questionnaire

CONTENTS

CONTENTS

Page

PART I: THEORETICAL FRAMEWORK

PART II: EMPIRICAL FRAMEWORK

Page

PART III: GENERAL CONCLUSIONS

References

Annex

Curriculum vitae

PART I:
THEORETICAL FRAMEWORK

1. Preventive approach to psychotic disorders

Mental disorder **prevention focuses on reducing risk factors** (which are associated with an increased probability of onset, greater severity and longer duration of major health problems) **and enhancing protective factors** (which are conditions that improve people's resistance to risk factors and disorders) associated with mental ill-health (Jané-Llopis & Anderson, 2006). To 'prevent' literally means 'to intervene or take steps in advance to stop something from happening'. However, there are different notions about that 'something' and they have been identified as the incidence of a disorder, its relapses, the disability associated with it, or the risks for a disorder, and this has led to confusion in the field of mental health regarding the term prevention (Mrazek & Haggerty, 1994). Historically, the public health concept of disease prevention has viewed **prevention as primary, secondary or tertiary** depending on whether the strategy prevents the disease itself, the severity of the disease or the associated disability, respectively. This system works well for medical disorders with a known etiology. Mental disorders, on the other hand, often occur due to the interaction of environmental and genetic factors at specific periods of life. It becomes difficult even to agree on the exact time of onset of a mental disorder, as the progression from the asymptomatic to symptomatic state may be insidious.

In the early 1990s, the Committee on Prevention of Mental Disorders of the Institute of Medicine proposed a new model of preventive intervention describing the three levels of primary prevention:

- **Universal level**: preventive interventions are targeted to the general public or to a whole population group that has not been identified on the basis of individual risk.
- **Selective level**: interventions are directed to asymptomatic populations whose risk of developing a mental disorder is significantly higher than that of the rest of the population.
- **Indicated level**: preventive interventions are targeted to high-risk individuals who are identified as having minimal, but detectable, signs or symptoms foreshadowing mental disorders, but who do not meet the diagnostic criteria for the disease.

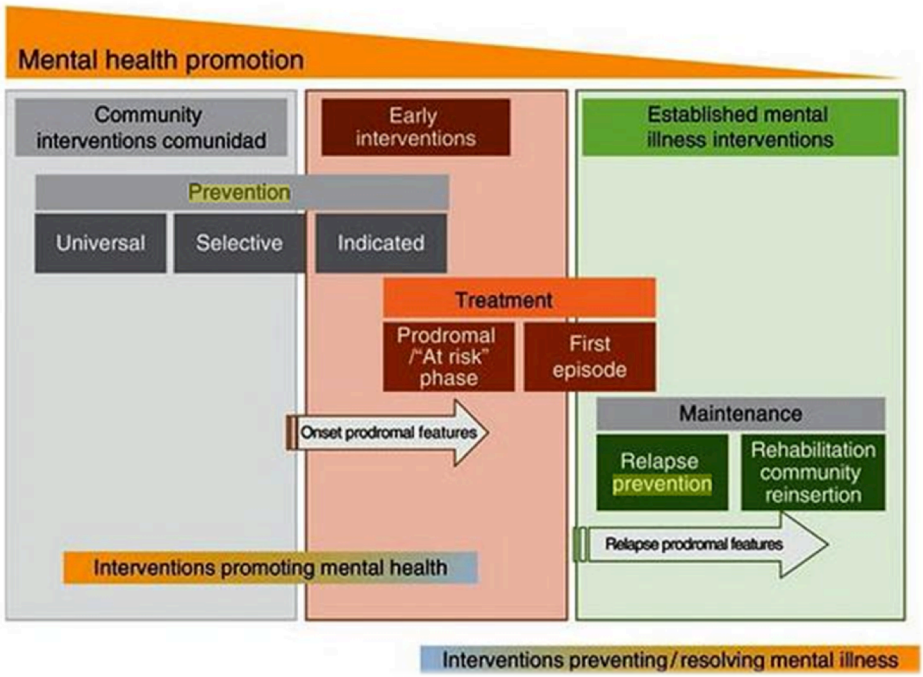


Fig. 1. A new prevention model in psychosis: from promoting mental health up to preventive interventions. [Source: Vázquez-Bourgon, Salvador-Carulla, Crespo-Facorro, & Vázquez-Barquero, 2013].

The relevance of this new model of prevention is due to the fact that it allows integrating the clinical manifestations into a comprehensive construct belonging to the different stages of the illness, in order to be maximally effective, with interventions directed to promoting mental health and preventing and treating mental illness (Fig. 1). It implies another way of conceptualizing prevention strategies based on a risk-benefit point of view, i.e. the risk to an individual of getting a disease against the cost, risk, and discomfort of the preventive strategy (Gordon, 1987).

Historically, for many years, schizophrenia and other psychotic disorders have been viewed pessimistically, characterized by high levels of stigma and neglect (Yung, Killackey, Nelson, & McGorry, 2010a). Prevention in these disorders has been a cherished ideal since the early years of this century, although it has been an elusive goal. In this sense, **the preventive approach has faced several barriers**, from the pessimism of the Kraepelinian framework, considering the impairment as unavoidable, to the lack of effective and non-iatrogenic interventions. Furthermore, it is possible that hopes for prevention have rested to an excessive degree on the emergence of effective forms of primary prevention. Arguably, this is because the focus for our preventive thinking has been more advanced than our knowledge base, and hence overly ambitious. We still have only a vague sense of the underlying risk factors and neurobiology of the psychoses, a prerequisite for primary prevention. This may have inadvertently contributed to paralysis in secondary prevention. However, in the last two decades, after an extended dormant period, the adoption of a clinical epidemiological perspective highlighting the preventive opportunities which exist, combined with encouraging advances in psychopharmacology and psychosocial treatment, has begun to create a climate of optimism: the ***early intervention movement***, which advocates rapid access to care and comprehensive treatment in the initial stages of disorder. The basis of this strategy is that the first few years of illness represent a 'critical period' (Birchwood, Fowler, & Jackson, 1998), during which treatment will be most effective and may prevent future deterioration and secondary morbidity. In general terms, **early intervention means intervening at the earliest possible phase of an illness**. Early intervention is recommened where there is evidence to show that (Mrazek, 1998):

- There is an effective and available 'mechanism' to detect an illness at an early phase. The 'mechanism' can include screening or assessment tools and should minimize the risk of identifying people as having the illness who do not actually have it (know as 'false positives') as well as the risk of not identifying people who do have the illness (known as 'false negatives');

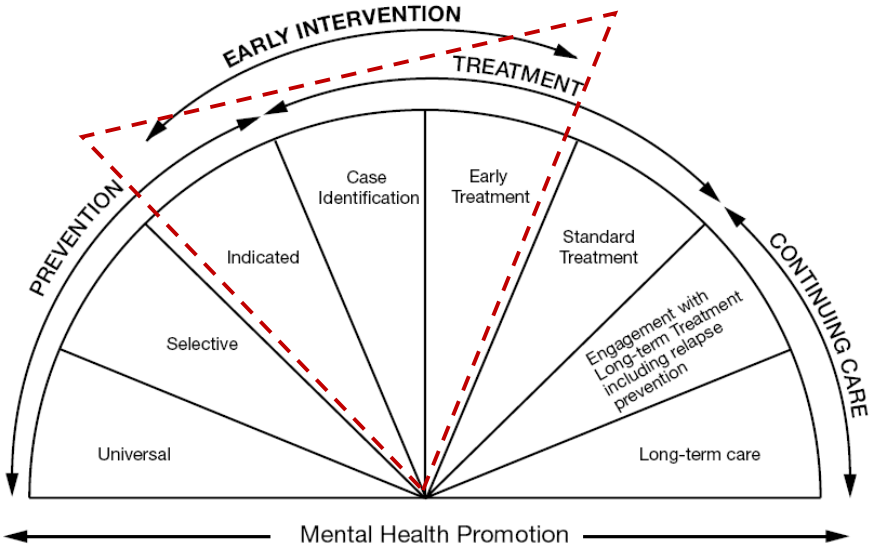


Fig.2. The mental health intervention spectrum for mental disorders. [Source: Modified from Mrazek, & Haggerty, 1994. (The red line indicates components of early intervention)].

- Intervening early will have a positive impact on health outcomes;
- Effective treatment for the illness is available; and
- The effective treatment can be accessed early by those who need it.

Early intervention should occur when warning signs or early symptoms begin to manifest. For individuals at high risk, early intervention may occur as an **indicated prevention** strategy before the onset of any signs or symptoms that reach clinical significance. Interventions that occur later in the process of illness onset, when symptoms have reached an acute stage, are classified as **case identification** and **treatment** (Fig. 2).
Early intervention is seen as beginning in the indicated level (for individuals with signs and symptoms) and continuing through to case identification. So, this new paradigm implies a dual focus of interest: on the one hand, an intervention more orientated towards **indicated prevention (early pre-psychotic intervention)** of persons who already exhibit risk symptoms requiring treatment, and on the other, targeted **secondary prevention (early psychotic intervention)** of patients with a full-fledged psychotic disorder, including two aspects: case identification and early treatment.

1.1. Indicated prevention in psychosis: early pre-psychotic intervention.

From the new framework of preventive intervention for mental disorder, based on the classification of the prevention of physical illness (Gordon, 1987) and the classic public health distinctions between primary, secondary and tertiary prevention, individuals with early and/or subthreshold features (and hence a degree of suffering and disability) can also be included in one of the three new levels of primary prevention (which classically has been targeted at asymptomatic individuals), specifically within the focus of indicated prevention. Then, **indicated prevention targets high-risk individuals** who do not meet the diagnostic criteria of a classification system such as the 10^{th} revision of the International Classification of Diseases (ICD-10) or the 5^{th} Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
One of the key challenges in attempting indicated prevention in psychosis is to determine which signs and symptoms are the **precursors** to the full threshold of psychotic spectrum disorders. The characterization and identification of the prodromal phase, in order for intervention to be provided, is the essence of indicated prevention, providing the possibility of (1) minimizing disability and adverse health and social impacts associated with the prodrome phase, (2) some recovery before symptoms and poor functioning become entrenched, and (3) preventing, delaying or ameliorating the onset of diagnosable psychotic disorder. For this purpose, two approaches have been carried out throughout the scientific literature (see section 3.2.1. Prodromal phase: Conceptualization and characterization of the prodromal psychosis onset):

a) **Retrospective approach** with studies about first-episode psychosis (FEP) (Häfner et al., 1995; Yung & McGorry, 1996) in which only those cases that have developed a psychosis are included in reconstructions of the prepsychotic phase. The prepsychotic features are described as prodromal since in this sample they are always followed by psychotic symptoms. The clinical features identified retrospectively in first-episode samples are mostly non-specific (Yung & McGorry, 1996) and have only a limited predictive power in relation to subsequent psychosis.
b) **Prospective approach** which implies considering new terms as 'at-risk mental state' (ARMS) (McGorry & Singh, 1995) or the notion of 'precursor' features used for the same purpose (Eaton, Badawi, & Melton, 1995). These terms indicate clinical features which can be assigned to estimate of risk of the full-fledged disorder although involving a false-positive rate. Also, this approach includes new strategies to improve detection of psychosis risk, such as 'close-in strategy' (Bell, 1992), which has great potential to overcome some of the weaknesses of traditional high-risk research while retaining genuine preventive credentials.

Given that the indicated prevention interventions are targeted to persons at high risk for mental disorders, it represents a step forward from the disadvantages of universal interventions (such as provision of small benefit effects because of small effect sizes or their high cost and the difficulty to evaluate, especially in the case of low incidence disorders such as the psychotic spectrum disorders) and selective interventions (using risk markers alone is too narrow a basis for screening and preventive intervention). **The indicated prevention has been considered as the basis for the early intervention paradigm**. In this context, indicated prevention pursues the objectives of (a) improvement of the burden of the early pre-clinical syndromes and (b) prevention of the development of the illness. In this sense, the indicated prevention has been considered the most feasible of the preventive models for realistic reduction in incidence in both high and low incidence disorders (Cuijpers, 2003). So, preventive interventions in psychotic disorder are now a realistic possibility for the first time and are being developed in many parts of the world (Edwards & McGorry, 2002).

1.2. Secondary prevention in psychosis: early intervention in FEP

Secondary prevention seeks to lower the rate of established cases of the disorder or illness in the population (prevalence) through early detection and treatment of diagnosable diseases. In first onset psychosis, early intervention means first intervening when the full-blown psychosis has appeared, to improve outcomes in established cases of psychosis by facilitating and consolidating recovery, and detecting hidden morbidity in the community by identifying untreated cases. Intervening at this earliest stage is relatively new for mental health. Although there are difficulties in identifying, accessing and treating young people in this phase, it is critical for improved outcomes. Increasing evidence shows that early, effective, comprehensive treatment and management of young people with first onset psychosis has a significant impact on medium and long term outcomes for the individual and their family.

Early intervention in FEP is addressed to two targets: a) the period of frank symptoms of psychosis that remains untreated, which may compound the issues of risk and the development of prolonged disability, and b) the critical period after the onset of the first psychotic episode, which can be up to five years in duration, when treatment needs to be comprehensive and phase-specific.

The underlying **principles of intervention in early psychosis** are threefold:
- Opportunities for clinical care should be made available in the shortest timeframe possible
- Assessment and prevention of secondary morbidity decreases the risk of mortality and morbidity in early psychosis
- Ongoing research is required to substantially test the efficacy of current treatments and to develop secondary prevention opportunities

The **aims of early detection** and diagnosis of psychotic illness are to reduce or prevent the:
- progression or worsening of symptoms/syndrome
- progression or worsening of associated neurobiological changes and neuropathology
- secondary psychiatry morbidity such as depression, anxiety, suicide and substance use
- significant deterioration in, or failure to achieve, role functioning
- individual and/or family's experience of trauma and/or stress often associated with severe psychotic illness, involuntary hospital admissions, etc.
- stigma, and provide early psychoeducation
- disruption to normal developmental processes
- costs to the community and government

The publication of some key systematic reviews and recent influential longitudinal research (Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005) have established that **longer duration of untreated psychosis (DUP) is both a marker and an independent risk factor for poor outcome**. DUP has been associated with slower and less complete recovery, more biological abnormalities, more relapses and poorer long-term outcomes (Harrigan, McGorry, & Krstev, 2003; Malla, Norman, McLean, Scholten, & Townsend, 2003; McGlashan, 1998;). Then, taking into account these findigns, **what are we waiting for?** Since the early 20th century, authors such as Bleuler (1908, p. 63) have advocated intervention as soon as possible: "The sooner the patients can be restored to an earlier life and the less they are allowed to withdraw into the world of their own ideas, the sooner do they become socially functional". Essentially, the answer to the question 'Why wait?' is that we have to take account of the risk/benefit ratio for patients, including issues of stigma, and carefully evaluate the optimal duration of treatments to be offered at this phase. Some people have expressed an appropriately cautious view that it could be potentially iatrogenic to treat at this phase, particularly when it comes to applying a diagnosis and using neuroleptic medication. Others, such as Mrazek & Haggerty (1994, p. 154) have emphasized the imperative to 'do something' when it is clear that a young person is in trouble, with their lifestyle and prospects collapsing around them: "The identification of individuals at this early stage, coupled with the introduction of pharmacological and psychosocial interventions, may prevent the development of the full-blown disorder". It is still a matter of debate in the scientific community.

In the last two decades, early intervention in psychotic disorders is increasingly seen as having the potential to produce **better outcomes** in these potentially adverse conditions, which generally strike during the critical developmental phase of adolescence or early adulthood (Birchwood, McGorry, & Jackson, 1997). Early psychosis programmes have been shown to decrease DUP (Malla et al., 2003; Yung, Organ, & Harris, 2003a) and hospitalization (Cullberg, Levander, Holmqvist, Mattsson, & Wieselgren, 2002; Yung et al., 2003a), decrease police involvement in admissions (Yung et al., 2003a), lower medication use (Cullberg et al., 2002), improve functional outcome (Harrigan et al., 2003), lower relapse rates (Linszen, Dingemans, & Lenior, 2001), improve treatment adherence (Jørgensen et al., 2000) and lead to greater patient satisfaction (Cullberg et al., 2002). However, to get appropriate, effective early intervention in psychotic disorders a previous step is necessary: '**case identification**'. For this purpose, we need to know in detail the early phases of psychosis, both risk factors and symptomatic aspects. In the last two decades considerable progress has been made, among which stands out an increased research focus on identifying early markers of psychotic illness and, importantly, better characterization of the early phases of psychotic disorder. So, **early intervention requires prior early detection** and that at-risk persons be aware of relevant premonitory signs and symptoms and seek help. As the success of preventive approaches also depends on reaching a sufficiently high rate of target persons, and, as retrospective studies suggest that only a minority of persons about to develop psychosis actively seek help for their problems (Köhn et al., 2004), more research is needed to develop a justified means for improving the identification of people in an early phase of psychosis.

2. Theoretical model:

2.1. Integrative models of psychotic spectrum disorders

Despite a century of research, the pathophysiological basis of psychosis remains unclear and, in the absence of a singular genetic or environmental pathogenic agent for psychotic spectrum disorders, attention has turned to disease models involving multiple factors. In this sense, **integrative models of**

psychotic spectrum disorders that have been shown increasing scientific evidence in recent years, have emerged in an attempt to unify several hypotheses. Modern integrative models of psychosis are usually grounded in the assumption that psychotic disorders are brain disorders and that a multitude of pathogenetic factors interact in persons in inter-individually different combinations. One early attempt of great influence was the '**two-hit hypothesis**' (Bayer, Falkai, & Maier, 1999) which suggests that a prenatal genetic or environmental 'first hit' disrupts some aspect of brain development, and establishes increased vulnerability to a second hit that may occur later in life. Neither insult by itself is sufficient to induce schizophrenia. Instead, the first hit 'primes' the nervous system for the second, which then precipitates disease symptoms. In this way, a two-hit model for psychosis would suggest that disruptions in the development of the central nervous system produce a vulnerability to the disorder but that the onset of symptoms in a vulnerable brain would be triggered by environmental factors. Likewise, new approaches have been developed on the assumption that **the phenotype of psychotic disorders is produced by the influence of multiple factors**. These approaches were extended into the '**three hit model**' (Keshavan, 1999) including neurodegenerative factors, which were thought to be induced or accelerated by the disease onset itself (i.e. developmental risk factors, precipitating factors, and neurodegenerative factors). These hypotheses have gained much empirical underpinning in recent years and can now be refined in that the pathophysiologic factors involved in each of the different 'hits' are beginning to be elucidated as interactions of time variable and partly overlapping factors.

In general, **'Multiple Hit' models** have suggested the importance of **additive and interactive effects** of environmental risk factors against a background of genetic predisposition. Ritsner (2011) proposed the **Multi-Hits Vulnerability Model (MHV Model)** (Fig. 3), which is based on interaction between four main hits:

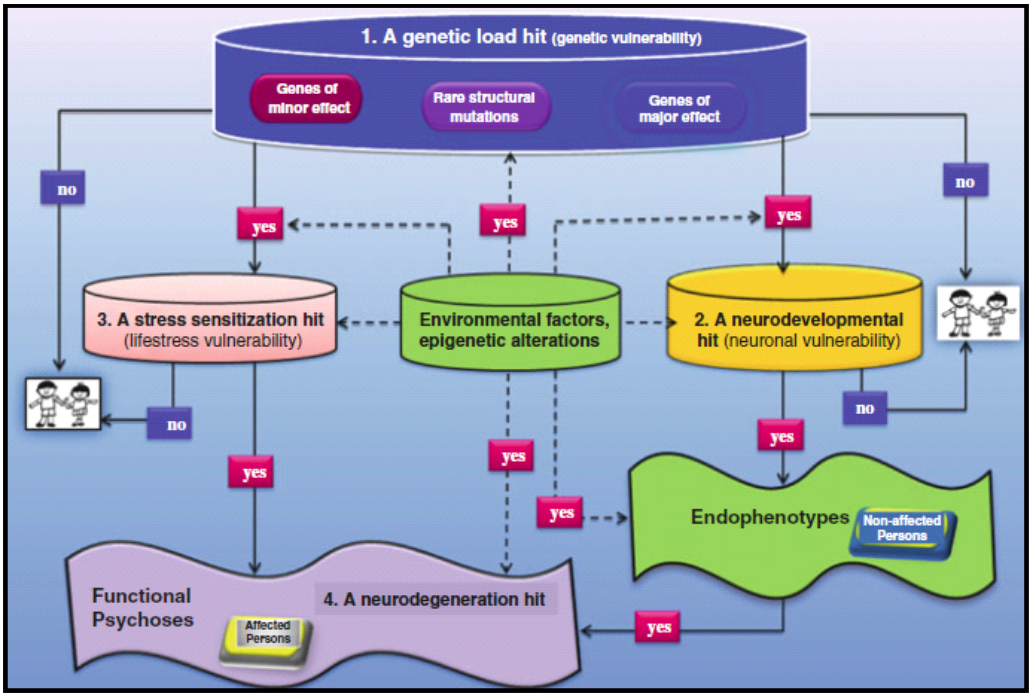


Fig. 3. A Multi-Hits Vulnerability Model of functional psychoses. [Source: Ritsner, 2011].

a) **a genetic load hit ('genetic vulnerability')**: systematic genome-wide association and follow-up studies have reported genome-wide significant association findings of common variants for schizophrenia and bipolar disorder. There is emerging evidence that some cases of psychosis (in particular, with schizophrenia) might be due to rare genetic structural variations, though the

majority of cases are putatively due to a cumulative effect of common variations in multiple genes, which in combination with environmental stressors may lead to the development of psychotic disorders (Schwab, & Wildenauer, 2009; Walsh et al., 2008). The aggregate data provide support for polygenic inheritance and for genetic overlap in psychosis.

b) **a neurodevelopmental hit ('neuronal vulnerability')**: the etiology of psychosis may involve pathologic processes, caused by both genetic and environmental factors, before the brain approaches its adult anatomical state in adolescence (Rapoport, Addington, Frangou, & Psych, 2005). So, it has been hypothesized that some event will disrupt the normal development of brain structure and function at a stage prior (pre- and perinatal period) to the brain having reached a stage of full maturity and will lie silent until after puberty, when maturational events lead to the emergence of the symptoms of psychosis (Weinberger, 1987). Two models have been proposed to explain this latent period:

- *the **early neurodevelopmental model***: this is based on the view that a fixed lesion from early life interacts with normal neurodevelopment occurring later, lying dormant until the brain matures sufficiently to call into operation the damaged systems (Murray & Lewis, 1987).

- *the **late neurodevelopmental model***: based on data that indicate substantial changes in brain biology during adolescence, this model proposes that psychosis may result from an abnormality in periadolescent synaptic pruning (Feinberg, 1983). Genetic predisposition may produce an inappropriately high 'synapse use threshold' and lead to excessive pruning (Pogue-Geile, 1997). Thereby, these neurodevelopmental abnormalities have been suggested to lead to the activation of pathologic neural circuits during adolescence or young adulthood, which leads to the emergence of psychotic symptoms (Fatemi, 2005). Furthermore, it has been postulated that the genes involved in the regulation of pruning are under some element of hormonal control and this may have an influence on the gender difference in age of onset of symptoms (Corroon, 2005).

The heterogeneity of the illness may be evidence of etiological heterogeneity; however, the neurodevelopmental theory may only hold true for a subtype of psychotic spectrum disorders. Therefore, we have to take into account other factors and interactions.

c) **a stress sensitization hit ('life stress vulnerability')**: sensitization refers to the observation that individuals who are exposed repeatedly to an environmental risk factor may develop progressively greater responses over time, finally resulting in a lasting change in response amplitude. It has been hypothesized that the process of sensitization is the substrate for the susceptibility to the psychosis-inducing effects of stress and dopamine-agonist drugs observed in patients with psychosis (Howes et al., 2004). Behavioral sensitization to daily life (environmental) stress may be a vulnerability marker for psychotic disorders, reflecting dopaminergic hyper-responsivity in response to environmental stimuli (Myin-Germeys, Delespaul, & van Os, 2005). The interpretation that daily life stress causes increases in psychosis intensity (i.e. behavioural sensitization) would fit with recent biological and psychological models of psychosis development. Although many questions remain, there is some evidence that environmental factors, which interact with multiple genes, in interaction with epigenetic factors, psychological or physiological alterations, may induce a final common pathway of cognitive biases and/or altered dopamine neurotransmission, broadly referred to as 'sensitization', facilitating the onset and persistence of psychotic symptoms (Collip, Myin-Germeys, & van Os, 2008). However, stress sensitization is most often unspecific for psychotic

spectrum disorders, since it can also trigger high blood pressure, diabetes, ulcers, and asthma, among other disorders.

d) **a neurodegeneration hit**: a neurodegenerative process is produced when brain tissue is destroyed. The opinion that schizophrenia is a degenerative disorder was held until the middle of the last century. During the 1980s and 1990s several longitudinal studies of neurocognitive functioning in patients with schizophrenia showed no evidence of decline in function over time. This was taken to indicate that there is no ongoing degenerative process in the brain, at least not after the onset of illness (Rund, 1998). Instead, a neurodevelopmental model emerged as the dominant explanatory framework for schizophrenia. However, a few years ago the hypothesis of schizophrenia as a degenerative disorder re-emerged. This was primarily based on several new longitudinal magnetic resonance imaging (MRI) studies that showed substantial increases in brain cavities, and corresponding excessive shrinkage of vital brain tissue, during the first years after the onset of illness. These studies have led some to suggest that the neurodegenerative hypothesis may have been overshadowed by the ascendancy of the neurodevelopmental hypothesis. However, we must not forget that there are no two studies that have found the exact same structural changes in this patient group (Weinberger & McClure, 2005). So, we cannot provide a definite answer as to whether psychotic disorders are degenerative disorders. In fact, longitudinal studies of neurocognitive functioning provide a relatively consistent indication that the impairment does not progressively worsen the first years after the onset of illness. This may be due to medication or other biological effects (Rund, 2009). Rund (2009) proposed several alternative interpretations that may explain the brain changes occurring after the onset of illness: a) degeneration occurs with varying degress of compensations or with regressive processes that are undetectable in macroscopic investigations of the brain; b) there is a reorganization of synaptic connections without any form of degeneration or regression; c) the brain more efficiently utilizes brain networks or enhances the ability to recruit alternative brain networks as needed, as Cognitive Reserve Theory suggests; or d) brain structural or volumetric changes affect certain sub-groups of patients more than others. In addition, Kalus et al. (2004) reported reduction of hippocampal volume in patients with schizophrenia, which was related to alterations in white matter coherence between hippocampal sub-structures. In particular, the hippocampal alterations could be related to the psychopathology of schizophrenia which could be more critical for sub-groups of patients with clearly defined cognitive impairments. Based on these results, Rund (2009) hypothesized that previous studies of neurodegeneration had not paid enough attention to the symptomatic heterogeneity of the disorder, and that this could be related to brain structural changes over time, pointing to a possible degenerative process. In these sense, the findings about progressive structural changes in the brain after debut of the illness are of significant importance for understanding the etiology of psychotic spectrum disorders and should not be underestimated.

In conclusion, **integrated models are based on complex gene-environment interactions with a range of prepsychotic factors being combined in individually different constellations to lead to psychotic disorders**. The disadvantages of these models are the as yet small evidence base and the complexity of the putative interactions with a multitude of interindividually and probably even time-variant pathophysiologic factors. The strengths are their empirical foundations, especially in genetic and neurophysiologic studies. This may hopefully lead to objective and quantifiable analyses of the individual risk factors, their interactions, and their role in the pathophysiology of psychotic symptoms. **A further step would be to broaden our knowledge about the profile of early phases of psychotic spectrum disorders regarding clinical and functional issues**. It may bring light in relation to the factors predisposing to the development of psychosis and factors precipitating its onset.

2.2. The continuum hypothesis of psychosis: clinical staging model

Converging evidence from critical studies comparing categorical and dimensional models of psychosis has demonstrated that symptoms and disease course, risk factors, endophenotypes, and putative neurobiological underpinnings are better explained in terms of continuous distributions (Peralta & Cuesta, 2007). In this sense, **the MHV Model must be understood from a continuum approach**. However, as with what is reflected in the DSM-5, the categories of psychotic disorders should not be ignored if we wish to broaden our knowledge about the psychotic spectrum disorders. The study of psychosis should be considered from an integrated model with categorical and dimensional models as complementary. In the line of this hybrid model included in the DSM-5, this work has taken into account the psychotic disorder categories with which we may establish the inclusion criteria and the analysis of dimensional structure to study early phases of psychosis.

The notion that apparently healthy people can experience psychotic symptoms such as delusions and hallucinations – the continuum concept – has been explored for over 100 years. Since around the mid-1980s it has gained a large number of adherents so that it is now becoming the accepted dogma. Ernst Kretschmer was the first to clearly articulate the continuum idea when he stated "endogenous psychoses are nothing other than marked accentuations of normal types of temperament" (Kretschmer, 1925). However, Paul Meehl is most often credited with providing the modern intellectual bedrock for the continuum theory (Meehl, 1962). Meehl was discussing what we would now call endophenotypes, or biomarkers, with respect to schizophrenia. He was prompted to examine the issue because of accumulating evidence that people with a strong family history of schizophrenia exhibit certain traits that fall short of the schizophrenia syndrome yet nevertheless seem abnormal or dysfunctional in some way ('schizotaxia'). What he really sought was a hard biological equivalent of what were then and remain somewhat vague and difficult to define personality characteristics (David, 2010).

⇒ Strengths and weakness of the continuum hypothesis

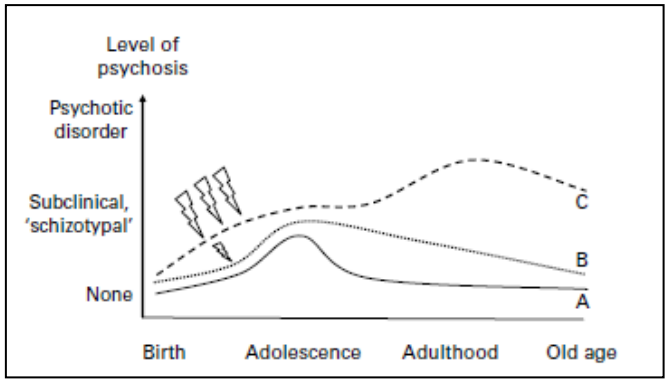
Among the **strengths** of the continuum hypothesis listed in the work of David (2010) are the following:

a) Psychotic symptoms are seen as **distortions or exaggerations** of common phenomena according to the medical model;

b) The continuum concept justifies the study of healthy subjects who may be more accessible than patients and certainly **free of many potential confounds** to research, particularly medication and other secondary effects of illness;

c) The **moral benefits** of this position: as mentioned by Bentall (2003) 'we are all a bit mad', which is bound to reduce stigma and help break down any alienating sense of 'us and them';

d) There is evidence of **continuity of the psychotic experiences over time**, until developing a psychotic spectrum disorder (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Poulton et al., 2000). The psychosis proneness-persistence-impairment model considers genetic background factors impacting on a broadly distributed and transitory population expression of psychosis during development, poor prognosis of which, in terms of persistence and clinical need, is predicted by environmental exposure interacting with genetic risk. There are processes of biological and psychological sensitization, which would explain differences in longitudinal trajectories of psychosis proneness as depicted in Fig.4 (Van Os, Linscott, Myin-Germys, Delespaul, & Krabbendam, 2009).



Person A has 'normal' developmental expression of subclinical psychotic experiences (*psychosis proneness)* that are transient.

Person B has similar expression but longer *persistence* due to additional but mild environmental exposure.

Person C has longer persistence due to severe repeated environmental exposure and transition to clinical psychotic disorder with significant *impairment*.

Fig.4. Sensitization and onset of psychotic disorder.
[Source: Van Os, et al., 2009].

So, a continuous phenotype implies that the same psychotic symptoms that are seen in patients with a psychotic disorder can also be observed in non-clinical populations (Van Os, et al. 2009).

Much of the evidence of continuum hypothesis has been generated with the aid of **standard questionnaires**, (i.e. the Peters Delusion Inventory (PDI) and the Diagnostic Interview Schedule for Children (DISC-C). However, most of these questionnaires **do not explore the phenomenology of psychotic experiences** and thus provide little information about the exact phenotype. So while standard questionnaires suggest a continuous phenotype of hallucinations throughout the population, detailed study of the phenomenology of these 'non-clinical psychotic phenomena' suggests that they are qualitatively dissimilar from the symptoms encountered in psychosis (Sommer, 2010). Other **weaknesses** in the evidence of the continuum hypothesis of psychosis are related to **methodological issues** such as setting a threshold above which a hallucination or delusion may be defined, to the nature of the questions and the expectations they engender in participants when they are assessed, and to the use of self-administered tools to assess psychotic symptoms, increasing the number of false positives in non-clinical groups (David, 2010; Ochoa et al., 2008).

⇒ Clinical staging model

From this continuum model, mental ill-health can be difficult to distinguish from transitory and normative changes in emotions and behavior, which are often regarded as part of normal development and the human condition, especially in young people. To date, we do not have a clear consensus about the criteria for defining the threshold of onset of psychotic episode (Yung, Nelson, Thompson, & Wood, 2010b). However, the **clinical staging model** represents an approximation to this question with clinical and etiological implications. It is a more flexible system linking the course, extension, and pattern of illness over time which moves away from traditional and artificial divisions based on cross-sectional symptom sets, propped up with course and outcome variables. Clinical staging differs from conventional diagnostic practice in that it defines not only the extent of progression of a disorder at a particular point in time but also where a person lies currently along the continuum of the course of an illness. Clinical staging, a deceptively simple and practical tool found useful in other areas of medicine, may provide a way forward (McGorry, Purcell, & Hickie, 2007), opening the door for better understanding of gene-environment interactions in the onset and course of psychiatric illness (Insel, 2007).

The **main objectives of the staging paradigm** extend through three areas: clinical, research and service provision (Table 1) (Vázquez-Bourgon et al., 2013).

Table 1. Main objectives of the staging paradigm.

Clinical objectives	To identify persons at risk of developing the illness
	To reduce or minimize disruption of normal developmetal processes
	To prevent or postpone the transition to full-blown disorder
	To provide early identification and treatment of the first episode
	To identify persons at risk of relapse and to prevent the development of a relapse
	To stimulate the acquisition of insight into the nature of the illness
	To promote the development of treatment adherence
	To prevent the development of psychiatric comorbidity
	To reduce social and personal costs associated with the disorder
	To promote quality of life and social integration and prevent stigma
Research objectives	To elucidate the biological and psychosocial basis of mental disorders
	To clarify the psychopathological and clinical structure of the early stages of the disorders
	To identify predictors of transition from one stage to the next and predictors of relapse
	To investigate the efficacy and cost-efficacy of early intervention strategies
Health service objectives	To develop novel phase-specific mental health services and programmes for the early phases of mental disorders, exploring their effective integration in the mental health service structure
	To investigate the cost-efficacy of the EIS

Although the application of the clinical staging model has proved very useful in medical care, it is only recently that it has been extended to the field of mental health. In fact, clinical staging in psychiatry was initially proposed by Fava and Kellner (1993), and it rapidly became focused on early signs of psychosis. The application of the clinical staging model is based on the idea that the longitudinal course of a disease is likely to progress from an 'at-risk' to a prodromal status, and finally to a fully developed diagnostic entity. It also implies that **the disease progresses through different stages** that are characterized by phase-specific clinical manifestations. One of the aims of this model is to prevent progression to more advanced stages or to promote regression to an earlier stage, including full and sustained remission. To achieve this, an accurate understanding of the social, biological, and personal risk and protective factors that influence progression from one stage to the next will be essential (McGorry, Nelson, Goldstone, & Yung, 2010). In other words, it is necessary to characterize well each of the discrete stages and their progression in order to anticipate preventive interventions. So, to define discrete stages according to progression of illness creates a framework oriented toward prevention and cure.

The different stages are defined in relation to the patient's psychopathology and psychosocial functioning, because biological markers are not identified yet. To guide clinicians in identifying the stages at which the individuals are at a particular point in time, different concepts have been proposed. In Table 2 are shown the stages corresponding to the early phases of psychosis until persistent frank symptoms happen, i.e. until stage 2 (the first episode of a full-threshold disorder).
From the staging paradigm it is possible to investigate the origin and nature of mental diseases without the spurious contamination of the illness chronicity and long-term treatment. This will promote a more precise clarification of the mechanisms and factors underlying the origin and clinical course of the disorder. Moreover, the information gathered along the way in which clinical, social and biological factors may condition the transition of the illness from one stage to the other should also facilitate the development of more effective interventions (Vázquez-Bourgon et al., 2013). In this sense, a detailed study of the possible factors that interfere in the course of the illness, in each of its phases, will allow the development of phase-specific evaluation and intervention procedures.

In conclusion, seeing psychotic phenomena as a point on a continuum with 'normal' experience is a useful heuristic device with many positive benefits, among them achieving an intervention model based on continuity risk.

Table 2. Clinical staging model framework for psychotic and severe mood disorders*.

Stage	Clinical definition	Target population and referral sources	Potential interventions
0	Increased risk of psychotic or severe mood disorder; no symptoms currently	First-degree relatives of probands (especially aged 12 to 25 years)	Improved mental health literacy, family education, drug education, and brief cognitive skills training
1a	Mild or nonspecific symptoms, including mild neurocognitive deficits of psychosis or severe mood disorders; mild functional change or decline	Screening or active case finding within teenage and emerging adult populations; referral by primary care physicians, school counselors, and self- and family referrals	Formal mental health literacy and first aid; supportive counseling and problem solving; family psychoeducation; exercise; active substance abuse reduction
1b	UHR: moderate but subthreshold symptoms, with moderate neurocognitive changes and functional decline to caseness (GAF 70)	Referral by educational agencies, primary care physicians, emergency departments, welfare agencies, drug and alcohol agencies, police and forensic services, and self- and family referrals	Family psychoeducation; individual and (or) group CBT; cognitive remediation and social cognition interventions; active substance abuse reduction; neuroprotective agents (for example, omega-3 and other candidates)
2	FEP or severe mood disorder (mania or severe or persistent depression); full threshold disorder with moderate-to-severe symptoms, neurocognitive deficits and functional decline (GAF 30-50)	Referral by primary care physicians, emergency departments, welfare agencies, specialist care agencies, drug and alcohol services, police and forensic services, and self- and family referrals	Family psychoeducation; CBT; active substance abuse reduction; atypical antipsychotic agents for psychotic symptoms, if present; antidepressant agents or mood stabilizers for full mood syndrome; vocational rehabilitation

*This table has been reproduced in a modified form. It was originally published in McGorry, Hickie, Yung, Pantelis, & Jackson, 2006.
GAF= global assessment of functioning (scale, 0-100); UHR= ultra high risk; CBT= cognitive behavior therapy; FEP= first-episode psychosis.

3. Early phases of incipient psychosis:

According to the clinical staging model psychosis runs across several stages, also defined as a **phasic course**, characterized by a sequential emergence of **premorbid (or stage 0)** (i.e. years prior to the onset of psychotic symptoms, often with trait-like deficits in psychopathology, behaviour and function), **prodromal (or stage 1)** (i.e. immediately preceding the onset of psychotic symptoms with sub-threshold positive symptoms and functional decline) and **psychotic phases (or stage 2)** (i.e. the frank emergence of psychotic symptoms in late adolescence or early adulthood (Keshavan & Amirsadri, 2007). In addition, genetic and environmental factors have been found to play a role in the etiology of psychotic disorders (Cardno et al., 1999; Tienari et al., 2004). While some factors may operate across several or all stage transitions, others may be stage-specific; for example, substance misuse or stress may be especially harmful in triggering the onset of the first episode of an illness, yet be less toxic subsequently (or vice versa) (McGorry et al., 2010). Then, it is important characterize each phase to integrate knowledge regarding etiologic and risk factors with the trajectory to psychosis and so, achieve a more appropriate phase-specific assessment and intervention model. This can provide a framework for understanding illness progression and act consequently as soon as possible.

Figure 5 illustrates features drawn from knowledge regarding **the evolution and trajectory of the psychotic disorders**. Perinatal, childhood, and adolescent and young adulthood periods are ripe for collection and measurement of early life risk variables; these include genetic and environmental factors such as advanced paternal age, obstetric and perinatal complications, childhood adversity and trauma, and cannabis or other

substance exposure. As time goes on, a minority of individuals will develop premorbid disturbances; persistent premorbid symptoms may or may not evolve into prodromal features with subclinical severity. In some cases, an Axis I psychotic disorder emerges. However, as with clinical high risk for psychosis, subjects will experience either minimal psychopathology, general non-psychotic psychopathology, or development of a non-psychotic disorder Axis I, which is also often influenced by similar early life variables (Shah, Tandon, & Keshavan, 2013).

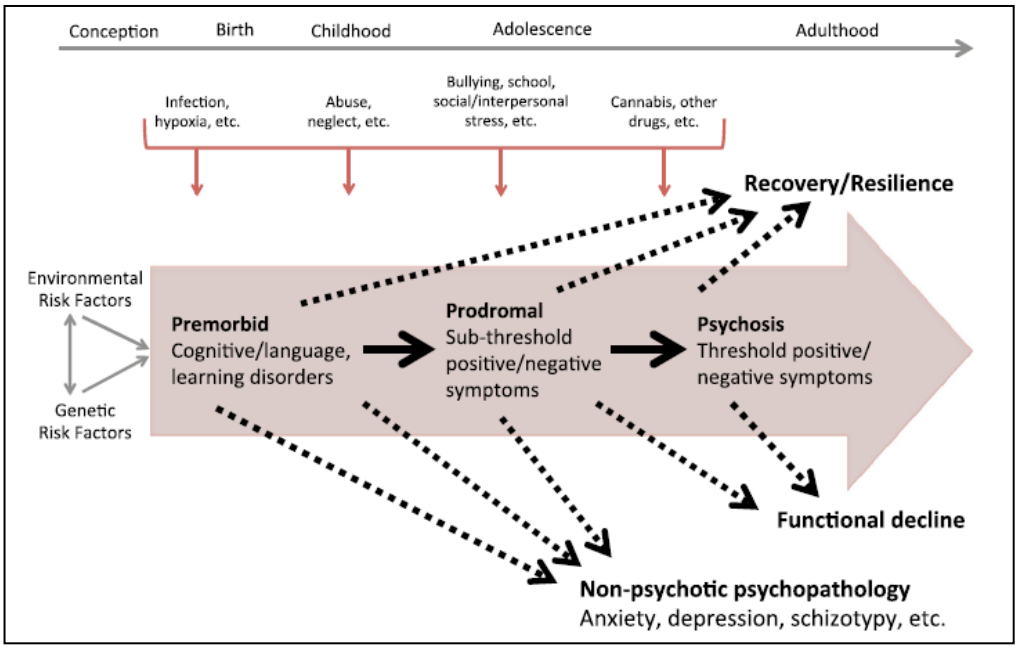


Fig.5. Risk factors, illness trajectories and outcomes for psychosis. [Source: Shah, et al., 2013]

3.1. Premorbid phase

The **premorbid phase is often only identifiable retrospectively** once a full-threshold episode has occurred (Yung et al., 2007a). This phase comprises a period of **relative normality** before patients exhibit any psychotic symptoms (other symptoms may be present, however, such as anxiety or depression). According to the characteristics or factors influencing this phase we can elucidate some aspects of the onset of the psychotic episode and its prognosis. Mäki et al. (2005) divided the premorbid predictors into genetic, biological and psychosocial risk factors at different stages of early life; among the latter are premorbid cognitive and scholastic performance, premorbid social adjustment and premorbid socio-sexual adjustment. These predisposing factors have been taken into account since a bit past the mid-20th century. For example, Chapman, Day, and Burstein (1961) considered a distinction in two dimensions of the psychotic disorders (specifically, of schizophrenia) as follows: ‘‘the distinction is usually justified by the differing prognosis of two symptom patterns. Briefly, a **process (or ‘typical’) schizophrenic** is said to be characterized by an inadequate pre-psychotic adjustment, with little interest in other people or the activities of life. The psychosis develops gradually from this pattern, with no identifiable precipitating stress. The symptoms usually include affective flattening with a clear sensorium. The prognosis is poor, and the disorder follows the deteriorating course described by Kraepelin for dementia praecox. The **reactive (or ‘atypical’) schizophrenic** is said to be characterized by a fairly normal prepsychotic adjustment, the psychotic symptoms appearing suddenly in response to severe stress. The symptoms include a clouded sensorium and marked affective display. The prognosis is good.’’ Therefore, the term process implies that the onset is not only slow and silent but also that it is biologically programmed into the system and

developmentally inevitable no matter what the environment. Reactive is the opposite. The development of disorder is rapid, stormy, and 'reactive' to identifiable environmental stresses and events. However, the use of terms like process and reactive has become outdated because they imply distinctive etiologies that cannot be tested (McGlashan, 2008). Nevertheless, analyzing premorbid functioning seems to be a useful method to learn more about the prognosis of the spectrum psychotic disorders and so to carry out a specific process of identification, assessment and intervention as soon as possible, before the harm is greater.

3.1.1. Conceptualization of premorbid adjustment (PA)

Strauss, Kokes, Klorman, and Sacksteder (1977) defined **PA** in schizophrenia as **those characteristics of a person, especially his interpersonal relations and occupational functioning, that can be found any time before the onset of florid symptoms of schizophrenia**. In this definition the main focus is on social adjustment; however, later studies broaden this approach considering that PA integrates the psychosocial functioning in educational, occupational, social and interpersonal relation areas (Addington, & Addington, 2005; Cannon-Spoor, Potkin, & Wyatt, 1982). So, although the use of the term PA in the wider literature has been debatable, it has been considered as a **multidimensional factor** by most researchers. Initially, Mukherjee, Reddy, and Schnur (1991) suggested that PA could be explained by two dimensions: social and academic. Krauss, Marwinski, Held, Rietschel, and Freyberger (1998), in an attempt to avoid the interdependence of the original Premorbid Adjustment Scale (PAS) subscales, found five independent dimensions which explained 70% of the total variance: (a) interpersonal relationships in childhood and early adolescence; (b) interpersonal relationships in late adolescence and adulthood; (c) scholastic performance and adaptation in school; (d) self-assertion; and (e) prodromal change. Subsequently, Allen, Frantom, Strauss, and Kammen (2001), and Norman, Malla, Manchanda, and Townsend (2005) provided more evidence for at least two domains of PA in schizophrenia, distinguishing between **academic PA** and **social PA**. Prior research has demonstrated **different correlates** for the two domains: premorbid social functioning is more strongly associated with symptom variables, specifically to higher severity of negative symptoms (Allen, Kelley, Miyatake, Gurklis, & van Kammen, 2001; McClellan, Breiger, McCurry, & Hlastala, 2003; Monte, Goulding, & Compton, 2008; Strauss et al., 2012), while academic functioning is associated with intellectual and neurocognitive functioning (Allen, Frantom, Strauss, & Kammen 2005; Allen et al., 2001; Monte et al., 2008; Norman et al., 2005; Strauss et al., 2012). So, by analyzing PA as a non-unitary construct it may be possible to learn the variables, and what each one may predict at the onset of psychosis.

The current trend is toward conceptualizing PA in **a developmental context**. The importance of distinguishing between these domains and examining them at each age level has clearly been demonstrated by the significant differences in patterns of academic and social deterioration: premorbid academic functioning is particularly susceptible to pronounced deterioration, most notably in later adolescence as schizophrenia onset becomes imminent (Allen et al., 2005; Monte et al., 2008; Strauss et al., 2012). However, an accelerated deterioration in social domain already occurs in childhood, especially in the schizophrenia subtype with predominantly negative symptoms. Low social drive may be a very early indicator of the neurodevelopmental abnormalities that later go on to be expressed as a schizophrenia phenotype characterized by primary and enduring negative symptoms (Strauss et al., 2012). However, these results were not entirely consistent with those found by other authors such as Larsen et al. (2004), who postulated that the patterns of premorbid development might be the product of two different but developmentally linked neurobiological processes: a) levels of social and academic functioning in childhood may be determined early in life, largely by neurodevelopmental processes related to genetics and perinatal forces (Murray & Lewis, 1987), and b) levels of social and academic functioning that decline later on,

especially in adolescence, may be determined by neuroregression processes such as developmentally determined reductions in cortical synaptic connectivity (McGlashan & Hoffman, 2000). Their results demostrated that the academic dimension was the more neurodevelopmentally determined. More than three-quarters of patients were stable over time in their childhood level of functioning, especially when that level was either poor or intermediate. In contrast, it appeared that social functioning was more neuroregressively determined. Only 57% of patients were stable at their original childhood level of social functioning. Deterioration described a relatively high fraction of the sample and affected both levels of childhood social functioning (intermediate and good). This suggests that it is important to assess young adults displaying a marked drop in social functioning as soon as possible for signs of early psychosis. It is likely that these discrepancies between studies are due to their studying different population types [i.e. Larsen et al. (2004) analyzed a sample of patients with first-episode non-affective psychosis including affective disorders with mood-incongruent delusions that were not included in the sample of patients with FEP examined in the study of Monte et al. (2008)], among other influential factors. It is possible that a particular premorbid manifestation might lead to a particular subtype of psychosis.

3.1.2. Measures of PA

Investigators and clinicians have searched for the factors that predict the occurrence or determine the outcome of psychosis. As the relationship of premorbid factors to outcome of psychosis became increasingly evident, studies focused on the identification of critical premorbid and outcome variables. In this context, researchers have developed **objective instruments** to identify and delineate the major PA variables that predict occurrence, symptoms, and outcome of psychosis. Below is a review of the main instruments for assessing PA:

- **Elgin Prognostic Scale (EPS)**: In 1941, Wittman developed the EPS, the first major scale that quantified dimensions of premorbid function. Based on a review of the results of 50 studies of prognosis in schizophrenia, Wittman devised 25 subscales, which measured PA, and 5 that were related to symptomatology. Specifically, the items rated childhood personality patterns, rate of onset, precipitating events, presenting symptoms, duration of psychosis, and body build. Each scale had several rating points, but only the end points of the scale were defined by descriptive statements. Each scale received an intuitive weight, reflecting its prognostic significance based on clinical judgment. Positive values were assigned to variables judged to be prognostically unfavorable, while variables with a favorable prognostic loading received negative values. The overall prognostic index consisted of the algebraic sum of all the weighted scores. Any anamnestic data sources available were considered acceptable for rating this instrument.

- **Phillips Scale**: In 1953, Phillips devised the second major and most widely used of the ordinal prognostic rating scales. The original **Phillips Prognostic Rating Scale** included three factors: (a) Premorbid History, (b) Possible Precipitating Factors, and (c) Signs of the Disorder. Each part was subdivided into scales with descriptive statements defining intermediate and end points of the dimensions considered relevant to specific content areas. An ordering of descriptors for the points was made on the basis of clinical judgment, with the best judged prognostic indicators assigned to 0 and the least optimistic indicators assigned to 6. Overall scores forming part I, Premorbid History, showed the highest relationship with this outcome criterion. The subscales from this content area, in descending order of their relationship to improvement, were (a) social aspects of recent sexual life, (b) recent sexual adjustment, and (c) recent and past adjustment in personal relationships. Harris (1975) devised an **abbreviated form of the Phillips Rating Scale of Premorbid History**. This

short form circumvents problems, such as redundancy of items and absence of relevant case record data, commonly faced in the use of the extended form. Based on previous research, the abbreviated scale was devised to measure the highest developmental task successfully negotiated by the patient. The scale is restricted to two items, one related to premorbid marriage and/or heterosexual adjustment and the other measuring premorbid social-personal adjustment. Each item allows a score of 0 (highest level of adjustment) to 6 (lowest level of adjustment). Each scale point is empirically defined by descriptor sentences.

- **Social Competence Scale (SCS)**: Zigler and Phillips (1961) constructed a prognostic instrument that was regarded as applicable to the general population. This scale is unique in being the only one of the major scales derived from theoretical suppositions as well as empirical findings. The central theoretical concept in the developmental formulation is that a patient's psychological resiliency and adaptive potential in responding to environmental stress or recovering from breakdown depends on his earlier coping with the societal tasks associated with successive developmental stages. Successful completion of age-appropriate tasks defines psychological maturity. Social competence is a valid global indicator of maturity level. The authors defined social competence by six variables: age, intelligence, education, occupation, employment history, and marital status. Each of these variables was divided into three categories ranging from low to high competence. Ratings were made from information available from case histories. A score of 0 was assigned to the lowest category, 1 to the middle category, and 2 to the highest category. The overall social competence score was the mean of all items that could be rated from case history data. This scale was developed to measure premorbid functioning in the general population.

- **Ullmann-Giovannoni Self-Report Process-Reactive Questionnaire**: Ullmann and Giovannoni (1964) developed an instrument to measure premorbid functioning more efficiently and with a more standard information source than had been possible with available instruments. A self-report format was selected to avoid the uneven levels and idiosyncratic nature of information available in hospital charts, structured questionnaires or clinical and research interviews. This instrument consisted of 24 true-false biographical items dealing with behavior related to demonstrating interaction with the environment. The 24 items of the questionnaire were selected from an initial pool of 77 true-false items tapping the content areas of social functioning and psychiatric symptomatology. Selected items had been judged to be related to the process-reactive continuum by three clinicians. A patient's score on the self-report questionnaire is the simple sum of responses answered in the reactive direction. In this direction 8 responses are false and 16 are true. Scores of 13 or more define the reactive range; scores of 12 or less define the process range.

- **Premorbid Asocial Adjustment Scale (PAAS)**: Based on an earlier work, Gittelman-Klein and Klein (1969) devised a premorbid function scale specifically to assess premorbid asocial adjustment in patients with schizophrenia. They suggested that premorbid asocial adjustment is a crucial aspect of poor premorbid functioning that has been confounded with other premorbid characteristics such as insidiousness of onset, and that it may be the major variable operative with predictive potential. PAAS is designed to measure premorbid social adjustment during two periods of life: preadolescence, and adolescence to adulthood. This discrimination of adjustment at different age levels was an important advance in delineating the longitudinal aspects of premorbid development. Ratings for each of the two life periods are made on three 7-point (0-6) subscales: (1) isolation, (2) peer relationships, and (3) interests. A seventh subscale, sociosexual adjustment, measures interpersonal heterosexual involvement between the ages of 16 and 20. The zero end of the dimensions is assigned to good clinical premorbid signs and the high end to poor premorbid signs.

Descriptive statements assigned to rating points function as empirical anchors. Overall scores are computed by averaging across all score items if at least three of the seven subscales have been rated. The temporal reference for rating the most recent time period is the time prior to the first manifestation of psychotic symptoms.

- **Defining Frame of Reference**: This is a 24-alternative-item developmental scale to measure premorbid and morbid functioning. The items are divided into four age ranges: birth to fifth year, fifth year to adolescence, adolescence to adulthood, and adulthood. Patients are assigned by raters' clinical judgment to process and reactive categories on the basis of scale ratings made from information available in case histories (Kantor, Wallner, & Winder, 1953).

- **Rorschach Indices of Premorbid Functioning**: The theoretical basis for this instrument combines psychoanalytic and genetic psychology concepts. The Rorschach has been used as a measure reflecting premorbid functioning in patients with schizophrenia. The Rorschach has not been used widely or been evaluated adequately as a prognosis instrument. In general, this method for studying PA has been overshadowed by the instruments composed of direct ratings of behavioral adjustment (Kantor & Herron, 1965).

- **Prognostic Scales of Vaillant, Stephens, and Astrup**: Several scales have been derived from the results of studies evaluating specific variables predictive of outcome in schizophrenia. These scales include a mixture of variables. Some are measures of PA, while others describe characteristics of the psychiatric disorder itself. Vaillant's (1962) literature search revealed a moderately consistent pattern of six variables related to good outcome in schizophrenia of which only schizoid premorbid personality measures adjustment prior to the onset of avert psychopathology. Using a similar approach, Astrup and Noreik (1966) and Setphens (1970) also developed multivariable, empirically based prognostic scales. Similar to the Vaillant scale, only some of the items of the scales measure premorbid characteristics. These are measures of premorbid social relationships, work record, absence of low intelligence quotient (IQ), and presence of severe pathology in family members.

- **Goldstein Premorbid Adjustment Scale**: This scale has seven items, each with 5-point scales for rating initiative of adolescents in interpersonal relations. It was devised for rating behaviour of patients between the ages of 16 and 20. Each of the rating points has a descriptive statement as an empirical anchor. The scale meets the need for measuring premorbid states in single adolescents (Rodnick & Goldstein, 1974).

- **Premorbid Adjustment Scale (PAS)** (Cannon-Spoor et al., 1982): The PAS is a compilation of items from each of the previous scales (EPS, Phillips Scale and PAAS). In recent decades, it has been the scale most widely used to measure PA, in both patients with a first psychotic episode and patients with a chronic course of illness. It assesses the degree to which a person has successfully attained certain developmental goals at various life stages preceding the initial onset of psychosis symptoms. Functioning is assessed across four age periods or subscales: childhood (up to 11 years), early adolescence (12- 15 years), late adolescence (16-18 years) and adulthood (19 years and above), across five major psychosocial domains: sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and socio-sexual adjustment. Socio-sexual functioning is not included as a psychological domain during the childhood period, just as scholastic performance and adaptation to school are not measured during the adulthood period. In addition to the 4 developmental subscales, the PAS also includes a section composed of 9 general items

relating to educational level, the functioning achieved by the individual in school or work before onset of psychosis, as well as the establishment of independence, level of overall functioning, personal and social adaptation, degree of interest in life and energy level of the individual. The PAS scale includes 26 items which have a scoring range from 0 to 6, where '0' denotes normal adjustment and '6' severe impairment. The rater selects the number that corresponds most closely to the descriptive phrase nearest it. Not every aspect included in a descriptive phrase is necessary for the rating. The ratings received for each item in a subscale are summed up and expressed as total obtained score. Scores for each of the subscales are calculated by dividing the total obtained score by the total possible score for that subscale. The possible score indicates the highest score obtainable by adding the maximum score for all items completed. The overall PAS score is calculated by averaging the scores obtained on each of the developmental subscales and on the general section. Ratings for both the subscales and the overall PAS score are expressed as decimal point numbers ranging from 0.0 to 1.0, where higher scores represent lower levels of PA.

- **Premorbid Social Adjustment Scale (PSA)** (Foerster, Lewis, Owen, & Murray, 1991): this is a modification of the PAS, focusing solely on social functioning restricted to childhood and early adolescence. Five items were included, each with an eight-point rating scale with explicit anchor points. The items covered socialization, peer relationships, scholastic performance, school adaptation, and hobbies and interests. Each item was rated for two periods roughly equivalent to time at primary school and time at secondary school: 5-11 years (PSA-1) and 12-16 years (PSA-2).

- **Modified Premorbid Adjustment Scale (MPAS)** (Gupta, Rajaprabhakaran, Arndt, Flaum, & Andreasen, 1995): this is an updated version of PAAS, incorporating elements of the EPS. The major modifications were in the socio-sexual section of the earlier scale, which seemed outdated. The MPAS is clinician-friendly and is intended to assess premorbid functioning with premorbid being defined as the period ending one year prior to the first hospital admission or psychiatric contact, or one year prior to the first evidence of characteristic florid psychotic symptomatology. This scale includes two measures of PA according to age group: childhood (ages 6–12, score range=0–10) and adolescence and young adulthood (ages 13–21, score range=0–13). The total score is obtained by summing up the two subscores. Higher scores indicate poorer premorbid functioning. The ratings are based on information obtained from the patient, family members, and medical records.

The available instruments, developed generally to predict global outcome functioning, measure specific dimensions of PA considered predictive of outcome. So, PA may also be a multidimensional concept. Furthermore, utilization of multidimensional premorbid and outcome measures will allow clarification of these relationships and the discovery of complex multiple relationships and interactions between variables. However, some limitations are found when these instruments are compared: a) all relevant PA dimensions are not included in or weighted similarly in all instruments; b) total scores of the PA scales are definitions of different types of premorbid status; c) each instrument appears to measure specific aspects of PA; d) investigators have used different cut-off points on the same scale to define good and poor premorbid groups; and e) in order to adjust the measurement of each premorbid variable to the age of the patient, all scales should use a developmental perspective.

To date, none of the above-mentioned scales has been validated in the Spanish population, except for the PAS scale that is part of this thesis (Barajas et al., 2013). The PAS is one of the most widely used measures of PA in schizophrenia populations, and it overcomes some the limitations mentioned previously. Nevertheless, greater effort should be made to get **a standard measure** to serve a common denominator for further study in this field and for comparing the results of the different studies. This is one of the purposes of obtaining a validated version in the Spanish population, among others.

3.1.3. Understanding PA: associations with outcome variables of FEP

Almost four decades ago Strauss and Carpenter (1977) suggested that it was possible to explain the various relationships between schizophrenia and its outcomes through three **hypotheses**:

a) Deficiencies in PA reflect vulnerability to, or are the early stages of, psychotic symptoms. Although there is no systematic evidence available about self-others differentiation difficulties prior to the onset of psychotic symptoms, it seems likely that these symptoms may reflect a problem with personal relationships having roots in the premorbid period (i.e. those specific delusions in which that patient believes the source of his actions comes from some other person).

b) Deficiencies in PA reflect inability to recover from schizophrenia. There is greater empirical support for this hypothesis. There is an association between poor premorbid functioning (especially in the area of social relationships) and poor outcome which has been demonstrated by a large number of controlled studies (Kokes, Strauss & Klorman, 1977).

c) The connection between poor premorbid functioning and apparent failure to recover is largely an artifact of research design. The authors suggested that poor premorbid patients have never functioned well and that their apparent failure to recover following an episode of psychotic symptoms is merely a reflection of a return to their poor prepsychotic level of functioning.

Then, the study of PA in the psychotic spectrum disorders has potential for clarifying etiological components of these disorders and revealing factors that help determine their course. The literature in this area is extensive, and the significantly related topics numerous. In recent decades, researchers have opted for a **retrospective approach** studying FEP to avoid confusing factors such as prolonged pharmacological treatments and mistakes in the recall of personal information. In order to provide a wide overview, the main outcome variables associated with PA in FEP studies, covering the **period from 2008-2014**, are shown in the Table 3.

Table 3. Relationship between PA and outcome variables at the onset of FEP.

Outcome variable	Study	Main findings about PA
Symptoms	Üçok and Ergül (2014)	Those with persistent negative symptoms after 2-year follow-up of FEP had lower premorbid functioning.
	Chang et al. (2013)	Social PA domain was strongly related to negative symptoms.
	Romm, Melle, Thoresen, Andreassen, and Rossberg (2012)	Severe social anxiety is associated with poor premorbid functioning.
	Chang et al. (2011)	Poor premorbid academic performance was found to be associated with persistent primary negative symptoms.
	Romm et al. (2011)	Premorbid social adjustment was significantly related to lower self-esteem and explained a significant proportion of the variance in self-esteem. PA is an important aspect in the development of self-esteem.
	Mahmoodi-Gharaei et al. (2010)	Poor PA in late adolescence was significantly associated with more severe negative symptoms.
	Romm et al. (2010)	Poor premorbid childhood adjustment was statistically significant associated with higher current severity of depressive symptoms.
	Jeppesen et al. (2008)	Poorer premorbid social adaptation was independently associated with more negative symptoms and smaller network at entry and 1-year follow-up.
	Monte et al. (2008)	Severity of negative symptoms was predicted by childhood and late adolescent social functioning scores, and severity of general psychopathology symptoms was predicted by late adolescent academic functioning, as well as childhood and late adolescent social functioning scores.

	Ruiz-Veguilla et al. (2008)	First-episode non-affective psychosis patients with predominant negative symptoms are more likely to correlate with higher presence of neurodevelopmental markers, such as poor social PA.
Insight	Ayesa-Arriola et al. (2014)	Adolescent adjustment was one of the predictors of insight into the need for treatment; and late adolescent adjustment was one of the predictors of insight into the social consequences. A subgroup of 'lacking insight' patients is characterized by lower levels of PA.
	González- Blanch et al. (2014)	The self-certainty dimension of cognitive insight was associated with premorbid IQ and premorbid academic adjustment.
	Cuesta, Peralta, Campos, and Garcia-Jalon (2011)	Insight improvement in patients with first-episode schizophrenia-spectrum disorders was related to premorbid abnormalities (in both adjustment and personality) at the 6-month follow-up.
	Parellada et al. (2011)	In early-onset FEP, poorer premorbid infancy adjustment was associated with poorer insight.
	Wiffen, Rabinowitz, Lex, and David (2010)	Insight was positively associated with better premorbid functioning in recent-onset of schizophrenia spectrum disorder patients. Insight appears to have trait-like qualities demonstrated by association with premorbid factors.
DUP	MacBeth and Gumley (2008)	There was no significant association between PA and DUP. Both PA and DUP confer independent effects on aspects of symptomatology in FEP.
Quality of life (QoL)	MacBeth, Gumley, Schwannauer, and Fisher (2015)	Higher scores for subjective QoL components were associated with better PA. Childhood PA predicted both physical and social relationship QoL.
Cognition and Meta-cognition	MacBeth et al. (2014)	Lower scores for metacognitive understanding of other's minds were significantly correlated with poorer early adolescent social adjustment. This finding suggests that FEP individuals with difficulties in understanding other's minds have more social deficits.
	Chang et al. (2013)	Academic PA domain was consistently linked to cognitive measures (executive functions and verbal fluency)
Occupational and social functioning	Ayesa-Arriola et al. (2013)	Poor premorbid social adjustment was a predictor of functional disability. The data support the notion that premorbid social adjustment is an important aspect in functional outcome over the course of the illness.
	Bratlien et al. (2013)	Premorbid social adjustment had the strongest association with measures of social funcionting.
	Turner et al. (2009)	Better academic PA was associated with being employed at onset of illness.
	Lucas, Redoblado-Hodge, Shores, Brennan, and Harris (2008)	Premorbid social adjustment in adolescence was found to be one of the significant predictors for functional outcome at years after onset of FEP.
	Jeppesen et al. (2008)	Poorer premorbid school adaptation was independently associated with poor vocational outcome at 1-year and 2-year follow-up.
Diagnoses	Owoeye et al. (2013)	Major depressive disorder with psychotic features was characterized by premorbid intellectual function and PA similar to those for schizophrenia.
	Payá et al. (2013)	First episodes of early-onset schizophrenia patients show more early social impairment than early-onset bipolar patients. Intellectual premorbid abnormalities are less specific and probably more linked to early-onset psychosis.
	Tarbox, Brown, and Haas (2012)	Social functioning is disrupted in the premorbid phase of both schizophrenia and schizoaffective disorder, but remains fairly stable in mood disorders with psychotic features. Premorbid decline in academic adjustment was observed for all groups (schizophrenia, schizoaffective disorder and mood disorder with psychotic features), but did not predict diagnosis at any stage of development.
	Ramirez et al. (2010)	A poor PA significantly predicted the presence of schizophrenia.
	Arranz et al. (2009)	Non-affective acute remitting psychosis (NARP) patients showed significantly better PA. NARP is a highly distinctive condition different from either affective psychosis or other non-affective psychosis such as schizophrenia.
Treatment/use services	Crespo-Facorro et al. (2013)	One of the variables associated with a reduced likelihood of responding to antipsychotic treatment was a poor PA during adolescence and adulthood.
	Macbeth, Gumley,	Poorer clinician-rated engagement was associated with poorer premorbid social

	Schwannauer, and Fisher (2013)	adjustment.
	Rabinowitz et al. (2011)	Good premorbid functioning corresponds with better treatment response in recent-onset psychosis as captured on both clinician and patient-reported measures.
	O'Callaghan et al. (2010)	Those who had a positive family history of mental illness and poorer PA were significantly less likely to seek help for themselves. Having better PA was associated with shorter help-seeking delays from the onset of illness.
Relapses/Recovery	Alvarez-Jimenez et al. (2012)	A poor PA significantly increases the risk for relapse, among other factors.
	Levy, Pawliuk, Joober, Abadi, and Malla (2012)	Relapsed patients differed from those who remained in remission only in the pattern of PA (greater proportion with deteriorating pattern), although this was not independent of other variables. A very low rate of relapse was associated, at least partially, with poor PA.
	Petersen et al. (2008)	Better PA was identified as a predictive factor of full recovery in a sample of first-episode schizophrenia spectrum disorders.
Suicide attempts	Bakst, Rabinowitz, and Bromet (2010)	Poor premorbid functioning was significantly associated with an increased likelihood of a suicide attempt prior to first psychiatric hospital admission and an increased likelihood of additional attempts during the four years after first hospitalization.
Cannabis use	Leeson, Harrison, Ron, Barnes, and Joyce (2012)	Cannabis users demonstrated better cognition at psychosis onset, which was explained by higher premorbid IQ. They also showed better social function and neither measure changed over the subsequent 15 months.
	Compton, Broussard, Ramsay, and Stewart (2011)	Participants using cannabis at ≤15 years had better early adolescence social functioning than those who had not used cannabis. Conversely, those who had used cannabis at ≤18 years had poorer late adolescence academic functioning. Findings suggest that cannabis use is associated with premorbid social and academic functioning.
	Rodríguez-Sánchez et al. (2010)	Cannabis users had a better social PA, particularly during the early periods of life. These patients appear to comprise a subgroup of patients with a better PA and premorbid frontal cognitive functions.
	Sevy et al. (2010)	Compared to non-substance abusing subjects, cannabis use disorders (CUD) subjects had better premorbid childhood social adjustment and a trend toward poorer premorbid childhood academic adjustment. Better premorbid childhood social adjustment was associated with a lifetime history of CUD.

In summary, these studies of FEP emphasize the prognostic importance of functioning prior to psychosis onset to predict outcome of psychosis. In this case, outcome is understood in a broad sense covering aspects such as clinical symptoms, cognitive and social functioning, quality of life, and use of services, among others.

In recent years, association between PA and future psychosis has also gained support from **prospective research** with clinically identified high-risk youth (i.e. presenting with subthreshold 'psychotic-like' positive symptoms indicative of elevated risk for developing a psychotic disorder). Reports from the Dutch Prediction of Psychosis Study (DUPS) (Carr et al., 2000) suggest a possible correlation between deterioration of functioning from childhood to early adolescence and subsequent transition to psychosis in high-risk youth (Dragt et al., 2011; Mason et al., 2004). A pattern of early functional deterioration among Clinical High-Risk (CHR) individuals is also consistent with results from phase one of the North American Prodrome Longitudinal Study (NAPLS-1) (Addington, Penn, Woods, Addington, & Perkins, 2008), including recent evidence that poor social adjustment in adolescence predicts transition to psychosis in NAPLS-1 CHR youth (Tarbox et al., 2013). In the European Prediction of Psychosis Study (EPOS), Salokangas et al. (2014) found that poor premorbid psychosocial adjustment, assessed in 245 young high-risk patients, predicted poor short-term functional outcome even when the effects of background, clinical symptoms, and

transition to psychosis had been taken into account. Difficulties in areas of psychosocial development in adolescence may reflect as psychotic development in adult life. These studies demonstrate that even at the pre-psychotic phase of the illness, these young people at risk for psychosis are demonstrating significant deficits in social functioning, supporting the idea that social deficits are present long before the onset of psychotic symptoms, similar to impairments found in patients with FEP and multi-episode schizophrenia (Addington et al., 2008). Cumulative evidence indicates that **adolescent social functioning provides information about risk for psychotic disorders and would be a useful component of a multivariate prediction algorithm** (Cannon et al., 2008) including other predictors which have been found in previous studies, such as clinical symptoms (Ruhrmann et al., 2010), cognitive status (Riecher-Rössler et al., 2009) and neuro-imaging (Smieskova et al., 2010).

In spite of the amount of data gathered and knowledge generated on the topic of PA, it is remarkable how little of this information is to be found in the Diagnostic and Statistical Manual of mental disorders (DSM). The literature on PA and its prognostic value remains informative and should be better represented in official nosology (McGlashan et al., 2008). Furthermore, in future studies it would be appropriate to determine the range of variables that could usefully be included as measures of PA in a specific scale considered as the gold standard. Some recommendations to consider **in future research** on PA are the following:

a) Broadening the multidimensional term of PA adding new components such as **objective measures of cognitive performance** (in addition to scholastic performance);
b) Defining in detail the type and characteristics of **the most crucial social relationships** as antecedents to symptomatology and course of disorder;
c) Including **PA as part of the basic assessment procedures** of the patients;
d) Continuing investigation of possible **interactions between PA patterns and outcome** of the psychotic spectrum disorders;
e) Further research about the **capacity of PA to predict signs and/or symptoms of the next stage** (stage 1: prodromal phase).

3.2. Prodromal phase

The period prior to a clear-cut diagnosis of a psychotic disorder has traditionally been referred to as the 'premorbid phase'. However, this term has led to some confusion because this period actually covers two phases, not one: the true premorbid phase and the **prodromal phase or prodrome**. The distinction between these two phases is illustrated in Figure 6.

In the premorbid phase, when deficits exist, they usually are manifest at birth and are subtle, stable, and usually not obvious or seriously disabling. However, **the 'prodromal' period refers to the period immediately preceding the onset of psychosis**, during which behaviour and functioning deteriorates from a stable 'premorbid' level of functioning and behavioural changes occur. The psychosis-risk symptoms begin and develop with increasing number, severity, and frequency. The timing is usually around puberty. Nevertheless, the boundaries between the premorbid and prodromal phase as well as between the prodromal phase and the onset of psychosis have been historically difficult to identify. In this sense, the characterization of the prodromal phase has been a matter of interest for many years.

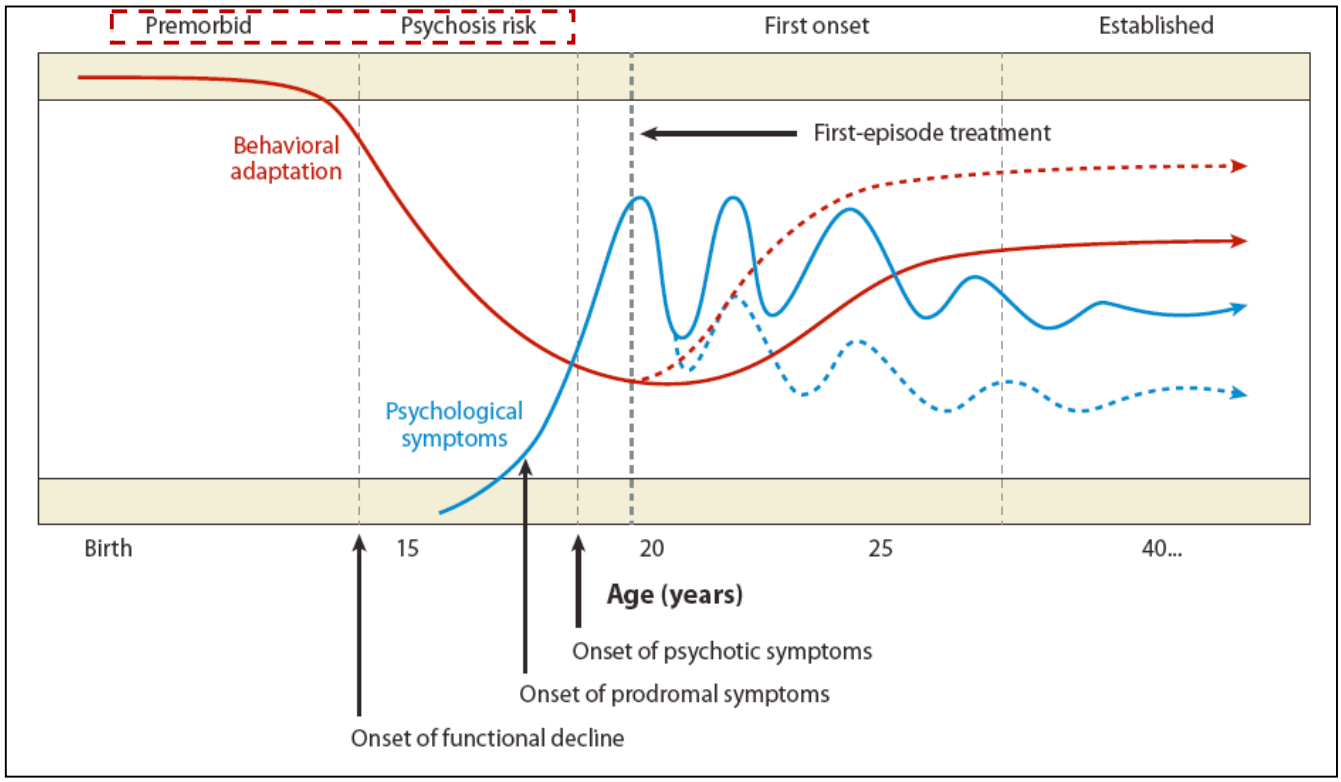


Fig. 6 The early stages of psychosis. [Source: Fusar-Poli, Carpenter, Woods & McGlashan, 2014a. (Note: Dashed lines represent the possible course of behavioural adaptation and psychological symptoms following first-episode treatments)].

The onset of psychotic disorders such as schizophrenia, with a prodromal phase prior to the onset of frank psychotic symptoms, has been known since the first descriptions of the illness were documented. As early as 1861, Wilhelm Griesinger described a **melancholic prodromal phase** of psychotic illness. Later, Kraepelin (1893) observed a gradual deterioration of mental functioning, disturbances of attention and daydreaming before the emergence of psychotic symptoms. According to Mayer-Gross (1932), difficulties with thinking and concentration as well as loss of activity marked an insidious onset before the first psychotic symptoms appear. Another classic author, pioneer in the study of the prodromal phase, was Bleuler (1911) who identified the **prophase**, characterized by irritability, introversion, eccentricity and changes of mood, 'latent schizophrenia'. Sullivan (1927) supplemented Bleuler's psychodevelopmental approach with a psychodynamic model. He explained the hysterical, neurasthenic and obsessive-compulsive symptoms, which often preceded the onset of psychosis for lengthy periods of time, as dysfunctional ways of coping with more profound disturbances in the prodromal illness phase. Likewise, Cameron (1938) described a prodromal phase characterized by social withdrawal, reduced work performance, affective flattening and bizarre beliefs as well as a continuous transition to ideas and delusions of persecution. In addition, Conrad (1958) distinguished **four phases of developing schizophrenia**: a) ***trema***, characterized by depression, anxiety, tension, irritability and mysterious experiences; b) ***apopheny***, corresponding to the transition from the nonspecific prodromal phase to incipient psychosis, which was presumed to be marked by predelusional mood; although not showing clear delusional content, it is frequently reported to precede full-blown delusional phenomena; c) ***anastrophae***, in which these new experiences become attributed to external causes: delusions and hallucinations; reality control and insight into illness are lost; and d) ***apocalypse***, corresponding to full-blown psychosis. This refers to a complete loss of structure in perception, experience and thought. Hambrecht and Häfner (1993) tested **Conrad's phase model** on Interview for the Retrospective Assessment of the Onset and course of Schizophrenia and other psychosis (IRAOS) data from the ABC (Age, Beginning and Course) Schizophrenia Study. In 76% of the cases, trema

preceded apopheny (i.e. a prodromal phase led to an incipient psychosis), but they failed to provide any evidence for the sequence of the other stages. Furthermore, Conrad did not give a clear description of the symptoms and their selection. For this reason, the operationalization of the Conrad model with IRAOS symptoms is somewhat arbitrary.
On the other hand, some authors have attempted to characterize the prodromal phase through a list of symptoms (Yung & McGorry, 1996). However, the prodromal phase is not captured by a simple list of symptoms at one point in time, but involves a process that is developing. Regarding this subject, three schools of thought have emerged:

a) The first group views that **nonspecific changes are followed by specific prepsychotic symptoms that are then followed by psychosis**. The subjective symptoms are usually accompanied by some deterioration of role functioning and some marked behavioral changes as well (Cameron, 1938).
b) In the second pattern, there are early specific changes in perception, attention, speech, or motility, followed by neurotic symptoms thought to be a reaction to these first changes, followed by psychosis (Chapman, 1966). **Specific subjective changes occur first, and are then followed by neurotic symptoms and behavioral changes**.
c) Finally, there is a **'Hybrid/Interactive' model of the prodrome**, which combines the patterns described earlier. In this conceptualization, people move in and out of symptomatic periods of both the nonspecific and the specific, attenuated psychotic, types. Both of these types may precede psychosis and may occur primarily. Reactive neurotic symptoms such as anxiety and depression can occur in response to specific symptoms, and to the behavioral changes that may result from any of these symptoms (Yung & McGorry, 1996).

The latter authors support the need for a more accurate characterization of the prodrome. This would help to identify high-risk persons during their first manifestations of the subtle changes suggesting impending psychosis. The authors urge that such people be studied in order to investigate the pathogenesis of psychosis and to identify clear markers that predict onset. If the prodrome can be recognized and treatment provided at this stage, then disability could be minimized, and some recovery may be possible before symptoms and poor functioning become entrenched, so the possibility of preventing, delaying or ameliorating the onset of diagnosable psychotic disorder arises. Thus, the pre-psychotic intervention would have a dual focus: a) treatment of the symptoms and disability that the individual is currently experiencing, and b) the prevention of full-blown disorder. It is therefore an example of what has been termed 'indicated prevention'.

3.2.1. Conceptualization and characterization of the prodromal psychosis onset

The term **'prodrome'** is derived from the Greek word *prodromos*, meaning the forerunner of an event (Fava & Kellner, 1991). It is a concept commonly used in clinical medicine and refers to the early symptoms and signs that a person experiences before the full-blown syndrome of an illness becomes evident. Thus, the term 'prodrome' has two implications: a) the person is symptomatic during this phase and may seek help at this stage for their problems and may therefore be detectable, and b) the person will develop a full-blown illness following the prodrome. In the case of psychotic spectrum disorders, **subtle 'attenuated' forms of psychotic symptoms** are likely to have been present prior to the psychotic symptoms being obvious. However, these symptoms may indicate the presence of a threshold or subthreshold mood disorder, substance use, a physical illness or simply a reaction to circumstances. A FEP cannot even be predicted from the presence of attenuated psychotic symptoms (APS), as these symptoms can also resolve before a full-blown psychotic disorder develops. So the diagnostic process occurs once frank psychotic

symptoms have appeared. In this sense, the prodrome is a retrospective concept, diagnosed only after the development of definitive symptoms and signs.

Although there is great variability between patients in how their prodromes manifest, certain symptoms and signs have frequently been described. Yung and McGorry (1996) reviewed the previous literature on prodrome, including descriptions of symptoms and signs in both non-affective and affective psychoses. They found that the ranking frequency of symptoms described in these first-episode studies showed the same phenomena consistently reported. The most commonly occurring prodromal symptoms, in descending order of frequency, were the following: **reduced concentration and attention; reduced drive and motivation; depression; sleep disturbance; anxiety; social withdrawal; suspiciousness; deterioration in role functioning; and irritability**. Two issues emerge from studying this list of prodromal symptoms. First, many of them are non-specific. That is, they occur frequently in the prodromes and threshold syndromes of non-psychotic disorders (Häfner, Maurer, Trendler, van der Heiden, & Schmidt, 2005). Second, a considerable number of psychiatric symptoms, disability, and self-harming and other health-damaging behaviours occur during the prodromal phase, even in the earliest stages (Yung, Phillips, & McGorry, 2004). However, this list obviously does not cover the full range of prodromal symptoms described in various studies. These are summarized in Table 4 and can be divided into **eight main subtypes** (Yung & McGorry, 1996).

Table 4. Prodromal features of schizophrenia.

1.- Neurotic symptoms: anxiety, restlessness, anger, irritability
2.- Mood-related symptoms: depression, anhedonia, guilt, suicidal ideas, mood swings
3.- Changes in volition: apathy, loss of drive, boredom, loss of interest, fatigue, reduce energy
4.- Cognitive changes: disturbance of attention and concentration, preoccupation, daydreaming, thought-blocking, reduced abstraction
5.- Physical symptoms: somatic complaints, weight loss, poor appetite, sleep disturbance
6.- Attenuated or subthreshold versions of psychotic symptoms: perceptual abnormalities, suspiciousness, change in sense of self, others or the world, change in affect, change in motility
7.- Other symptoms: obsessive-compulsive phenomena, dissociative phenomena, increased interpersonal sensitivity
8.- Behavioural changes: deterioration in role-functioning, social withdrawal, impulsivity, odd behaviour, aggressive, disruptive behaviour

[Source: Yung & McGorry, 1996].

Another important body of literature relevant to the characterization and conceptualization of the initial psychotic prodrome is that of Huber (1966) from Bonn, Germany. They proposed that the earliest manifestations of schizophrenia were **'basic symptoms' (BS)** defined as **subtle self-experienced deficits, including cognitive, affective and social disturbances** which are also commonly described in the early prodromal phase (Gross, 1989). The term BS was originally chosen to express two assumptions: first, that these symptoms form the psychopathological base from which Schneiderian first-rank symptoms develop, and second, that they were more closely related to the underlying schizophrenic-disease process than positive psychotic symptoms. These BS are different from Bleulerian fundamental symptoms and their modern operationalized successors, the negative symptoms (Klosterkötter, Ebel, Schultze-Lutter, & Steinmeyer, 1996). Negative symptoms are externally observed by others, but BS can only be subjectively identified by the person experiencing them.

Furthermore, prodromal symptoms can follow **different courses**. They can occur and then resolve spontaneously without any treatment-seeking, they can occur intermittently, perhaps in response to some stressor, or they can be present chronically but without resulting in distress or help-seeking, in addition to the possibility that they can worsen and develop into a full-blown psychotic disorder. Likewise, psychotic symptoms rarely arise suddenly, but are more likely to gradually evolve and worsen, from an attenuated

state to a full threshold state. Most clinicians have no difficulty in diagnosing a full-blown psychotic syndrome in a patient, but more subtle early psychotic features may be more difficult to recognize. Some of the reasons why **recognizing the onset of psychosis prospectively is not always clear-cut** are summarized in the Table 5:

Table 5. Defining the onset of psychosis prospectively – situations that complicate the definition.

a) Gradual onset… o of symptoms, especially symptoms which seem to evolve out of underlying personality
b) Fluctuations… o in intensity and frequency of the symptoms o in level of insight into the symptoms
c) Appraisal of the symptoms: o Individual may not be aware that the experiences are unusual or abnormal o Individual may attribute them to a variety of sources, some plausible o Observers may attribute the symptoms to a range of plausible explanations o One individual may not be distressed by the same type of symptoms that another would be disturbed by
d) Lack of terminology: o Individual may not have the language to describe the phenomena
e) Variability in the impact of the symptoms: o Individual may not be disabled by or seek help for the symptoms

[Source: Yung, et al., 2004]

Several researchers have examined the issue of which features are characteristic of the psychotic prodrome. However, due to these difficulties, the first studies included detailed **retrospective descriptions** of the symptoms and signs leading up to a FEP. **The ABC study of Häfner's group** in Germany is an example of this (Häfner et al., 1998c). This study was planned in 1985/1986 with the aim of conducting a 12-year research project on topics of the general and clinical epidemiology of schizophrenia. The initial aims were: (1) to elucidate the possible causes of the sex difference in age at first admission for schizophrenia, and (2) to analyse the early course of the disorder from onset until first contact and its implications for further course and outcome. A total of 232 patients in their FEP were collected using the standardized structured IRAOS (Häfner et al., 1992). The main findings of the second aim indicated that **the prodrome was initiated by nonspecific and negative symptoms in 73% of cases**, which lasted on average 4.8 years. The psychotic prephase, from the appearance of the first psychotic symptom until the climax of the episode, operationalized by the first maximum of the sum score for positive symptoms, lasted 1.1 years. Only 7% experienced illness onset with purely positive symptoms and 20% with both positive and negative symptoms occurring within the same month. According to Häfner & Maurer (2001), the prodrome is 1 year or longer in 68% of cases and less than 1 year in 32%, with only 18% appearing abruptly only 4 weeks prior to onset. Among the ten most frequent initial symptoms, equally frequent in men and women (except worrying), there were no positive symptoms. Two symptom dimensions clearly predominated: affective symptoms, such as depressive mood, feelings of guilt and anxiety, and negative symptoms, such as trouble with thinking and concentration, loss of energy, slowness, poor work performance and social withdrawal. According to the development of initial symptoms, nonspecific and negative symptoms precede the first psychotic symptoms by several years. At illness onset, symptoms increase exponentially. In the psychotic episode, negative and nonspecific symptoms also increase steeply. After the climax of the episode, symptoms diminish in all three dimensions. Psychotic symptoms usually subside more rapidly than negative symptoms, which frequently take more time to remit. The first to appear, 4.5 to 4 years before first admission, were affective symptoms. Next to emerge, 4 to 1.5 years before first admission, were negative symptoms, which showed considerable overlap with affective symptoms. Dysthymic symptoms, including menstrual disturbances and disturbances of appetite and sleep, headache, etc., appeared about 3 to 1.5 years before first admission. Negative and nonspecific signs of mental disorder initiated the

prodrome 2.3 years (median) prior to onset. Finally, about one year before first admission, psychotic symptoms manifested themselves (median: 0.8 years). **The year prior to onset in particular was marked by considerable symptomatic activity, particularly in the last 4–6 months, which sees an acceleration of positive symptoms.** However, these data are based on mean values and cannot be regarded as characteristic of all cases of patients with schizophrenia. These findings are important in that they represent the first and largest empirical study of the prodrome based on careful retrospective systematic assessment.

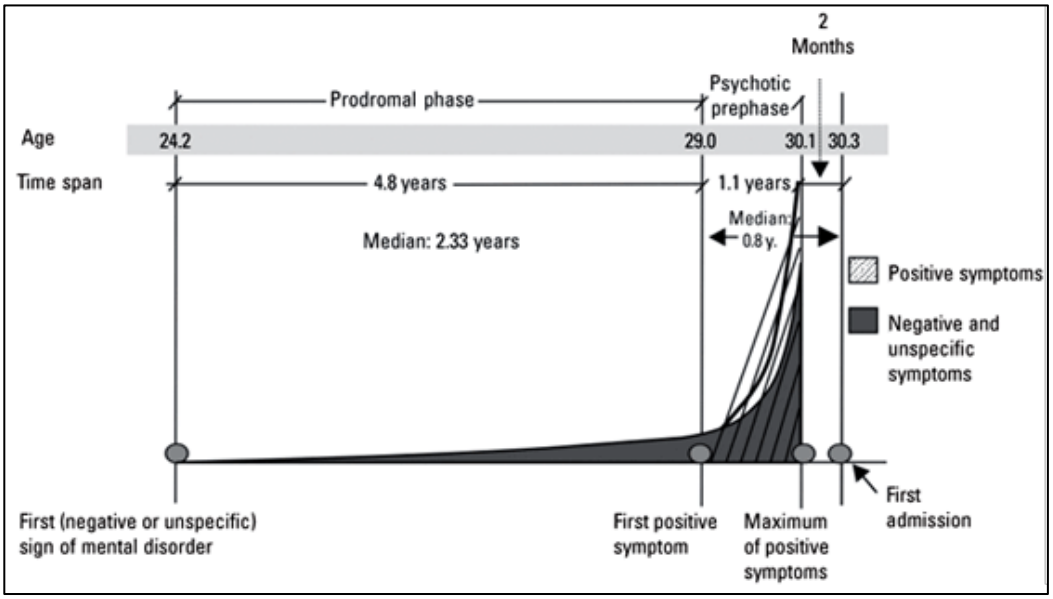


Fig 7. The early stages of schizophrenia from first sign of mental disorder to first admission. [Source: Häfner et al., 1995. ABC first-episode sample N=232].

Figure 7 depicts, on the basis of mean values from the ABC study data, age of onset and duration of the prodromal stage, psychotic prephase until the climax of the first episode as well as time to first admission.

After the retrospective studies, in the last decade of the past century began the expansion of **prospective studies** aiming to identify the earliest manifestations of psychotic illnesses already identified in previous studies. This perspective has significant implications for clinical practice and for research. One of the pioneers was McGorry who suggests that a more accurate term for this period would be '**ARMS**' (McGorry & Singh, 1995). When the focus for recognizing the 'prodrome' is shifted using a prospective approach, the term 'prodrome' cannot be used. The term 'prodrome' implies inevitable progression to full-blown illness.

Due to the non-specific nature of prodromal symptoms there are problems with using them alone to identify people thought to be at incipient risk of onset of psychotic disorder. Using symptoms alone would result in a **high false-positive rate**. Consequently, some added criteria were needed to focus on those most likely to be in the prodromal phase of a psychotic disorder. In order to address this issue, McGorry's group used a sequential screening approach or **'close-in strategy'** (Bell, 1992), which requires **multiple risk factors to be combined**, such as family history, age and clinical need for care. This had the effect of concentrating the level of risk in the selected sample to create an enriched cohort. In other words, an individual must meet a wider range of conditions to be included in the high-risk sample rather than in the traditional studies (i.e. general population studies or genetic high-risk studies). In order to improve the accuracy of identifying the high-risk cohort further, Bell recommended also using signs of behavioural difficulties in adolescence as selection criteria, such as the inclusion of clinical features. This also allows the approach to become more clinical—to move away from traditional screening paradigms and to focus on

help-seeking troubled young people who are therefore highly 'incipient' and frankly symptomatic. Also, close-in strategy involves shortening the period of follow-up necessary (12 months) to observe the transition to in contrast to the traditional approach that employs a much longer follow-up period.

To date, it is known that in the psychosis-risk phase, functioning declines in a clearly downward, usually accelerating trajectory. The psychosis-risk symptoms begin and develop with increasing number, severity, and frequency. The sample that McGorry's group identified using the close-in strategy was named **'UHR group'**. The term highlights that the group is different from the 'high-risk' groups identified in traditional genetic studies. Yung et al. (2003b) defined the **UHR criteria** for young person aged between 14 and 30 as follows: **a) APS group:** have experienced subthreshold, attenuated positive psychotic symptoms during the past year; **b) brief limited intermittent psychotic symptoms (BLIPS) group:** have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated; and **c) trait and state risk factor group:** have a first-degree relative with a psychotic disorder or the identified client has a schizotypal personality disorder and has experienced a significant decrease in functioning during the previous year. These criteria have been adopted and adapted in a number of other settings around the world (Olsen & Rosenbaum, 2006b). Using this approach, however, means that some people who are genuinely at risk may not meet the criteria, that is, specificity is given priority over sensitivity. In this sense, such persons may have an incipient major mood disorder, or an anxiety disorder, or may simply be reacting to an environmental or situational crisis and never go on to develop the psychotic disorders (false positives).

These criteria have necessarily also been developed to define the onset of frank psychotic disorder. These are not identical to DSM criteria, 4th edition, (DSM-IV) (American Psychiatric Association, 1994) but are designed to define the minimal point at which antipsychotic treatment is indicated (see section 3.3. Initial psychotic phase). Traditionally, the DSM-IV (APA, 1994) or ICD-10 (World Health Organization, 1992) defines psychosis onset (brief psychotic disorder/acute and transient psychosis) as an illness lasting from one day to one month, with an eventual return to the premorbid level of functioning. This threshold for psychosis onset is lower than the high-risk threshold proposed by the McGorry group. In fact, under the traditional DSM/ICD category, psychosis can be diagnosed if one psychotic symptom occurs for one day only. In contrast, according to the criteria of McGorry's group, the threshold of psychosis is defined as the occurrence of at least one fully (positive) psychotic symptom several times a week for over one week (Yung et al., 2003b). However, the additional caveat in this psychosis onset definition is that the transition criterion to psychosis is heavily weighted toward positive psychotic symptoms. As a consequence, high-risk subjects who develop severe negative symptoms or functional impairments (but no severe positive symptoms) are not considered to have transitioned to psychosis (Fusar-Poli & van Os, 2013). In this sense, the emergence in recent years of **new tools to assess risk of psychosis** has allowed developing **new criteria definitions**, which integrate negative symptoms or BS, among other symptoms, in order to improve the detection of the high-risk population and the transition to psychosis as well as to extend the study of markers that predict onset of psychosis. However, the availability of different competing psychometric instruments to measure the psychosis risk is not helping current APS research or improving clinical practice. Despite addressing overlapping features, diagnostic concordance of the instruments is unknown. This results in difficulties in comparing across studies and in generalizing the results found. For these reasons, among others, **the evidence in the field was not considered sufficient to bring a new APS syndrome in the DSM-5** (APA, 2013) main text. In addition, it should be kept in mind that APS in DSM-5 refers only to the most common of the three UHR syndromes diagnosed using the research instruments (i.e., APS). Also, the UHR and BS research diagnoses are each made using a structured interview for which raters undergo specific training, whereas the clinical diagnosis of APS is designed to employ an unstructured clinical interview by clinicians who have limited specific training regarding APS (Fusar-Poli et

al., 2014a). Fusar-Poli et al. (2014a, p. 181) established a set of recommendations among which was the need for psychometric standardization: "A consensus on an approach that assures a basic similarity in study cohorts is essencial for rapid progress".

However, we must not forget that this new way to identify high-risk persons during their first manifestations of the subtle changes suggesting impending psychosis is a procedure more accurate in prodromal phase characterization than those used in traditional diagnostic manuals. So, several groups around the world have devised diagnostic criteria and assessment tools (Cornblatt, et al., 2003; Miller et al., 2003; Yung et al., 2005) to reliably identify such UHR individuals who have a significantly greater likelihood than the general population of developing a psychotic disorder—22% at one year follow-up compared to a 0.015% annual incidence of schizophrenia (Fusar-Poli et al., 2012a; Tandon, Keshavan, & Nasrallah, 2008). A summary of the main instruments most widely used in both research and clinical practice is shown in the next section (Table 6).

3.2.2. Tools to assess the prodromal phase

If the **conversion to psychosis** is defined as the transition from a status without a psychotic disorder, but mostly with prodromal symptoms, to a diagnosis of a psychotic disorder, the development of instruments to evaluate the risk of conversion to psychosis would make it possible to identify individuals who will develop psychosis before the disease sets in and therefore before their lives are disrupted. These people could then receive treatment to mitigate, delay, or even prevent the undesirable consequences. For more than 20 years, such instruments have been developed and tested around the world, starting with the scales created by Chapman and Chapman (1987). However, **traditional psychopathological assessment instruments were not sufficiently sensitive to subthreshold conditions of psychosis**. Furthermore, the conversion rate in the cohorts of individuals identified as being at risk of developing psychosis are relatively low, and it has also been observed that conversion rates decline with time (Yung et al., 2007b). This context poses a risk of stigmatization given that a significant proportion of these people will not actually develop psychosis. In an attempt to overcome these obstacles and ethical issues, research teams have sought to improve the performance of their instruments for evaluating the risk of conversion to psychosis, and a number of new tools have been constructed.

Several previous studies (Daneault, Stip & Refer-O-Scope Group, 2013; Olsen & Rosenbaum, 2006a) have provided an overview of existing instruments used for assessing individuals assumed to be at increased risk of psychosis, as well as to evaluate the risk rates of conversion to psychosis over time. These studies have considered **several approaches** that predominate in the research on the prodrome of psychosis in order to classify these instruments: a) **the APS approach**, which includes the instruments that pay most attention to the late prodromal phase to identify individuals at risk of imminent conversion to psychosis; b) **the BS approach**, which is based on a detailed phenomenological way of describing disturbances prior to onset of psychosis, which presumably characterizes the early prodromal phase; and c) **the APS-BS approach** comprising tools that combine theoretical concepts from both previous approaches. Additionally, if the instruments are compared two different types of tools can be detected: **structured or semi-structured interviews** that require the presence of specialized investigators, and **shorter questionnaires** some of which may be self-administered (risk assessment tools and screening instruments).

Table 6 shows a classification of the main instruments according to the following two criteria: approach and type of instrument. Below is a brief description of each of the following instruments.

Table 6. Classification of the main instruments according to approach and type of instrument.

	Structured or semi-structured interviews	Risk assessment tools* and screening instruments
APS approach	**CAARMS** (Comprehensive Assessment of At-Risk Mental States) **SIPS** (Structured Interview for Prodromal Symptoms); **SOPS** (Scale of Prodromal Symptoms)	**PQ** (Prodromal Questionnaire); **PQ-B** (Prodromal Questionnaire- Brief); **PQ-16** (Prodromal Questionnaire-16 items) **SIPS-screen or PRIME**[1]**-screen** (Prodromal Symptoms Screen questionnaire)**; PS-revised** (or PRIME-screen revised) **Y-PARQ*** (Youth Psychosis At-Risk Questionnaire);
BS approach	**BSABS** (Boon Scale for the Assessment of Basic Symptoms) **SPI-A** (Schizophrenia Prediction Instrument – adult version); **SPI-CY** (SPI – child and youth version) **IRAOS** (Interview for the Retrospective Assessment of the Onset and course of Schizophrenia and other psychosis)	**ESI*** (Eppendorf schizophrenia inventory)
APS-BS approach	**ERIraos** (Early Recognition Inventory for the restrospective assessment of the onset of schizophrenia)	**BSIP*** (Basel Screening Instrument for Psychosis) **PROD-screen** (Screen for PRODromal symptoms of psychosis) **ERIraos- CL** (ERIraos-checklist)

[1]PRIME: Prevention through Risk Identification, Management and Education

CAARMS (Comprehensive Assessment of At-Risk Mental States) (Yung et al., 2002): this is the diagnostic interview and rating system developed by Australian researchers to assess psychosis risk criteria prospectively. The CAARMS manual (Yung, Phillips, McGorry, Ward, & Thompson, 2000) provides detailed definitions, questions, and anchor points for eliciting and rating 28 symptoms across seven dimensions of psychopathology, including positive symptoms, cognitive change, emotional disturbance, negative symptoms, behavioural change, motor physical change, and general psychopathology. Only scores on the subscale of positive symptoms are included when evaluating the UHR criteria. For several symptoms, both subjective experience and objective observation is rated separately. Dimensions of intensity (0-6), frequency/duration (0-6) and fluctuation of symptoms (0-2) are scored for each individual item. The starting date and ending date of each symptom are also annotated. The level of distress is measured only in the positive symptoms (0-100). The CAARMS has two functions: a) to provide a comprehensive assessment of psychopathology thought to indicate imminent development of a FEP disorder, and b) to determine if an individual meets UHR status based on criteria derived from the CAARMS assessment. It is designed for repeated use over time, for example, monthly to 6-monthly. An early version of the CAARMS demonstrated good reliability and predictive validity (Yung et al., 1996; Yung et al., 2003b), and a revised version, the CAARMS II, demonstrates good to excellent concurrent, discriminative, and predictive validity as well as excellent interrater reliability (Yung et al., 2005).

SIPS (Structured Interview for Prodromal Symptoms) (Miller et al., 1999): this is a semi-structured interview developed by American researchers, which elicits information regarding the presence and severity of 19 symptoms across four domains of psychopathology, including positive, negative, disorganization, and general symptoms. SIPS is composed of: Criteria of Prodromal Syndromes (COPS), Presence of Psychosis Scale, Scale of Prodromal Syndromes (**SOPS**), General Assessment of Functioning (GAF), a checklist for schizotypal personality disorder and a questionnaire of family history of mental illness (Miller et al., 2003). Only the ratings on positive symptoms (SOPS, P1-P5) are used for an evaluation of the subject meeting the COPS. Intensity of symptoms is rated (0-6), ascertained from information about onset, duration, frequency, intensity, degree of affect and conviction. The main goal of the SIPS interview is to identify operationally the presence of a prodromal state, to measure symptom severity over time, and to

evaluate conversion to actual psychosis. The instrument has demonstrated good psychometric properties (Miller et al., 2003; Miller et al., 2002). The SIPS has been used to detect patients at risk of conversion to psychosis, not only when they present attenuated positive symptoms (or CHR+) but also if they manifest attenuated negative symptoms (or CHR-) (Cornblatt, Lencz, & Kane, 2003).

BSABS (Boon Scale for the Assessment of Basic Symtpoms) (Gross, Huber, Klosterkötter, & Linz, 1987): this is an instrument developed by German researchers, which represents a detailed outline of the so called BS of schizophrenia. The scale consists of six subscales of BS: A + B, scales of dynamic deficits; C, cognitive disturbances; D, coenesthetic (body misperception) experiences; E, central vegetative disturbances; and F, autoprotective behavior. Each BS is rated as present or absent. Examples of statements revealing the presence of the individual BS are given in the manual together with useful questions. Specific disturbances of cognition, speech and perception have shown a significant predictive value of developing schizophrenia. In a study of 110 out-patients with at least one BS, 70% developed schizophrenia in an average follow-up of 9.6 years (specificity 0.59, false-positive predictions 20%). In the control group of 50 out-patients without BS, the absence of BS excluded schizophrenia with a probability of 96% (sensitivity 0.98, false-negative predictions 1.3%) (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001).

SPI-A (Schizophrenia Prediction Instrument – Adult version) (Schultze-Lutter, & Klosterkötter, 2004): this was developed applying cluster and facet analyses to data from 79 subjects in a prodromal phase from the Cologne Early Recognition (CER) study and from 346 remitted patients with schizophrenia (Schultze-Lutter et al., 2004). The SPI-A assesses a wide range of subtle, self-experienced disturbances first described as BS. It provides important insight into subclinical complaints and deficits that often precede frank psychotic episodes and which are maintained during remission. Primarily designed to support the prediction of FEP, it also facilitates a broad range of clinical and research issues across the different states of the illness. The SPI-A is a semistructured interview, which consists of 34 BS rated from 0 (absent/never present) to 6 (extreme/present daily) and which cluster into 6 sub-scales of 5 to 6 items each: (A) affective-dynamic disturbances; (B) cognitive-attentional impediments; (C) cognitive disturbances; (D) disturbances in experiencing the self and surroundings; (E) body perception disturbances; and (F) perception disturbances. So patient responses are elicited in a semistructured interview via general guiding questions that are followed by increasingly specific inquiries. Only subjectively experienced symptoms that were not present in what the person considers his/her premorbid stage are assessed as a definite basic symptom. The SPI-A has good interrater reliability and good construct and predictive validity (Schultze-Lutter, Klosterkötter, Picker, Steinmeyer, & Ruhrmann, 2007). Additionally, a child and youth version (**SPI-CY**) has been developed, which consists of 4 sub-scales (adynamia; perception disturbances, neuroticism; and thought and motor disturbances), each including 8 to 19 items rated on a 7-point severity scale according to their maximum frequency during the previous 3 months. SPI-CY items can be assessed from approximately age 8 onwards, because a certain degree of social maturity is necessary for the self-reflection that enables detection of BS as self-experienced aberrations from the child's 'normal' mode of experience. Furthermore, a few SPI-CY items are recommended for use only with adolescents who are 13 or older (Schultze-Lutter et al., 2012).

IRAOS (Interview for the Retrospective Assessment of the Onset of Schizophrenia) (Häfner et al., 1992): this is a semi-structured, clinical interview which was developed within the framework of the ABC study for systematic research on the onset of schizophrenia. With the IRAOS, social course, course of symptoms, disability and treatment from the first signs or indicators of illness until the time of interview can be traced. It is of special interest for assessing individual premorbid (social) development, the onset and course of prodromal signs and symptoms, functional impairment, and social disability in early intervention programmes. It was originally developed for the assessment of the onset and course of schizophrenia. The

current, second version has been extended to encompass all psychotic disorders (affective and non-affective). The IRAOS consists of five sections: a) Part I contains general information on the patient and other closer informants; b) Part II consists of socio-demographic data about education, vocational training, work, partner, living conditions and income as well as questions about the biographical development in these areas since birth; c) Part III records the course of the illness; all inpatient and outpatient treatments and forms of treatment during the episodes, and during the intervals between two episodes, are recorded; d) Part IV collects retrospective data on the symptomatic course until the time of the interview. It records non-specific signs, social disabilities, and psychotic, depressive and manic symptoms including some BS. Apart from this direct recording of 128 indicators, part IV also contains an open question about the earliest indicators perceived by the patient and a full assessment of the onset of illness by the interviewer; e) In part V the interviewer assesses the quality of the data collected. Duration depends on the complexity of the individual's biography, age, and ability to concentrate. Mean duration is 1.5-2 hours per interview, and about the same amount of time is needed for coding the information. On the whole, the reliability measures have proved to be sufficiently high (e.g. kappa between 0.73 and 1.00 with regard to the determination of the exactness of the onset of symptoms). Also, the validity of the content of the IRAOS is well founded, mainly due to its construction on the basis of expert assessments and the orientation of the research criteria across the ICD-10.

ERIraos (Early Recognition Inventory for the retrospective assessment of the onset of schizophrenia) (Maurer, Hörrmann, Trendler, Schmidt, & Häfner, 2006; Rausch et al., 2013): this is a comprehensive instrument which was established in an attempt to combine the APS and BS approaches. As a result, it provides a tool which allows characterizing prodromal phase (both early and late prodromal phase) across phenomenological description of each one of them. It is possible to learn accurately the transformations occurring in the individual experiences of each person during psychotic development and improve early detection. ERIraos is a sequential two-step procedure of risk assessment for psychosis onset. First, potential at-risk persons are identified using a checklist (ERIraos-CL). It includes 15-item grouped into (1) unspecific symptoms (questions 1-5), (2) specific at risk mntal states (ARMS)-symptoms (questions 6-10), and (3) specific symptoms occurring in late ARMS and /or FEP (e.g. BLIPS) (questions 11-15). Subjects are asked to report whether the evaluated symptoms occurred within the previous 12 months without any regard to frequency, duration or intensity. Patients with at least one positive score in symptom group 2 or 3 are considered positive and are further characterized by ERIraos symptom list (ERIraos-SL). This is the core element of the ERIraos, which initially included 110 symptoms and currently includes the 50 most predictive symptoms at onset of psychosis, including BS, APS and BLIPS. For each of the 50 symtpoms subjects are asked to report (A) if this specific symptoms was present in the previous four weeks, (B) if it already occurred within the previous 12 months, (C) if there was a deterioration during the previous 12 months and (D) if there is a current emotional strain regarding this symptom (score range 0-200, cut-off=30). The absence of an increased risk of psychosis is assumed, when no BLIPS, no APS or less than two BS and no transgression of the cut-off score are present. An early ARMS is defined by a transgression of the cut-off or the presence of at least two BS, while a late ARMS is defined by the presence of at least one BLIPS or APS, independent of the score achieved. ERIraos-SL can be used in its prospective form to detect early and late stages of psychosis and in its retrospective form to study the course of psychosis from the first manifestations of illness until the onset to full blown psychosis, as well as the long-term course of the disorder. Finally, the research version of ERIraos also includes a set of modules and associated instruments designed for the assessment of risk factors, of which only 6 are evaluated in clinical version (use of alcohol and drugs, difficulties in social relationships, current pharmacological treatment, family psychiatric history, obstetric complications, and abnormalities in childhood development).

Additionally, in an effort to simplify the assessment process, a variety of risk assessment tools or **screening instruments** have been developed to serve as more efficient ways of identifying at-risk individuals. Some of the most widely used, among others, are the following:

PQ (Prodromal Questionnaire) (Loewy, Bearden, Johnson, Raine, & Cannon, 2005): this is a screening self-report questionnaire developed at the University of California, Los Angeles (UCLA), which contains 92 items. Most items were adapted from the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991) and from probe questions in the SIPS (Miller et al., 1999); some original items were also added based on the authors' own experience. The items are answered true/false and added up to form four major subscales: 1) Positive symptoms (e.g. unusual thinking and perceptual abnormalities); 2) Negative symptoms (e.g. flat affect and social isolation); 3) Disorganized symptoms (e.g. odd behavior); and 4) General symptoms (e.g. depression and role functioning). The PQ is not diagnostic but rather is intended for use as a tool to pre-select patients for more intensive interviewing. A good concurrent validity of PQ-positive subscale against SIPS on prodromal/psychosis outcome vs. neither was demonstrated in a study of 113 individuals referred to an early detection and intervention clinic, of which 39 were in a SIPS-defined putative prodromal state. So, the concurrent validity data indicate that the PQ can distinguish participants with prodromal/psychotic-syndrome SIPS diagnoses from those with no SIPS diagnosis. With a cut-off at 8 or more items of positive symptoms, sensitivity is 90%, specificity 49%, while a cut-off at 14 or more items of positive symptoms results in a sensitivity of 71% and specificity of 81%. The instrument, however, is not sensitive to the threshold between prodromal and psychotic state. The detailed diagnostic definitions of psychosis provided by the SIPS are based on the severity, frequency and duration of symptoms, dimensions that cannot be efficiently assessed with a brief screen and thus are not assessed by the PQ (Loewy et al., 2005). A brief version (**PQ-B**) was developed by the authors of the original version, which contains a total of 21 items. In addition to positive symptoms, one item on social functioning and one item on academic/occupational functioning were added. Items are answered yes/no. Items marked 'no' are scored as zero. For each item marked 'yes', participants indicate their agreement with the statement "When this happens, I feel frightened, concerned, or it causes problems for me", on a Likert-type scale ranging from 'strongly disagree' (scored as one) to 'strongly agree' (scored as five). Total distress score are calculated by summing the distress scores for items that are marked 'true'. The PQ-B showed good preliminary concurrent validity with interview-based SIPS diagnoses. With a sample of 141 adolescents and young adults referred for assessment to prodromal research centers, the instrument achieved specificity of 0.68 and sensitivity of 0.88 with regard to SIPS diagnoses using a cut-off distress score thereshold of six or greater on the weighted distress measure. The PQ-B maintained the sensitivity of the original, while adding questions about related distress and impairment that improved specificity (Loewy, Pearson, Vinogradov, Bearden, & Cannon, 2011). Recently, a 16-item short screening version (**PQ-16**) was created for the attenuated psychosis syndrome with good psychometric properties in an adult population seeking help for nonpsychotic disorders in routine mental health care. The newly developed PQ-16 has good concurrent validity with both the interview-based CAARMS diagnoses and also in comparison to the original PQ. A cutoff of 6 or more symptoms on the PQ-16 has a high true positive rate (87%) and high specificity (87%) when differentiating UHR/psychosis from those with no CAARMS diagnosis. The PQ-16 predicted UHR/psychosis with high sensitivity and high specificity, comparable to the original version of the PQ (Ising et al., 2012).

SIPS-screen or PRIME-screen (Miller, Chicchetti, Markovich, McGlashan, & Woods, 2004): this was developed by the PRIME group at Yale University. The PRIME screen is a short self-administered questionnaire based on the positive symptom portion of the SIPS and it requires only minutes to complete. Its 12 questions ask about the occurrence of attenuated positive symptom experiences over the last year with responses measured according to degress ranging from 0 (definitely disagree) to 6 (definitely agree)

according to the SIPS rating scale. Items scored as five (somewhat agree) or six (definitely agree) were counted as a positive response, and the screenter total was obtained by counting how many items the respondent endorsed by circling five or six. Authors recommend using a threshold of two or more 'somewhat agree' item endorsements to categorize positive vs. negative responders. Early validation measurements for the PRIME in a patient sample against the SIPS showed a sensitivity of 0.90 and a specificity of 1.0 (Miller et al., 2004). Later validation studies of the PRIME screen in clinical samples have found a specificity of 0.74 and sensitivity of 1.00 in a Japanese youth sample (Kobayashi et al., 2008) and a specificity and sensitivity of 0.66 and 0.75 respectively in a United States sample (Kline et al., 2012). A revised version (PRIME screen – revised, **PS-R**) has been developed by a Japanese team, which includes all the items of the original PRIME screen and new questions about how long the change in function, behavior or thought had been apparent: less than 1 month, between 1 month and 1 year, more than 1 year. In other words, this version adds a section on the duration of symptoms to improve its specificity (symptoms present for a longer time are considered to be more representative of being at risk of conversion to psychosis) (Kobayashi et al., 2008).

Y-PARQ (Youth Psychosis At-Risk Questionnaire) (Ord, Myles-Worsley, Blailes, & Ngiralmau, 2004): this is a screening instrument developed in Utah (USA). It is a 92-item questionnaire describing positive, affective and negative symptoms of prodromal schizophrenia to which the person responds 'yes', 'no' or 'unknown'. This instrument is based on CAARMS and was developed for the Palau Early Psychosis Study, which investigated teens on a Pacific island where there are elevated rates of familial schizophrenia (Myles-Worsley et al., 2007). High scores of the 24 most discriminating positive symptom questions were used for identifying potential prodromal adolescents. Preliminary data from 74 potential prodromal adolescents showed a positive predictive value of a CAARMS-defined ARMS of 82.4% and a sensitivity of 98.4%.

ESI (Eppendorf Schizophrenia Inventory) (Mass et al., 2000): this is a clinical measure for self-experience disturbances in cognitive, linguistic, sensomotoric and coenesthetic (body misperception) domains as found in pre-psychotic states, i.e. in subjects with prodromal or APS as well as in schizophrenia patients. It is inspired by the BSABS, the Frankfurt Complaint Questionnaire (FCQ) (Süllwold & Huber, 1986) and the SPQ (Raine, 1991). This questionnaire contains 40 items whereof 34 are combined into four scales (Mass, Haasen, & Borgart, 2005): (1) Attention and Speech Impairment (AS), mainly describing impairments of the appropriate reception and interpretation of environmental stimuli, above all affecting speech; (2) Ideas of Reference (IR), representing a tendency to interpret trivial events in an excessively meaningful way and a delusional mood; (3) Auditory Uncertainty (AU), an inability to discriminate between thoughts and words which actually have been heard; and (4) Deviant Perception (DP), referring to aberrations of perceptual processes, especially involving disturbances of the body-image. Moreover, the ESI contains a five-item Frankness-scale (FR; score>2) to control for socially desirable tendencies and one item (item 40; score=0) assessing general survey motivation. While AS represents a mediating vulnerability factor, IR, AU, and DP are assumed to provide reversible indicators of psychotic exacerbations. ESI-items provide a four-point response format from 'strongly disagree' (0) through 'strongly agree' (3), which are added up in the mentioned subscale-scores. The ESI proved able to distinguish between patients with active psychosis and subjects at risk of conversion (Niessen et al., 2010).

BSIP (Basel Screening Instrument for Psychosis) (Riecher-Rössler et al., 2007): this is a 46-item checklist that has been developed and based upon prodromal symptoms (most of which are relatively unspecific) of the DSM, 3rd edition (DSM-III) (APA, 1980), and other prodromal symptoms that have been derived from the literature. It also includes prepsychotic symptoms rated by the Brief Psychiatric Rating Scale (BPRS) and other domains such as social decline, drug abuse, past history of mental disorders, a family history (first or second degree relatives) with schizophrenia or psychoses, and age of less than 30 for female and less than

25 for male subjects. In combination with the four psychosis items of the BPRS, it allows classifying of patients' risk for psychosis according to the criteria established by Yung et al. (1998). Interrater-reliability for high-risk individuals was high (Kappa 0.87). Predictive validity was comparable to other, more comprehensive instruments: 16 (32%) of 50 individuals classified as being at risk for psychosis by the BSIP in fact developed frank psychosis within a follow-up period of two to five years. The BSIP is the first screening instrument for the early detection of psychosis which has been validated based on transition to psychosis (Riecher-Rössler et al., 2008). It is not a screening instrument to be used in the general population, but in the help-seeking population, and it has to be administered by experienced psychiatrists.

PROD-screen (Screen for PRODromal symptoms of psychosis) (Heinimaa et al., 2003): this is a 29-question screening questionnaire, developed in Finland, to detect persons with elevated risk of psychosis, who will subsequently be assessed with SIPS. It is based on items from SIPS, IRAOS and BSABS. In addition, nine questions inquiring about general and affective symptomatology were included. In general, the instrument contains background data, 7 items of general functioning (current situation and changes during past year), 10 items of general symptoms and 12 items of more specific psychosis-like character (Salokangas et al., 2001). The symptom section covers both current (present during the last year) and lifetime (present earlier than the last year) presence. Because of its concise and simple format, it can be self-administered or administered over the telephone to identify subjects who should be evaluated in more depth with a semi-structured interview. In studies of validity and reliability, PROD-screen has correctly identified a SIPS-defined prodromal state in 77% of cases from a mixed sample, distinguishing prodromal from non-prodromal subjects with a sensitivity of 80% and a specificity of 75%. PROD-screen is useful in mixed populations, first-degree relatives, and probably also the general population, but it is not very useful in highly symptomatic individuals like psychiatric out-patients (Heinimaa et al., 2003).

To date, a small number of these instruments have been validated in a Spanish population (e.g. SOPS, Lemos et al., 2006; PRIME-screen, Fresan, Apiquián, Ulloa & Nicolini, 2007). In this sense, there is still much to be done. Currently, some of them are being validated by the author of this thesis (CAARMS interview and ERIraos-SL), this being one of her lines of future research.

Increasingly, research teams combine evaluation tools of both approaches (APS and BS), using a sequential procedure of risk assessment for psychosis onset across screening instruments and interviews. The BS criterion 'cognitive disturbances' (COGDIS) frequently co-occurs with symptomatic UHR criteria (APS and BLIPS) in help-seeking at-risk samples (Ruhrmann et al., 2010), and this co-occurrence was suggested to define a more homogeneus sample of clinically and neurocognitively impaired persons. It is postulated that this combination will make it possible to identify the groups of subjects who are most representative of patients who will develop psychosis (Simon et al., 2006). Therefore, **a combined APS and BS approach may improve the prediction of psychosis and the identification of a more homogeneous risk group**: a) increasing sensitivity in persons truly at risk for psycshosis, and b) reducing the risk of false-positive prediction (i.e. considerably increases specificity) (Schultze-Lutter, Klosterkötter & Ruhrmann, 2014). A recently developed example of these comprehensive instruments, which combines both approaches, is the ERIraos. As noted by Olsen and Rosenbaum (2006a), in order to increase sensitivity of research on the possible pre-onset phase of psychosis, more attention should be given to phenomenological aspects.

In general, a screening instrument is administered first, to be followed by a detailed examination of respondents with an established comprehensive diagnostic measure that serves as a gold standard for identifying the specified set of symptoms. In this sense, screening instruments must effectively and reliably distinguish respondents who are at high risk for psychosis from those who are not. In addition to the screening instruments already mentioned, over recent years there has been extensive development of

these tools not only aimed at detecting basic and/or APS but also **subclinical psychotic-like experiences**, such as [Community Assessment of Psychic Experiences (**CAPE-42**), Interview for psychosis-like symptoms (**PLIKSi**), Adolescent Psychotic-Like Symptom Screener (**APSS**) or Self-Screen-Prodrome (**SPro**), among others] (Addington, Stowkowy, & Weiser, 2015; Kline & Schiffman, 2014).

3.2.3. Understanding of the prodromal phase as predictor of outcome in the FEP

Several research groups have focused on the possibility of defining a prodromal set of symptoms and signs that may predict the development of FEP. Particularly, as mentioned above, two main approaches (BS and APS approaches) have independently provided the rationale for the development of reliable predictive psychometric scales, which include the criteria definition for identifying people at risk of psychosis. On the one hand, the **UHR criteria** aim to predict an imminent transition to psychosis, and on the other, **BS based criteria** which are not thought to define an imminent risk of psychosis but to enable a true early detection, which not only precedes the onset of psychosis, but also any significant decline in social and role functioning that has frequently taken place already at the time UHR criteria are met (Ruhrmann, Schultze-Lutter, Schmidt, Kaiser, & Klosterkötter, 2014). However, recent studies have shown that **the UHR approach is less selective than BS criteria** in discriminating individuals at risk of developing schizophrenia from those who are going to be affected by other psychotic disorders (Fusar-Poli et al., 2013a; Ruhrmann et al., 2010), suggesting that the populations of patients selected or the ability to identify a peculiar psychopathological pattern through the two predictive approaches may partially differ. In the last few years, these two approaches have been partially conjoined in an attempt to improve the sensitivity (ability to identify positive subjects) and specificity (ability to avoid negative cases) of predictive psychometric scales, with consequent modifications of their selectivity in predicting the development of a specific psychotic disorder. In this line of thought, the **EPOS study** used COGDIS and UHR criteria as alternative inclusion criteria (Ruhrmann et al., 2010). They concluded that the **combination of UHR and COGDIS allows for better sensitivity and it serves as a first-step detection tool** for a generally increased risk of psychosis. Later, a recent meta-analysis on the diagnostic outcome revealed that 73% of those developing an FEP developed an ICD/DSM schizophrenia spectrum disorder (SSD) and only 11% affective psychosis [risk ratio (RR) 5.43] (Fusar-Poli et al., 2013a). If BS criteria were part of the inclusion criteria, the RR for SSD increased to 17.1. In the line of this last finding, in a naturalistic 48-month follow-up study analyzing the conversion rate to FEP, Schultze-Lutter, Klosterkötter, and Ruhrmann (2014) suggest that the combination of symptomatic UHR criteria (mainly APS) and self-reported cognitive disturbances (i.e., COGDIS) indicate a higher medium-term risk for conversion to psychosis than the singular presence of either criterion; the 48-month hazard risk (hr) of 0.66 observed for the combination of UHR and COGDIS was clearly higher than the hr that resulted from (1) their independent use (either one approach irrespective of the presence of the other), (2) their alternative use (at least any one criterion), and (3) their exclusive use (one criterion but not the other). Moreover, **the conversion rate of UHR + COGDIS was considerably higher** than the conversion rates reported in other studies (Fusar-Poli et al., 2012a). Also, the high predictive performance of the co-occurrence of COGDIS and UHR, in nearly all APS cases, is well in line with the role of impairment cognition in frank psychosis, one of the eight dimensions of psychotic symptom severity in DSM-5. In spite of this and the fact that some specific features of the prodromal phase of psychosis have already been identified, the Psychotic Disorders Workgroup proposed including APS as a category in the appendix (Section 3) of the DSM-5 (APA, 2013) as a condition for further study (Carpenter & van Os, 2011; Tandon, Shah, Keshavan & Tandon, 2012b). However, there is a uniform consensus among the experts that APS is a condition that warrants systematic attention (Yung et al., 2012). The **five principal areas of debate** put forth by the experts who recommend inclusion of APS in the appendix instead of the main body of the diagnostic manual were (Fusar-Poli et al., 2014a):

1) A majority of individuals with current APS have some **other current psychiatric comorbidity** (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014b) and exhibit a range of psychiatric outcomes other than conversion to psychosis, which should be considered.
2) A substantial proportion of individuals with APS **do not go on to develop major psychopathology** (i.e. there are many false positives) and in some cases even fully remit (Simon & Umbricht, 2010; Simon et al., 2011). Allocating these individuals prematurely to a DSM-5 Section II disorder would result in an unintentional scenario with unwarranted treatment regimens and imminent stigma (Yung et al., 2012).
3) It is unclear whether APS represents **a trait or state vulnerability** and its relationship to schizotypal personality disorder is not clear.
4) It is unclear if **the distress and/or disability** resulting in help-seeking behaviour by this group of individuals is related to APS or comorbid mental disorder; help-seeking is part of its definition in DSM-5.
5) There was concern about **potential stigma and inappropriate antipsychotic utilization** in individuals with APS (Jacobs, Kline, & Schiffman, 2012).

In this sense, the workgroup concluded that there were reasons to continue to evaluate this clinical entity, and provision of specific criteria and description would help in this effort.

Several approaches have been outlined to improve our knowledge about APS. One of them is a possible avenue of research suggested by Yung et al. (2012), which consists in **refining the risk factors for different outcomes of psychosis**. It may be that **added criteria are necessary to enrich risk-samples for psychosis**, such as basic and negative symptoms and decline in cognitive and social skills (Cornblatt et al., 2012; Klosterkötter, Schultze-Lutter, Bechdolf, & Ruhrmann, 2011). In this line, recent findings point out that while current symptomatic at-risk criteria according to the UHR and BS approach have proven to be good starting points, studies so far clearly indicate that **additional predictors are needed to increase specificity and sensitivity**, and so get an improvement of risk enrichment with an optimized prediction model (Fusar-Poli et al., 2013b; Michel et al., 2014; Nieman et al., 2014).

Different international studies [The Personal Assessment and Crisis Evaluation (PACE), NAPLS and EPOS studies], using multivariate prediction models, have replicated several **predictors of conversion to psychosis** (Cannon et al., 2008; Ruhrmann et al., 2010; Yung et al., 2003b). In summary, severity of subthreshold positive symptoms, poorer functioning, and genetic risk appear to be consistent predictors of conversion to psychosis. However, the findings of the latest research with respect to prediction of psychotic disorder, published 2010-2014, show variables that are not directly related to the inclusion criteria currently used to detect risk-sample for psychosis. The table 7 is an attempt to show this issue:

Table 7. Clinical, cognitive and functional predictors of psychotic disorders spectrum.

	Study	Main variable	Main conclusions
Clinical predictors	Velthorst et al. (2013a)	SIPS symptoms	Transition to psychosis was significantly associated with quantitative differences in baseline SIPS scores. The results of this study suggest a 'quasi'-continuous extended psychosis phenotype.
	Bodatsch, Klosterkötter, Müller, and Ruhrmann (2013)	Basic symptoms	The at-risk state seems to be associated with information processing disturbances. Neurophysiological studies revealed that disturbances of sensory processing may assist psychosis prediction in allowing for a quantification of risk in terms of magnitude and time.

	Salokangas et al. (2013a)	Schizotypal features	Presence of ideas of reference and lack of close interpersonal relations increase the risk of full-blown psychosis among CHR patients. This co-ocurrence makes the risk of psychosis very high.
	Shah et al. (2012)	Schizotypy and symptomatology	Clinical measures of schizotypy were directly predictive of conversion, with early (familial, biological, socioenvironmental) and cognitive risk factors indirectly predictive of psychosis through increased baseline clinical symptomatology. The high specificity and low sensitivity found using a combination of such variables suggests that their utility may be in confirmatory testing among already selected high-risk individuals, rather than for initial screening.
	Salokangas et al. (2012)	Clinical diagnoses	Both life-time and current mood and anxiety disorders are highly prevalent among clinical help-seeking CHR patients. Among CHR patients, occurrence of bipolar, somatoform and depressive disorders seems to predict transition to psychosis, while occurrence of anxiety disorder may predict non-transition to psychosis.
	Tandon et al. (2012a)	Early prodromal symptoms	A relatively simple set of clinical measures can be utilized to prospectively identify familial high-risk individuals who convert to psychosis with high specificity and sensitivity. Measures of cognitive or social function to the index of psychosis-proneness decrease its predictive ability, reducing its specifity and/or sensitivity.
	Parnas et al. (2011)	Self-experiences	High levels of perplexity and self-disorder baseline scores yielded the best prediction of the subsequent development of schizophrenia spectrum disorders.
	Bearden, Wu, Caplan, and Cannon (2011)	Formal thought disorder	CHR patients who subsequently converted to psychosis showed an elevated rate of illogical thinking and poverty of content in their speech. Then, putatively prodromal individuals evidence signs of communication disturbance that are qualitatively similar to those seen in schizophrenia and are predictive of both conversion to psychosis and psychosocial outcome.
	Thompson, Nelson, and Yung (2010)	Unusual thought content	Three variables were found to be associated with transition to psychosis: high unusual thought content scores, low functioning, and genetic risk with functional decline. Using a combination of clinical variables, the predictive validity of determining whether a UHR individual develops a psychotic disorder was improved above UHR criteria alone.
	Zimmermann et al. (2010)	Negative symtpoms	Prediction of transition to psychosis is possible using combined information from a negative symptom scale and EEG spectral data.
Cognitive predictors	Lee et al. (2014)	Attention, verbal memory, verbal fluency, visual memory	Remitter CHR subjects showed better performance at baseline on tasks of attention, immediate/delayed verbal memory, verbal fluency, and immediate visual memory compared with converter CHR subjects.
	Riecher-Rössler et al. (2013)	Neurocognitive functioning	The risk for psychosis should be assessed in a stepwise procedure. In a first step, a clinically oriented screening (BSIP) should be conducted. If an at-risk status is found, further assessments in various domains (psychopathology and neuropsychology domains) should be done in a specialised centre.
	De Herdt et al. (2013)	Working memory and visual learning	Psychosis converters performed significantly worse compared to non-converters in 2 neurocognitive domains (working memory and visual learning). The addition of visual learning and working memory tasks to psychosis regression models might contribute to the predictive power of these models.
	Fusar-Poli et al. (2012b)	Verbal fluency and memory functioning	Impairment in verbal fluency and memory functioning was associated with the onset of psychotic symptoms and may be useful in predicting psychosis and targeting early interventions.

	Valli, Tognin, Fusar-Poli, and Mechelli (2012)	Verbal memory	Some areas of cognition, particularly verbal memory, can increase the accuracy obtained in the identification of individuals developing psychosis beyond that based purely on psychopathological measures, suggesting that the inclusion of neurocognitive tests of domains for which there is evidence of prediction potential could be useful in a stepwise assessment of risk.
	Koutsouleris et al. (2012)	Executive functioning and verbal learning/memory	Patterns distinguishing the early or late ARMS from healthy controls primarily involved the verbal learning/memory domains, while executive functioning and verbal IQ deficits were particularly characteristic of the late ARMS. Disease transition was mainly predicted by executive and verbal learning impairments.
	Woodberry et al. (2010)	Verbal IQ, verbal memory and olfactory identification	Individuals who subsequently developed psychotic-level symptoms demonstrated large impairments in verbal IQ, verbal memory and olfactory identification comparable in magnitude to first episode samples. CHR status may be associated with moderate generalized cognitive impairments marked by some degree of selective impairment in olfaction and verbal memory. Impairments were greatest in those who later developed psychotic symptoms.
	Seidman et al. (2010)	Verbal memory	Neuropsychological functioning in the CHR group was significantly lower in persons who progressed to psychosis than in those who did not. This dysfunction is generally of moderate severity but less than in first-episode schizophrenia. Neuropsychological functioning did not contribute uniquely to the prediction of psychosis beyond clinical criteria, but worse verbal memory predicted more rapid conversion.
	Becker et al. (2010)	Verbal fluency	Verbal fluency (semantic category) is disturbed in UHR-patients make the transition to psychosis and could contribute to an improved prediction of transition to psychosis in UHR-psychosis.
	Riecher-Rössler et al. (2009)	Processing speed	Best transition predictors within this population were selected APS (suspiciousness), negative symptoms (anhedonia/asociality), and cognitive deficits (reduced speed of information processing). Prediction of transitions could be improved by a stronger weighting of certain early symptoms and by introducing neurocognitive tests into a stepwise risk assessment.
Functinal predictors	Tarbox et al. (2014)	Premorbid social development	Results support diagnostic specificity of premorbid social dysfunction to schizophrenia in CHR youth and underscore an important role for social maladjustment in the developmental pathology of schizophrenia and its prediction.
	Velthorst, and de Haan (2014)	Social and role functioning	UHR adolescents show functional limitations are already manifest in the phase preceding a clinical psychotic disorder. Impairments in both social and role functioning contribute to the prediction of a FEP in UHR young persons.
	Tarbox et al. (2013)	Early adolescent social development	Deterioration of academic and total functioning, although observed, did not predict conversion to psychosis. However, early adolescent social dysfunction was an important early predictor of conversion.
	Nieman et al. (2014)	Premorbid adjustment	Results suggest that predicting an FEP in CHR subjects could be improved with a model including PA and information-processing variables in a multistep algorithm combining risk detection and stratification.
	Carrión et al. (2013)	Functional outcome: social and role functioning	Results from this study support the increasing emphasis on functional decline as a critically important outcome that parallels conversion to psychosis. Poor functional outcomes were not entirely dependent on positive symptoms and the development of psychosis.
	Velthorst et al. (2013b)	Decline in functioning	UHR individuals with deteriorating functioning were at higher risk of transition than those whose functioning was low at baseline but improved over time. Then, with the addition of the 'low functioning'

			criterion to the UHR criteria, we may miss out on some true positive cases.
	Dragt et al. (2011)	Enviromental factors and social adjusment	Environmental characteristics (urbanicity and receiving state benefits) and social adjustment (social-sexual aspects and social-personal adjustment) are predictive of transition to psychosis in subjects at UHR. These characteristics should be implemented in a model for prediction of psychosis.
	Velthorst et al. (2010)	Social disability	CHR patients who make the transition to psychosis displayed significantly greater difficulties in making new friends, maintaining a friendship, dealing with people they do not know and joining community activities compared with the non-transition CHR patients. Certain domains of social disability might contribute to the prediction of psychosis.

Current criteria for ARMS have strong predictive validity; however, high rates of non-conversion, representing potential **'false-positive' cases**, underline the need for improved prediction algorithms. So, this review is the reflection of the need to employ **additional predictors**, without compromising sensitivity and increasing specificity, to improve risk estimation across multivariable algorithms. Enhancing prediction allows for improved accuracy of identification and can better inform the timing and need for interventions. In addition, increasing diagnostic accuracy serves to reduce stigma and exposure to potential adverse events among individuals who do not transition to psychosis (Gee & Cannon et al., 2011). However, few studies have used these potential predictors for this purpose; most of them have merely been examined for their predictive value in risk sample identified with UHR and/or BS criteria. In this sense, the EPOS study (Ruhrmann et al., 2010) introduced **a risk stratification model** that considers risk not only at an 'all-or-nothing' level but at interindividually different levels with regard to severity and time to transition. This new approach implies **a two-step procedure** in which help-seeking individuals are first screened using both UHR and COGDIS criteria (risk identification phase) and then classified using a prognostic index based on six empirically derived variables (positive symptoms, bizarre thinking, sleep disturbances, a schizotypal disorder, level of functioning in the past year, and years of education) highly predictive of transition to psychosis (risk classification phase). Then, UHR and COGDIS criteria together serve as a first-step detection tool for a generally increased risk of psychosis, and the prognostic scores serve as a multivariate second-step tool for further risk classification in terms of magnitude and time. The final model allows for stratification of the sample into four classifications of risk, thus moving from a one-threshold approach to **a more continuous risk estimation**. This 4-class model represents an improvement in the prediction of psychosis by enabling a differentiation of the individual risk in terms of magnitude and time.

This approach implies several **advantages** (Piras et al., 2014; Ruhrman et al., 2010):

a) Allows obtaining **high specifity without loss of sensitivity** because a patient continues to be generally considered at risk once screened positive for inclusion criteria.
b) Allows the **detection of the very early risk signs** of mental disturbances to reduce the impact of risk factors.
c) Allows understanding the **risk concept as a complex and dynamic construct** vs. the current definition of risk as a static and stable concept over time.
d) Allows tailoring preventive measures to individual needs with opportunity to **re-evaluate the course of risk and needs periodically**.
e) Provides an **opportunity for monitoring patient mental conditions and differentiating therapies**, depending on the appearance and patterns of prodromal signs.
f) Could also **help solve the problem of risk enrichment** by providing the required robust basis for calculation of sample size and follow-up period.

g) Offers **empirically derived algorithms and risk staging models** (or their combination), which appear to be the most promising strategies to improve the predictive power and reliability of psychometric scales.

This approach provides a strategy to **combine the high sensitivity of risk criteria (UHR or/and BS) with an individual risk estimation** with potentially individually tailored interventions. This more individualized risk estimation or clinical staging of risk, if validated in future studies, could significantly advance the development of risk-adapted inclusion criteria for future randomized preventive trials. In the first application of this approach in the EPOS study, only clinical and demographic variables were considered. Future research should be orientated towards learning whether multi-step detection procedures using new multivariate algorithms, including additional parameters already identified in previous studies as potential predictors (see Table 7), in combination with a risk staging model, could improve the individualization of prediction of psychosis as well as of functional outcome.

3.3. Initial psychotic phase

A frequently noted problem in schizophrenia and psychotic spectrum disorder studies is the wide variability of findings in the literature. This variability is commonly attributed to the presumed **heterogeneity** of this set of disorders, but an equally important cause may be the widely **discrepant definition and criteria** used for the populations in the studies, making comparability of studies quite difficult. Use of patients with varying degrees of chronicity and at varying stages of treatment makes generalitzation of any findings unwise. From the National Plan for Schizophrenia Research, designed by the National Institute of Mental Health in 1988, one of the specific recommendations was that collaborative efforts should be pursued for the study of sufficiently large samples of patients experiencing their FEP. These samples offer a unique opportunity to better understand the nature of schizophrenia and psychotic spectrum disorders by examining subjects **before extended neuroleptic treatment and the development of chronic symptoms** (Kirch, Keith, & Matthews, 1992).

Keshavan and Schooler (1992) described several **advantages of the first-episode strategy**:

(1) the **confounding effects of chronicity and institutionalization** on the parameters being studied can be minimized (e.g. relapses, institucional long stays, functional and cognitive impairment, among other);

(2) the possibility of obtaining **drug-naïve subjects**, particularly valuable for biological research, is unique to this population;

(3) initiation of research at this stage offers the opportunity to carry out **prospective longitudinal studies** of biology, course, and outcome;

(4) the likelihood of **detecting biological or psychological factors** that are etiologically or pathophysiologically significant may be higher at illness onset;

(5) studies of first episode patients can increase understanding of the substantial variability in **clinical morbidity** seen in the first few years after schizophrenia onset;

(6) reasonable **sample sizes** can be collected so that hypotheses about the etiology and course of the disorder can be tested; and

(7) **relevant risk factors** may be more accurately evaluated earlier rather than later in the illness.

However, there are two major difficulties in conducting research with patients early in the course of the illness. First, the **number of incident cases** in any given center is comparatively small, so amassing a sample of reasonable size may take far longer than accruing a sample of mixed chronicity. Second, **diagnosis of patients experiencing a first episode** is difficult and almost certainly requires subsequent rediagnosis for

many patients, some of whom will receive other diagnoses (Keshavan & Schooler, 1992). Further, studies that focus on the first-episode population have frequently reported conflicting findings, possibly because of widely varying definitions of the population.

Nowadays, a substantial **lack of consistency persists in the definition** and characterization of patients in the studies of FEP in the literature. This significant variability in definition and application across different clinical and research programmes threatens meaningful integration of findings from these populations (Keshavan & Schooler, 1992; Sharpe, 1997) and may ultimately hinder our progress in identifying key elements of the early course and treatment of psychotic disorders. In a recent review investigating how FEP was operationally defined, Breitborde, Srihari, and Woods (2009) established **three definition categories**: **(i) first treatment contact** (individuals who present at a clinical setting with psychosis and who have never previously presented at a clinical setting with psychosis are identified as experiencing their 'first-episode'); **(ii) duration of antipsychotic medication use** (individuals who have yet to receive appropriate treatment for their psychosis, defined as receiving antipsychotic medication for a specific duration of time); and **(iii) duration of psychosis** (individuals who have experienced psychotic symptoms for less than a pre-specified amount of time). Each definitional category implies a number of strengths and weaknesses, which are summarized in Table 8.

Table 8. Strengths and weaknesses of operational definitions for FEP.

Operational definition category	Strengths	Weaknesses
First treatment contact	Relatively simple to comprehend and apply reliably	The first treatment contact for individuals with psychotic disorders often occurs well after the initial onset of symptoms
	Reflects an intuitively appealing way to organize clinical care around a naturally occurring service need	An individual's 'first contact' is often not the first attempt to seek treatment
		This definition may be an overly conservative proxy for identifying people early in the course of a psychotic illness; individuals who are still early in the course of a psychotic disorder but who have experienced psychotic symptoms for 1 year or more may be excluded
Duration of antipsychotic medication use	It provides a clear, objective criterion for clinicians and researchers	It can be an unsatisfactory proxy for the first episode of a psychotic illness: e.g. this definition would identify an individual who has not received appropriate treatment with antipsychotic medication as experiencing his or her FEP even if he or she had experienced psychotic symptoms for many years
	It has demonstrated feasibility in several studies testing clinical interventions for FEP	The growing use of antipsychotic medications for non-psychotic disorders, especially among children and adolescents, raises doubts with regard to the utility of the duration of antipsychotic medication use in demarcating the first episode of a psychotic disorder
		There is considerable variation in the acceptable duration of medication use.
		This definition may be an overly conservative proxy for identifying people early in the course of a psychotic illness: individuals who are still early in the course of a psychotic disorder but who have experienced psychotic symptoms for 1 year or

		more may be excluded
Duration of psychosis	It possesses the highest construct validity; it attempts to address more directly the goal of identifying individuals early in the course of illness	The retrospective assessment of the onset of psychotic symptoms is fraught with methodological difficulties
	This limits inappropriate inclusion of latecomers or 'chronic' patients who are experiencing their 'first treatment contact' and exclusion of those who happen to have been exposed to antipsychotic medication for too long but are better conceptualized as early in illness course	Lack of a validated durational criterion for demarcating the end of the first episode of a psychotic disorder.
	There is promising evidence suggesting that individuals experiencing their FEP can provide relatively precise estimates of the onset of psychotic symptoms	
	Programmes now have access to several reliable measures that facilitate the collection of estimates of the onset of psychotic symptoms (e.g. IRAOS)	

Breitborde et al. (2009) suggest a pragmatic solution that can address the varying needs of specific clinical and research settings: the operational definitions for FEP should include a 'duration of psychosis' criterion while simultaneously tracking specific measures that would allow for comparison with data from other populations (e.g. date of first contact with treatment setting, duration of antipsychotic medication use, etc.).

The term FEP as currently used within clinical and research settings may be misleading regardless of which operational definition is used. This term is typically used to refer to individuals early in the course of a psychotic illness or treatment rather than individuals who are truly in the midst of a first 'episode' of illness. These authors proposed an alternative of **'recent-onset of psychosis'** with related definitions **based on 'duration of psychosis'**. The term 'recent-onset psychosis' more accurately describes the populations actually studied so far and, conceptually, may be more accurate than the term FEP given that psychotic disorders do not always follow an episodic course.

Finally, a crucial issue is defining key variables associated with the study of FEP, which need to be collected and provided in the literature to permit cross-study comparison and meaningful interpretation of data. Among these variables of interest are the following: **age at onset** and **gender differences** in FEP. These variables, in addition to being important factors toward understanding the heterogeneity of psychosis disorders spectrum, have frequently been used as control variables in the research setting.

3.3.1. Age of onset in FEP

In all areas of medicine, the study of the age of onset of illnesses has attracted increasing interest over time. An examination of the age of onset distributions is important for at least two reasons (Kessler et al., 2007): a) information on age of onset allows us **to distinguish between lifetime prevalence** (the proportion of the population who had a disorder at some time in their life up to their age at interview) **and projected lifetime risk** (the estimated proportion of the population who will have the disorder by the end of their life); b) an understanding of age of onset is important **for targeting research on prevention of mental disorders** (Amminger et al., 2006b), early intervention with prodromal or incipient mental disorders

(Klosterkötter et al., 2005), and primary intervention of secondary disorders (Kendall & Kessler, 2002). In the absence of age of onset information, we would have no way of knowing the appropriate age range to target preventive interventions.

In psychosis, a key variable in the definition of FEP is onset. Further, **'age at onset'** is considered a prognostic factor of importance to clinicians evaluating FEP. However, defining onset involves many **difficulties**:

(1) This date must be inevitably based on **retrospective data**, which carries an inherent risk of biased or distorted recall. Further, the illness state may affect accuracy of recall. For these reasons, onset information should be collected when patients are symptomatically stable, corroborating this information with family members and other informants.
(2) It is unclear whether the onset should be dated from the presentation of the **first symptom** or from the date that criteria for **full syndrome** were first met.
(3) **The distinction between a prodrome and a psychotic episode is also unclear**, and some form of severity criterion needs to be used (e.g. using severity level, frequency and duration of positive psychotic symptoms of the CAARMS interview).
(4) **What constitutes the prodrome is controversial** (see section 3.2.1. Conceptualization and characterization of the prodromal psychosis onset).

With these aspects in mind, onset of the following significant clinical events should be dated as carefully as possible in order to characterize the onset of psychosis: a) decline in social functioning regardless of relationship to psychopathology; b) first onset of any psychiatric symptoms; c) first onset of early psychotic symptoms; d) first onset of negative symptoms; e) first treatment, which could influence the course and duration of the first episode; and e) first hospital admission.

In general terms, schizophrenia and related psychotic disorders often have their **onset in adolescence or early adulthood** with consequent impact on psychosocial functioning and quality of life (Häfner, Hambrecht, Loffler, Munk-Jorgensen, & Riecher-Rössler, 1998b; Ritsner et al., 2003). Schizophrenia spectrum diagnoses account for approximately two-thirds of all psychotic disorders. In this group of diagnoses, **the highest rates were in the 16-25 year-old age group, with a slight second peak in the 46-55 year-old group, and a third peak in the over-65 group** (Castle & Murray, 1993). In an epidemiologic study of FEP (Amminger et al., 2006a), treating all people between 15 and 29 years old, the median age of initial presentation in this cohort was 22 with an inter-quartile range of 19-25. The same median and inter-quartile range existed for patients with schizophrenia spectrum diagnoses (69%) and those with non-schizophrenia spectrum diagnoses (31%).
However, age at onset of psychosis can not be understood without mentioning the **gender variable**. It is well established that the morbid risk for schizophrenia changes with age and that gender has a strong influence on age at onset. It is widely accepted that **men tend to manifest schizophrenia onset for the first time at an earlier age than women, by 3-5 years** (Beratis, Gabriel, & Hoidas, 1994; Häfner et al., 1998a; Jablensky, 1995; McGrath, 2006) **or 4-6 years** (Rabinowitz, Levine, & Häfner, 2006). **The age of onset distribution curves are different for the sexes**. In men age at onset peaks between ages 18-25, whereas in women this peak occurs between ages 25-35 (Angermeyer & Kuhn, 1988).
In the ABC Study (Häfner et al., 1993; Häfner et al., 1998a; Häfner et al., 1998c), based on the first sign of a mental disorder, males showed a single marked peak of onset between ages 15-25 followed by a steady decline and females showed a lower and broader peak between ages 15-30 with a second smaller peak between ages 45-49. From age 30, the sex ratio reversed in favor of females, leading to equal lifetime incidence in the sexes (Fig. 8).

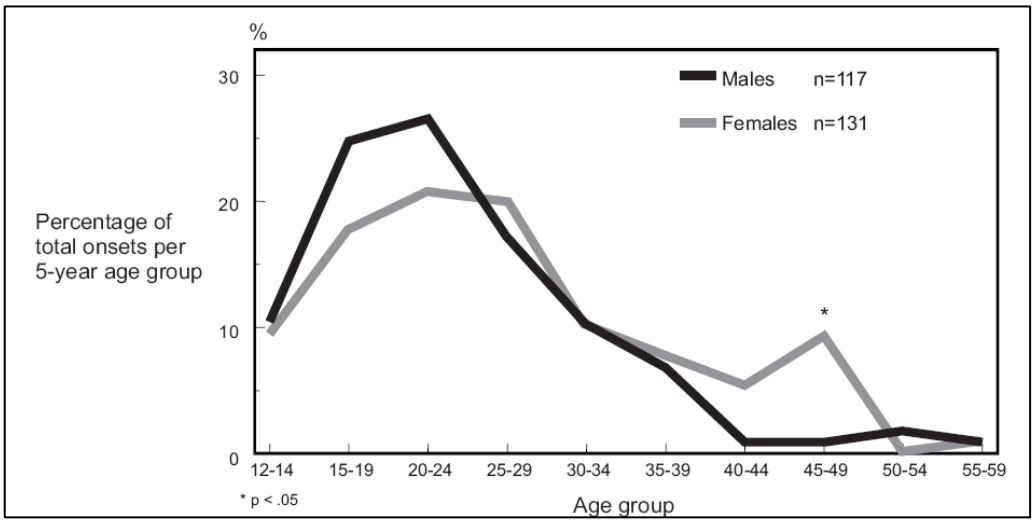


Fig.8. Distribution of age at onset of schizophrenia (first ever sign of mental disorder) by sex. [Source: Häfner, et al., 1993].

In another study based on first contact (Castle & Murray, 1993) comparable results were obtained, but with females showing a third peak of onset in very old age. Furthermore, males had a single prominent peak of incidence in their late teens and twenties (nearly half of the male patients had an onset of illness before the age of 25 years); thereafter there was a monotonous decline (only 12 percent of male patients first manifested their illness between the ages of 46 and 65, and 4 percent after 65 years of age). In contrast, females had a peak in their twenties (less than a third of females had manifested their illness by the age of 25), followed by a second smaller peak between ages 46-55 (20 percent had an onset of illness between the ages of 46 and 65 years) and a third small peak over the age of 65 (18 percent had onset after the age of 65). Thus, men show a modal incidence in their early twenties and perhaps a second peak around middle age. Women also show modal onset in their early twenties, but this is a lower frequency, somewhat broader mode, and it is followed by a more pronounced peak in middle age than men. From the age of 40, the sex ratio favored females. In a subsequent study of Castle, Sham and Murray (1998), males showed evidence of two age at onset distributions, with modes at 21.4 years and 39.2 years. Females also showed evidence of two distributions, with the suggestion of a third peak. The modes of the three distributions in females were 22.4, 36.6 and 61.5 years. In summary, in these studies **a switch is observed from an age at onset with male predominance during the early twenties to an age at onset with female predominance at older ages, with men showing two peaks and women three peaks of age at onset**.

Possible explanations for these gender differences include **males and females being differentially susceptible to subtypes of illness** with different mean ages at onset (Murray, O'Callaghan, Castle & Lewis, 1992); **precipitating factors operating at different stages of life in males and females** [e.g. testosterone surge in adolescent males, with testosterone, via agonistic effects on the dopaminergic neurotransmission, accelerating the onset of schizophrenia (Seeman, 1985); the major prevalence of women once they are over 40 could be explained by the reduction of estrongens after menopause according to the estrogenic hypothesis of schizophrenia (Riecher-Rössler, Häfner, Stumbaum, Maurer & Schmidt, 1994)], **and/or an X-linked susceptibility locus that determines the age at onset** (DeLisi, 1992). The interaction between these determinants has prompted increasing focus on generating and testing models of interaction between specific biological factors (vulnerability to schizophrenia), non-specific biological factors (elevation of the vulnerability threshold by estrogen), developmental factors (e.g. level of development at onset, influence of cognitive maturity on symptom formation) and environmental factors.

The gender differences in age of onset have been shown to exist irrespective of culture (Cetingök, Chu, & Park, 1990; Jablensky et al., 1992), definition of onset (first sign of mental disorder, first psychotic symptom, age of diagnosis, first treatment, first hospital admission) (Häfner et al., 1993), or definition of

illness (various diagnostic systems including different versions of ICD and DSM) (Häfner et al., 1989). Besides, the findings of early age of onset in men have been replicated in FEP (Häfner et al., 1998a; Larsen, McGlashan, & Moe, 1996), indicating a consistency with the results found in schizophrenia. However, **gender differences in age at onset in FEP have been a controversial issue** because a number of studies have failed to find gender differences (Addington, Addington, & Patten, 1996; Barajas et al., 2007; Eaton, Thara, Federman, Melton, & Liang, 1995; Folnegović & Folnegović-Smalc, 1994; Gangadhar, Panner Selvan, Subbakrishna, & Janakiramaiah, 2002; Naqvi, Khan, & Faizi, 2005; Thorup, Waltoft, Pedersen, Mortensen, & Nordentoft, 2007).

A number of factors, apart from gender, have been shown to influence the age at onset in schizophrenia. Some of these factors reportedly associated with an early onset of illness include: (1) a positive family history for psychosis (Alda et al., 1996; Esteberg, Trotman, Holtzman, Compton, & Walker, 2010); (2) obstetric complications (Rubio-Abadal et al., 2015; Verdoux et al., 1997); (3) poor social premorbid and occupational adjustment (Foerster et al., 1991); (4) premorbid personality disorder (Jablensky & Cole, 1997); (5) being unmarried (Häfner et al., 1993); (6) cannabis use (Large, Sharma, Compton, Slade, & Nielssen, 2011); (7) a more chronic form of the disorder (Vyas, Patel, & Puri, 2011); (8) more severe cognitive deficits (Rajji, Ismail, & Mulsant, 2009); and (9) more neurological soft signs (Biswas, Malhotra, Malhotra & Gupta, 2007). In FEP studies, similar results in patients with an earlier onset of episode have been obtained in the following variables: (1) poor PA (Ballageer, Malla, Machanda, Takhar, & Haricharan, 2005; Joa et al., 2009; Schimmelmann, Conus, Cotton, McGorry, & Lambert, 2007); (2) longer DUP (Ballageer et al., 2005; Joa et al., 2009; Schimmelmann et al., 2007) and (3) more depressive symptoms and a higher level of lifetime suicidal plans or attempts (Joa et al., 2009). These findings support the view that severity of the disease process may be associated with different ages at onset; indeed late adolescence is likely to reflect a critical period in brain development, making it particularly vulnerable for the onset of psychopathology (Paus, Keshavan, & Giedd, 2008).

The variations in the presentation of **adolescent- vs. adult-onset psychosis** may have important implications for designing and delivering treatment to adolescents. It is likely that nonaffective psychosis presenting during adolescence is an earlier and perhaps more severe presentation of the adult disorder, with some variations in symptoms expressed across the spectrum of development and age. It has been suggested that adolescent-onset psychosis is more difficult to diagnose than adult psychotic disorder, that such diagnosis is less stable over time (Mezenes & Milovan, 2000), and that **adolescent onset is associated with greater severity of illness and worse outcome** (Schmidt, Blanz, Dippe, Koppe, & Lay, 1995). In a study focused on examining whether FEP patients with onset during adolescence differ significantly from those with young-adult onset, it was observed that patients with adolescent onset of psychosis were more likely to present with clinical characteristics that portend a poorer outcome (with a higher level of primary negative symptoms, longer delays in treatment, and greater likelihood of displaying bizarre behavior), and may require a different approach to early identification and treatment (Ballageer et al., 2005). A better understanding of age-related differences in psychotic spectrum disorders may help to develop treatment more specifically adapted to the needs of adolescent patients in first-episode services. In a recent study, Amminger et al. (2011) found that individuals with an early onset who received early intervention and treatment had significantly fewer positive symptoms and significantly superior functioning on measures assessing global functioning, social/occupational and community functioning compared to patients with adult-onset disorder treated equally. Their findings suggest that **early detection and specialized treatment for first-episode psychotic patients may specifically improve long-term functional outcome, and to some extent symptomatic outcome** in people with early-onset schizophrenia as compared to adult-onset schizophrenia.

Also, a **differential expression** of the illness has been observed according to age at onset of psychotic spectrum disorders in relation to the emergence and systematization of a few positive symptoms. In the ABC study sample, while positive and negative core symptoms occured at fairly similar rates, paranoid and systematised delusions showed a significant and linear increase from very low rates in the early onset group to very high rates in old age. In contrast, disorders of the self and incoherence of thinking showed a significant linear decrease, from maximum rates in early onset cases to almost zero in late-onset illness (Häfner, Maurer, & an der Heiden, 2013). These authors give a possible interpretation to these findings in terms of developmental psychology. **At an early stage of brain and personality development, pathological processes such as schizophrenia associated with considerable cerebral dysfunction may easily disturb central mental functions in an immature brain**. Lower stages of cognitive development and a not yet stable personality presumably produce a greater number of cognitively poorly elaborated symptoms and signs of mental disorganization. **At a later age, mature brains and stable mental functions are probably less liable to disruption**. In keeping with this hypothesis, schizophrenias with onset in childhood or early adolescence are usually associated with more severe and more basic pathology, such as excessive anxiety, fluctuating disturbances of attention and consciousness, and profound changes in self-perception and perception of others (Eggers, 2011; Remschmidt, 2004). So, the fact that these severe basic syndromes become less frequent with increasing age of onset in schizophrenia might be accounted for by brain maturation and a greater stability of personality. The increased frequency of systematised and paranoid delusions later in life indicates that the disorder is faced with more solid defence mechanisms, which promote reaction patterns typical of that age, e.g. rational processing by way of systematic delusions and externalisation by way of paranoid delusions. With aging there is a stronger tendency to cope by externalization, that is, to explain failures, mishaps or guilt by external factors.

Because of the different social conditions at the beginning of the disorder, the age differences have a great practical impact, especially in terms of the social consequences of the disorder. In a study examining a population-based first-episode sample, Häfner et al. (1998c) observed that, **due to the better social conditions at onset, patients with late onset showed slightly better 5-year social outcomes than early-onset cases**. But age at onset has a different effect on the social course of the disorder. **By the 5-year follow-up after first admission late-onset patients have suffered pronounced social decline** from their previous social statuses, whereas early-onset cases on average have mostly retained their (lower) social statuses. Also, in relation to gender, it is commonly reported that **social course of schizophrenia is less favourable in men than in women** (Häfner et al., 2013). Men develop schizophrenia several years earlier than women, at an age coinciding with the period of greatest social advancement, so their social development might be disrupted to a greater extent. In constrast, women's greater age at onset might permit them to achieve a higher level of social development and, hence, better starting conditions before the illness strikes them. The pronounced difference in the social course of early- and late-onset schizophrenia can thus be attributed to three conditions: (1) if onset occurs at early stages of social development, it usually leads to stagnation at the low social level achieved by that time; (2) late-onset patients have accomplished more social roles and hence, on average, have reached higher levels of social development (they have more to lose as a consequence of the disorder than early-onset patients; nevertheless, late-onset patients usually manage to retain some of the acquired social advantages, so that in their case the disorder mostly has a better social outcome than in early-onset cases); and (3) when onset occurs after retirement age, social outcome will presumably be less affected, because the patients have acquired more inalienable rights and in most cases the occupational-status characteristics can no longer be lost.

3.3.2. Gender differences in FEP

There is increasing evidence that for schizophrenia and related psychotic disorders as for many other phenomena, gender is an important factor to be considered to understand the heterogeneity of these disorders. Gender differences in the clinical expression and outcome of schizophrenia and FEP have long been recognized in the literature on schizophrenia and other psychoses (Abel, Drake, & Goldstein, 2010; Koster, Lajer, Lindhardt, & Rosenbaum, 2008; Leung & Chue, 2000; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012; Seeman, 2012). Thereby, **men and women experience psychosis differently and often require different intervention methods** regarding doses and/or types of medications, staging of interventions and array of treatments offered (Kulkarni et al., 2008; Smith, 2010; Usall et al., 2011). These studies have meant an advance in the adaptation and improvement of therapeutic strategies targeting this population.

In relation to **epidemiological characteristics** of a disorder, these can provide important clues in the search for etiology and are essential in the development of evidence-based treatment models. No gender differences in prevalence of schizophrenia have been found in recent studies (McGrath, Saha, Chant, & Welham, 2008; Perälä et al., 2007; Saha, Chant, Welham, & McGrath, 2005). Nevertheless, the most replicated result of incidence studies is **a higher rate in males vs. females** in patients with schizophrenia or/and schizophrenia-like psychosis (Castle, Wessely, & Murray, 1993; McGrath et al., 2008). In an incidence population study, a meta-analysis by Aleman, Kahn and Selten (2003) confirmed this result, with the men having a higher incidence (ratio 1.42; 95% [CI], 1.30–1.56). It is possible that the stricter the diagnostic criteria for schizophrenia (i.e. age cut-off or a narrower definition of schizophrenia in terms of symptomatology and duration of symptoms), the greater the exclusion for women, resulting in a higher proportion of men diagnosed. However, other authors have attributed this discrepancy in gender differences between incidence and prevalence to clinical variables: a higher suicide rate in men with schizophrenia compared with women (Seeman, 2012) or a higher trend to briefer episodes of psychosis, with more complete resolution, in women (Castagnini & Berrios, 2009).

Regarding **symptom expression**, the study of gender differences has important implications for several reasons. For example, symptom presentation likely plays an important role in determining treatment regimens and understanding gender differences in treatment response. To date, the results in psychosis spectrum disorder studies regarding this area are inconclusive, with studies showing a similar clinical expression of psychosis across gender lines (Barajas et al., 2010; Hayashi, Igarashi, Yamashina, & Suda, 2002; Lindström & Von Knorring, 1994), and others showing gender differences (Cotton et al., 2009; Galderisi, Bucci, Üçok, & Peuskens, 2012; Gur, Petty, Turetsky, & Gur, 1996; Morgan, Castle, & Jablensky, 2008; Szymanski et al., 1995). A number of factors may account for this, including medication status (higher doses of typical antipsychotics contributing to negative symptomatology), diagnostic stringency (use of stricter criteria excluding women with affective symptoms), age at onset (negative symptoms are more prominent in younger men than in younger women) and sampling bias (inadequate sample size or over-representation of men). Nevertheless, the most replicated findings, in samples of patients with psychotic spectrum disorders, suggest that **affective symptoms are more common in women while negative symptoms tend to be more predominant in men**.

In general terms, psychosis spectrum disorder studies analyzing **premorbid and social functioning show better performance in women** (Andia et al., 1995; Cotton et al., 2009; Grossman, Harrow, Rosen, Faull, & Strauss, 2008; Häfner et al., 1993; Usall, Haro, Ochoa, Márquez, & Araya, 2002; Vila-Rodriguez, Ochoa, Autonell, Usall, & Haro, 2011). However, not all studies confirm this finding (Bottlender, Strauß, & Möller, 2010; Galderisi et al., 2012). Methodological issues might explain these discrepancies (i.e. small sample size, lack of sample-gender representativeness or measures used to assess social functioning). In relation to premorbid functioning, most studies in psychotic disorder samples have found gender differences, this being worse in men than in women (Barajas et al., 2010; Morgan et al., 2008; Norman et al., 2005). These

findings have clinical implications because there are suggestions that deficits in social functioning are often predictors of later social functioning (Addington et al., 2008).

Finally, studies analyzing **cognitive function** in patients with psychosis spectrum disorders have reported gender differences on neuropsychological testing (Bozikas et al., 2010; Lewine, Walker, Shurett, Caudle, & Haden, 1996; Purcell, Lewine, Caudle, & Price, 1998; Vaskinn et al., 2011). However, similar to prior findings reported above, these differences have not been tested in all studies (Goldberg, Gold, Torrey & Weinberger, 1995; Moriarty et al., 2001) and their nature is controversial. As indicated previously in other topics, these discrepancies could be partly related to methodological issues (i.e. samples of convenience including not representative male and female patients, analysis not controlling clinical variables, lack of normal comparison group or lack of consensus in measures used). Among studies showing gender differences, the finding most often replicated indicates **higher levels of cognitive functioning in women**.

Then, taking into account gender differences found from the dimensional perspective of psychosis, it would be reasonable to consider different expression of the illness from early phases of psychosis, even before the illness appears. If gender-related factors are equally meaningful over the entire psychosis continuum, it is reasonable to expect that **gender differences could also already be identified in sub-clinical psychosis**. It would then be presumed that the same (continuous) development pattern by gender exists from gestation of psychosis until the psychosis threshold.

To date, only a few studies have focused on the characterization of clinical phenomenology regarding gender in population at high risk of psychosis. Some findings found in the scientific literature regarding **gender differences in high-risk populations** are related to parameters examined above in studies about schizophrenia and related psychotic disorders: incidence, clinical expression, social functioning and cognitive impairment:

- **Epidemiological indicators:** inconsistent results were found regarding conversion to psychosis with **studies showing a greater risk for conversion in men** (Nordentoft et al., 2006; Ziermans, Schothorst, Sprong, & van Engeland, 2011) **and others indicating no gender differences** (Lemos-Giráldez et al., 2009; Walder et al., 2013). The disparity found between these findings, as in the schizophrenia studies, could be due to clinical and/or methodological factors; the lack of consensus among the studies in defining a patient at high risk for psychosis, as well as the lack of differential detection strategies according to gender, are some possible explanations. More studies analyzing gender differences regarding transition to psychosis are needed.
- **Clinical expression:** prior to the expression of full-blown psychosis, **young men were rated as having more severe negative symptoms than women** (Corcoran et al., 2011; Willhite et al., 2008). Men with UHR for psychosis had more 'typical' symptoms of schizophrenia than women. In contrast, other studies of individuals with UHR for psychosis did not find gender differences in the expression of symptoms (Cocchi et al., 2014; Lemos-Giráldez et al., 2009). As mentioned previously, methodological and clinical variables could influence the discrepancy of the results found, as occurs in schizophrenia and FEP studies.
- **Social functioning:** Most studies indicated gender differences in premorbid (Tarbox et al., 2013) and psychosocial functioning (Salokangas et al., 2013b; Walder et al., 2013; Willhite et al., 2008), this **being worse in men**. These results support the continuum hypothesis in the development of psychosis, taking into account a differential expression of social functioning according to gender from premorbid phases, which is worse in men. Recent studies have indicated that **social and role (school/work) functioning are key predictors of conversion among UHR youth** (Cornblatt et al., 2012; Dragt et al., 2011). Therefore, prevention strategies could be improved with a more comprehensive approach that involves developmentally earlier functional deficits. However, it has been suggested that social functioning as a predictor of psychosis onset may be stronger for men than women (Tarbox et al., 2013; Walder et al., 2013; Willhite et al., 2008). So, to understand the early development of psychosis

it is essential to consider sexually differentiated predictors. It may be helpful to improve risk identification using algorithms that take into account the gender variable.

- **Cognitive impairment:** studies examining cognition in those at elevated risk for psychosis have confirmed that **cognitive deficits are already present before the first episode** (Brewer et al., 2006; Hawkins et al., 2008; Seidman et al., 2010). These studies report widespread cognitive deficits intermediate to healthy control and FEP samples. These results suggest the importance of considering sexually differentiated patterns of cognitive decline in prodromal individuals. However, these studies have several methodological limitations (i.e., small samples, lack of power to detect differences, and a limited longitudinal framework, among others) that make it difficult to generalize the results. In this sense more research about cognition functioning is required, also taking into account gender factor from the incipient phases of psychosis. To date, scarce research has been performed in this direction indicating **a differential gender effect that varies by risk status** (i.e. women who convert performed worse on several neurocognitive measures than same-gender subjects who do not convert; however, there were no significant differences between men converters and nonconverters) (Walder, Mittal, Trotman, McMillan, & Walker, 2008).

Table 9 presents a summary of the most relevant findings and their clinical and research implications about gender differences in individuals at high risk of psychosis.

Table 9. Main gender differences in individuals at high risk of psychosis.

Main topic	Conclusion and clinical implications
Transition to psychosis	Inconsistent results were found in relation to transition to psychosis: some studies did not show gender differences and others indicated a greater risk for conversion to psychosis in men. It might be suggested that differential precipitating factors exist according to gender which are involved in conversion to psychosis and their identification should be useful in clinical practice.
Clinical expression	Men at-risk for psychosis have more severe negative symptoms than women before full-blown psychosis, it being more difficult to detect them across current risk criteria for psychosis focused on positive attenuated symptoms. In addition, developing targeted interventions to decrease the severity of negative symptoms during the prodromal phase, more severe in men, would improve the general functioning and quality of life for patients from earlier phases of psychosis.
Social functioning	Men show lower functioning and social support than women before full-blown psychosis. Also, social functioning is a stronger predictor of psychosis onset in men than women. Psychosocial interventions targeted at this population would be helpful to improve the prognosis of the illness.
Cognitive impairment	The limited scientific evidence about cognitive impairment in prodromal phase according to gender has indicated a differential sex effect that varies by risk status. However, the lack of studies does not allow us to generalize from the results. It is necessary to broaden our knowledge in this area and so be able to implement the findings in clinical practice.

In summary, many of the studies analyzed suggest that **differences between men and women in the expression of psychosis extend across a continuum, from the subclinical forms of illness to the debut of psychosis,** mainly in aspects of clinical expression (such as more negative symptoms in men) and social functioning (such as premorbid and psychosocial functioning, worse in men). In light of these results and according to the continuum hypothesis (Van Os et al., 2009), gender-related factors as identified in full-blown psychosis are equally meaningful over the entire psychosis continuum and 'true' gender differences can also be identified in sub-clinical psychosis. However, the small number of studies with high risk of psychosis samples and their significant methodological and clinical limitations do not allow for firm conclusions.

PART II:
EMPIRICAL FRAMEWORK

4. Rationale of the empirical framework:

The early phases of the illness represent an important period, both from a research viewpoint and also in relation to the outcome of the illness and any one individual's future prognosis. Although the first-episode strategy has helped to clarify some important concepts, many questions remain unanswered. What is the relationship if any between risk factors? How do genetic and environmental risk factors interact? Do sencondary prevention programmes work? What are the true or independent predictors of outcome? Which predictors are characteristic of premorbid and prodromal phase? What is the influence of gender along the continuum of psychosis? This thesis attempts to answer some of these questions as detailed below.

This work research, presented as a compendium of publications, is focused **on the characterization of early phases of psychosis, particularly in relation to premorbid and prodromal factors associated with onset of psychosis.** From a continuum hypothesis, the development of full-blown psychosis is already differentially programmed from the previous phases at the onset of illness. In this sense, it is important to accurately characterize the period prior to the onset of psychotic symptoms in patients with psychotic spectrum disorders as this might provide clues to etiology, course and prognosis. However, one of the difficulties found in the scientific literature is related to the characterization and evaluation of the premorbid and prodromal period.

In relation to the premorbid phase, the deficiencies in PA could reflect vulnerability to psychotic symptoms. In the past decade, some studies have already demonstrated the presence of functional changes prior to the start of the prodromic and psychotic phases and found deterioration in the premorbid phase in patients with schizophrenia (Haas & Sweeney, 1992). In a subsequent study, Strous et al. (2004) suggested that prior to the start of acute psychosis, **there are specific precursors reflected in the premorbid functioning, which could explain later manifestation of the disease**. Thus, the premorbid functioning measures could be indicative of increased risk for the development of psychotic illness, which would manifest itself in a subtle form before the appearance of first psychotic symptoms. For this reason, it seems truly important to assess functioning across different age groups to prevent or detect these symptoms. So, a standard scale has been necessary to achieve scientific rigor and comparability between studies and to serve as a common denominator. For this purpose the PAS was created and designed to evaluate the level of functioning in four areas, from a developmental perspective: sociability and withdrawal; peer relationships; ability to function outside the nuclear family; and capacity to form intimate socio-sexual ties. This scale allows assessment of premorbid functioning across different age ranges and detection of possible changes in functioning, in both adult and adolescent patients. Furthermore, it may serve as a possible predictor in patients who could develop psychotic symptoms. This tool has been used in the main scientific research about PA in psychosis and for this reason it is necessary to have a validated version in the Spanish population.

Furthermore, the dimensionality of PA has been a debated issue, with attempts to determine whether PA is a unitary construct or composed of several domains, independent of each other, with differential patterns of deterioration and possible specific correlates. This differentiation would be helpful to know specific predictors in the premorbid phase.

In relation to the prodromal phase, although not every patient reports prodromal symptoms, approximately 80% to 90% of patients with psychotic spectrum disorder have described a variety of subacute symptoms in the months and years preceding psychosis. For this reason, in the last two decades,

great research efforts have been made to develop and test operational criteria based mainly on subthreshold levels of psychotic symptoms (Cornblatt et al., 2003; Klosterkötter et al., 2001; Yung et al., 1998). However, the current high-risk definitions used in the scientific literature continue to generate high false-positive rates, i.e. detecting people who do not develop psychosis over time. In this sense, **having an effective mechanism to detect risk of psychosis could contribute to the development of more appropriate indicated prevention tasks.** To date, there is a lack of consensus on the specific symptoms to include in the definition of the population at risk of psychosis, which focuses almost exclusively on positive symptoms. However, **positive symptoms per se do not make good predictors of psychosis** (Addington et al., 2011). Recent findings suggest that negative symptoms, cognitive impairment and a decline in functioning at baseline (Demjaha, Valmaggia, Stahl, Byrne, McGuire, 2012; Seidman et al., 2010; Valmaggia et al., 2013) are strongly associated with higher risk of transition to psychosis at follow-up. Furthermore, a **combination of potential psychopathological predictors with other risk factors** could help to create a new algorithm to identify who is at risk with accuracy. We still need to know **the predictive capacity of different kinds of prodromal dimensions** involved in the onset and course of the illness. Nevertheless, not only are qualitative criteria (type of prodromal symptoms) important to predict full-blown psychosis, but also quantitative criteria (accumulation of prodromal symptoms) could be important to provide evidence that the development of full-blown psychosis is already programmed from the prodromal phase. These issues are analyzed in some of the items that are part of the compendium publication of this thesis.

In relation to the initial psychotic phase, there is a wide variability of findings in the literature that in part could be attributed to the presumed heterogeneity of the set of disorders which are included in the definition of an FEP. However there are common denominators, which could be helpful to learn in depth how the onset of psychotic illness occurs. So, one part of this research work aims to shed light on two key variables commonly associated with the study of FEP: **age at onset** and **gender differences**. The study of these variables can help to clarify the differential expression of illness in patients with a recent-onset of psychosis and it represents **important factors in the understanding of the manifestation and development of the psychotic spectrum disorders**. Besides, these characteristics should be taken into account to extend our knowledge about the different types of onset of psychosis and they could have implications in intervention strategies, making it possible to maximize the impact of these treatments taking gender and age at onset into account.
Further, from a dimensional approach, age- and gender-related factors are understood as equally meaningful over the entire psychosis continuum. In this sense, the new prospective approaches could benefit from findings in retrospective studies with samples of FEP, considering these variables in the algorithms to detect high-risk population for psychosis.

In summary, if the heterogeneity of the psychotic spectrum begins early, long before the onset of psychosis, it is possible that f**actors influencing the premorbid and prodromal phases might be understood as risk factors modulating the expression of psychotic symptoms**. Then, broadening our knowledge regarding the characterisation of the period prior to the onset of overt psychotic symptoms might contribute to uncovering clues to etiology, course and prognosis of psychotic spectrum disorders. Thus, future preventive efforts may be critical in the premorbid and prodromal periods to minimise or prevent further impairments that have already begun to develop by the time of symptom onset. This new approach, based on incipient phases of psychosis, entails a number of advantages over previous studies with chronic samples, such as the absence of confounding effects of variables such as pharmacological treatment and factors associated with chronicity, among others. This type of research allows monitoring and evaluating the prognosis of these patients and adapting the therapeutic project of patients to their specific characteristics and needs.

Thus, **the present thesis has clear preventive implications**. It seeks to broaden our knowledge about how patients with an FEP express the disease in its earlier stages as well as what premorbid and prodromal factors are associated with a poor outcome at the onset of psychosis.

The **specific aims** of this thesis are:

- ✓ To examine the psychometric propierties of the Spanish version of the PAS (PAS-S)
- ✓ To study the dimensional structure of PAS as associated factors with clinical, social and cognitive outcome
- ✓ To assess the predictive capacity of the prodromal symptoms to the development of an FEP
- ✓ To describe gender differences in psychosis from a dimensional approach
- ✓ To analyze clinical differences according to the onset of psychosis

To accomplish these objectives, **a sample of consecutive patients with recent-onset FEP** was examined. The patients were recruited from adult mental health services (AMHS) at Parc Sanitari Sant Joan de Déu and from the child and adolescent mental health services (CAMHS) at the Hospital San Joan de Déu, either at a hospital or at community psychiatric services belonging to the metropolitan area and outskirts of Barcelona, Spain. Patients were entered into the study if they: (1) had two or more psychotic symptoms (delusions, hallucinations, disorganised speech, catatonic or disorganised behaviour, and negative symptoms) as indicated in criterion A of schizophrenia disorder (DSM-IV-TR; APA, 2000); (2) were aged between 7 and 65; (3) had had an initial psychiatric visit at any centre participating in the study; (4) had had initial contact with the mental health services within the previous 6 months; and (5) had experienced onset of psychotic symptoms less than a year earlier. Patients were excluded if they: (1) had been diagnosed with intellectual disabilities (premorbid IQ<70), head injury, dementia or any organic psychoses; or (2) had an inadequate command of Spanish or Catalan. The set of diagnoses that include the concept of FEP is as follows: schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; substance-induced psychotic disorder; bipolar disorder with psychotic features; major depression with psychotic features; and psychotic disorder not otherwise specified. In some of the studies of this thesis patients with chronic schizophrenia are included in the final sample (Study 1 and Study 2). The inclusion criteria for the chronic schizophrenia subsample were: (a) primary diagnosis of schizophrenia (DSM-IV-TR criteria) (APA, 2000); (b) age between 18 and 65; (c) living in the catchment areas of the participating community mental health centres; and (d) having had at least one outpatient visit during the 6 months prior to the beginning of the study.

This thesis is composed of six articles, five of which are published (or under review for publication) in JCR indexed journals. Each of them describes one empirical study focused on the different initial phases of psychotic illness, with the patients with a recent-onset of psychosis being the main target population of interest.

Thus, in relation to the **premorbid phase**:

- **Study 1** shows the psychometric properties of the Spanish version of the PAS (PAS-S). It was administered to individuals experiencing a FEP in adult and adolescent patients and people with schizophrenia who have chronic illness course.
- Examining the same sample, **study 2** analyzes the factor model of PA and the course of its domains. Also this study shows the associations between PA domains and clinical, social and cognitive

correlates after the onset of psychosis and describes similarities and differences in relation to the course and correlates of PA domains in two subsamples (FEP and chronic schizophrenia).

In relation to the **prodromal phase**:

- **Study 3** shows the characterization of the prodromal phase through analyzing the frequency of the experienced prodromal symptoms, as well as studying the relationship between the number and nature of prodromal symptoms and the severity of psychopathology at the onset of FEP. Also, this study assesses the predictive capacity of the prodromal symptoms to the development at the onset of psychosis.
- **Study 4** summarizes the findings in the scientific literature regarding gender differences in high-risk populations, taking into account parameters studied in populations with schizophrenia and other psychotic disorders, such as incidence, clinical expression, duration of untreated illness (DUI), social functioning, and cognitive impairment prior to full-blown psychosis development.

In relation to the **initial psychotic phase**:

- **Study 5** describes gender differences in a group of patients with FEP in different aspects: socio-demographic features, characteristics of the phases prior to disease onset (premorbid and prodromic periods), clinical manifestation of psychotic symptoms and possible corresponding cognitive alterations after disease onset, using the age at onset of first psychotic episode as a control variable.
- **Study 6** assesses whether there are differences in the age at onset of FEP by gender. Also, this study examines men and women separately, to investigate whether there are differences in the type and severity of psychotic symptoms depending on age at onset of FEP.

These studies were carried out in public mental health centers supported by Fondo de Investigaciones Sanitarias (FIS PI05/1115), Instituto de Salud Carlos III (Spain), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) (Spain), Caja Navarra (Spain) and Fundació Marató de TV3 (Catalonia, Spain).

The articles of this compendium can be found in two sections: in the next section (5. Empirical studies) are included the articles (study 1, study 2, study 4 and study 5) which are published in scientific journals with impact factor and in the annex section are included the articles published in scientific journals without impact factor (study 6) or under review (study 3). In these studies, a detailed description of specific aspects about method and results are shown. The main conclusions, clinical implications and methodological limitations are included in part III of this research work.

⇒ National and international research stays:

The author of this thesis has broadened her knowledge about FEP population, in both clinical and research domains, during two research stays:

- ✓ One of them at the **Birmingham Early Intervention Service (EIS)** of Birmingham & Solihull Mental Health NHS Foundation Trust and at the **School of Psychology, University of Birmingham** (Birmingham, United Kingdom), supervised by Prof. Max Birchwood and Prof. Chris Jackson, and financied by Fondo de Investigación Sanitaria del Instituto Carlos III, Ministerio de Investigación e Innovación (Spain). This stay has allowed improvement in methodological issues of this research work and familiarization with new research projects (e.g. “A National Evaluation of Early Intervention for Psychosis Services: DUP, Service Engagement and Outcome. The National EDEN Project.”), as well as

the clinical implications of their findings (e.g. the development and impact of EIS in the West Midlands). Also, it has allowed extending knowledge about clinical issues by carrying out interviews and monitoring of patients (applying assessment protocols and establishing individualized therapeutic project) and writing clinical reports. The author of this thesis participated in the specific clinical and research activities of two young peoples' sevices for 6 months: a) the EIS - Birmingham East North team (BEN team), who care for young adults experiencing an early episode of untreated psychosis throughout the 'critical period' (on average the first three years). This service aims to treat and support young people in order to reduce the debilitating effects of psychotic illness by reducing hospitalisation and symptoms, improving service users' social functioning (especially their employment and employability, quality of life, service satisfaction), and assisting with their recovery and aspirations; and b) the Early Detection and Intervention Team (ED:IT team), who care for young people who are in distress and considered at UHR of developing an FEP. The aims of this service are to prevent or delay the onset of psychosis and reduce the DUP across Birmingham.

- ✓ Another one of the stays was at the **Department of Research of the Adolescent Psychiatry Unit, University Hospital Gregorio Marañón** (Madrid, Spain), supervised by Dr. Celso Arango, and financied by Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). It is a reference center in the study about FEP of early onset with broad experience with regard to clinical, structural and brain functioning variables, treatment, metabolism and neurocognition. During the stay, the author of this thesis carried out clinical activities related to monitoring tasks of inpatient clinical cases supervised by clinicians of the Adolescent Psychiatry Unit. Likewise, these activities were combined with the following research tasks: training activities in neurocognitive batteries and clinical diagnosis tools, critical analysis of articles and participation in national and multicentric research projects financed by the Red Nacional de Primeros Episodios Psicóticos de Inicio en la Adolescencia (RETIC G03/032), carrying out legwork tasks, data analysis, wording and review of research articles of different research projects in progress. This stay enabled the author of this thesis to improve her knowledge in the field of early-onset psychosis.

5. Empirical studies:

5.1. About premorbid phase:

STUDY 1: Spanish validation of the Premorbid Adjustment Scale (PAS-S)

A. Barajas[a,b,c,d,e], S. Ochoa[b], I. Baños[b,d], M. Dolz[c], V. Villalta-Gil[b,d,f], M. Vilaplana[b], J. Autonell[b], B. Sánchez[c], J.A. Cervilla[b,g], A. Foix[b], J.E. Obiols[e], J.M. Haro[b], GENIPE group[1], J. Usall[b]

[a] Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain
[b] Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain
[c] Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[d] Fundació Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[e] Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
[f] Departament de Psiquiatria i Medicina Legal. Facultat de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
[g] Departamento de Medicina legal, Toxicología y Psiquiatría, Instituto de Neurociencias, Facultad de Medicina, Universidad Granada, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Granada, Spain

[1] GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, De Miquel L, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

Comprehensive Psychiatry 2013; 54: 187 –194

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Comprehensive Psychiatry 54 (2013) 187–194

Comprehensive PSYCHIATRY

www.elsevier.com/locate/comppsych

Spanish validation of the Premorbid Adjustment Scale (PAS-S)

Ana Barajas[a,b,c,d,e,*], Susana Ochoa[b,*], Iris Baños[b,d], Montse Dolz[c], Victoria Villalta-Gil[b,d,f], Miriam Vilaplana[b], Jaume Autonell[b], Bernardo Sánchez[c], Jorge A. Cervilla[b,g], Alexandrina Foix[b], Jordi E. Obiols[e], Josep Maria Haro[b] GENIPE group[1], Judith Usall[b]

[a]*Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain*
[b]*Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain*
[c]*Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain*
[d]*Fundació Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain*
[e]*Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain*
[f]*Departament de Psiquiatria i Medicina Legal. Facultat de Medicina. Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain*
[g]*Departamento de Medicina legal, Toxicología y Psiquiatría, Instituto de Neurociencias, Facultad de Medicina, Universidad Granada, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Granada, Spain*

Abstract

Background: The Premorbid Adjustment Scale (PAS) has been the most widely used scale to quantify premorbid status in schizophrenia, coming to be regarded as the gold standard of retrospective assessment instruments.
Aims: To examine the psychometric properties of the Spanish version of the PAS (PAS-S).
Method: Retrospective study of 140 individuals experiencing a first episode of psychosis (n=77) and individuals who have schizophrenia (n=63), both adult and adolescent patients. Data were collected through a socio-demographic questionnaire and a battery of instruments which includes the following scales: PAS-S, PANSS, LSP, GAF and DAS-sv. The Cronbach's alpha was performed to assess the internal consistency of PAS-S. Pearson's correlations were performed to assess the convergent and discriminant validity.
Results: The Cronbach's alpha of the PAS-S scale was 0.85. The correlation between social PAS-S and total PAS-S was 0.85 ($p<0.001$); while for academic PAS-S and total PAS-S it was 0.53 ($p<0.001$). Significant correlations were observed between all the scores of each age period evaluated across the PAS-S scale, with a significance value less than 0.001. There was a relationship between negative symptoms and social PAS-S (0.20, $p<0.05$) and total PAS-S (0.22, $p<0.05$), but not with academic PAS-S. However, there was a correlation between academic PAS-S and general subscale of the PANSS (0.19, $p<0.05$). Social PAS-S was related to disability measures (DAS-sv); and academic PAS-S showed discriminant validity with most of the variables of social functioning. PAS-S did not show association with the total LSP scale (discriminant validity).
Conclusion: The Spanish version of the Premorbid Adjustment Scale showed appropriate psychometric properties in patients experiencing a first episode of psychosis and who have a chronic evolution of the illness. Moreover, each domain of the PAS-S (social and academic premorbid functioning) showed a differential relationship to other characteristics such as psychotic symptoms, disability or social functioning after onset of illness.

* Corresponding author. Parc Sanitari Sant Joan de Déu. CIBERSAM, C/ Antoni Pujades 42. CP 08830, Sant Boi de Llobregat, Spain. Tel.: +34 93 640 63 50; fax: +34 93 630 53 19.
E-mail addresses: ana.barajas@chmcorts.com (A. Barajas), sochoa@pssjd.org (S. Ochoa).

[1] GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, De Miquel L, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

0010-440X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.comppsych.2012.07.007

1. Introduction

There is consistent evidence showing that a large number of people affected by schizophrenia spectrum disorders show poor adjustment prior to initiation of the illness. Poor premorbid functioning has been associated with more severe negative symptoms especially at the onset of illness [1], more severe neuropsychological impairment [2,3], poorer treatment response, more extrapyramidal symptoms, the need for higher doses of antipsychotics [4], and more hospital stays [5]. Therefore, it is important to accurately characterize the period prior to the onset of psychotic symptoms in patients with psychotic spectrum disorders as it might provide clues to etiology, course and prognosis. However, one of the difficulties found in the scientific literature is related to the definition and evaluation of the premorbid period.

Premorbid adjustment (PA) has classically been defined as psychosocial functioning in the areas of education, occupation, social and interpersonal relationships before evidence of characteristic positive symptomatology [6]. However, it is possible that negative symptoms may predate positive symptoms and the onset of psychotic illness, so it would therefore be marked by negative rather than by positive symptoms [7]. Furthermore, psychosocial functioning comprises many components; it is difficult to define and therefore difficult to assess.

In 1941, Wittman developed the Elgin Prognostic Scale [8], the first major scale that quantified the dimensions of premorbid function. Since then, several scales have been created to measure this period such as: the Phillips Scale [9]; the Asocial Adjustment Scale [10]; the Premorbid Adjustment Survey [11]; and the Kantor Scale [12]. However, a standard scale was necessary to achieve scientific rigor and comparability between studies and to serve as a common denominator. For this purpose the Premorbid Adjustment Scale (PAS) was created, developed by Cannon-Spoor et al [6]. This scale compiles original, adopted and modified items from three past scales (the Phillips Scale; the Premorbid Social Adjustment Scale; and the Elgin Scale) and was developed as a research instrument. The PAS is designed to evaluate the level of functioning in four areas, from a developmental perspective: sociability and withdrawal; peer relationships; ability to function outside the nuclear family; and capacity to form intimate socio-sexual ties. The PAS includes an overall section that assesses the best level of functioning achieved by the individual, as well as characteristics of illness onset and other general information. According to the above definition of PA, a poor PA is understood as the deterioration in individual adjustment in these areas and, according to the evaluation tool, the Premorbid Adjustment Scale (PAS), it includes a 6-month period before the appearance of psychotic symptoms, or 6-months before the first psychiatric hospital admission or psychiatric contact, or 6-months before evidence of characteristic florid psychotic symptomatology [6].

In the last decade, in an attempt to study the question more closely, there have been a number of studies aimed at analyzing PA as a non-unitary construct, suggesting that PA could be divided into two wide domains which correspond to the social-academic differentiation. The importance of distinguishing between these domains and examining them at each age level, has clearly been demonstrated by the significant differences in patterns of academic and social deterioration: premorbid academic functioning is particularly susceptible to pronounced deterioration, most notably in later adolescence as schizophrenia onset becomes imminent [13-15]. However, an accelerated deterioration in social domain occurs already in childhood, especially in schizophrenia subtype with predominantly negative symptoms [15]. Additionally, prior research has demonstrated different correlates for both domains, premorbid social functioning is more strongly associated with symptom variables, specifically to higher severity of negative symptoms [14-17], while academic functioning is associated with intellectual and neurocognitive functioning [13-16,18]. Thereby, distinguishing between these two premorbid domains may be theoretically important because of potential differences in incidence rates and deterioration courses.

The PAS has been the most widely used scale to quantify premorbid status in patients with a first psychotic episode [7,14,18] and individuals who have a chronic course of illness [13,15], which provides support to validate their use in both populations, coming to be regarded as the gold standard for retrospective approaches. However, it is limited in its scope, as it assesses psychosocial functioning while neglecting cognitive ability.

Despite its widespread use in research, relatively little is known about the reliability and validity of the instrument. To date, the PAS has been formally translated for use in research programs in Poland [19], Norway [20], Germany [21], Spain (Mexican version) [22] and Spain [23], but it has only been validated in the German [21], Israeli [24], and Mexican [22] populations.

The purpose of the current study was to translate and back-translate the PAS and to examine the psychometric properties of the Spanish version of the PAS-S. We therefore administered the PAS-S to individuals experiencing a first episode of psychosis and people with schizophrenia who have chronic illness course, both in adult and adolescent patients.

2. Method

2.1. Sample

Our sample was composed of people experiencing a first psychotic episode and people with schizophrenia. The patients with a first psychotic episode were included consecutively as they arrived to the adult mental health services at the *Parc Sanitari Sant Joan de Déu* or the child and adolescent mental health services at the *Hospital Sant*

Joan de Déu, either in hospital or community psychiatric services. The patients with schizophrenia were randomly selected from a computerized register of five Community Mental Health Centers (CMHC) belonging to the *Parc Sanitari Sant Joan de Déu*. All the participating centres are part of the metropolitan area and outskirts of Barcelona, encompassing a reference population of approximately 1,000,000 people.

The inclusion criteria for people experiencing a first psychotic episode were: two or more psychotic symptoms (delusions, hallucinations, disorganized speech, catatonic or disorganized behavior and negative symptoms); aged between 7 and 65 years; first psychiatric visit to any centre participating in the study; less than 6 months since first contact with mental health services; and less than a year of symptom evolution. The set of diagnoses that includes the concept of first psychotic episode are the following: schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; substance-induced psychotic disorder; bipolar disorder with psychotic features; major depression with psychotic features; and psychotic disorder not otherwise specified. The inclusion criteria for people with schizophrenia were: (a) primary diagnosis of schizophrenia (DSM-IV-TR criteria) [25]; (b) age between 18 and 65 years; (c) to live in the catchment areas of the participating CMHC; and (d) to at least have received one outpatient visit during the 6 months previous to the beginning of the study. Patients diagnosed with intellectual disability, cranioencephalic trauma or dementia, were excluded from the study.

All individuals selected were informed of the objectives and methodology of this study by their psychiatrist or researcher and they signed the required informed consent. In cases where the patients were minors, informed consent was obtained from their parents or caregivers. The study design was approved by the Ethical and Research Committee of the *Parc Sanitari Sant Joan de Déu* and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. Instruments

General s*ociodemographic characteristics* of the sample were collected, such as gender, marital status, occupational status, diagnosis, and age (Table 1). Diagnoses were established according to DSM-IV-TR criteria [25] assessed by an experienced psychiatrist. Consensus diagnoses were established with lead researchers (SO, JA, JMH) in those cases where presence or absence of psychotic spectrum disorders was in doubt.

Other information was obtained from the following set of psychometric instruments:

- The *Premorbid Adjustment Scale-Spanish (PAS-S)* [6] assesses the degree to which a person has successfully attained certain developmental goals at various life stages preceding the initial onset of psychosis symptoms. Thereby, functioning is assessed across four age periods or subscales: childhood (up to 11 years), early adolescence (12-15 years), late adolescence (16-18 years) and adulthood (19 years and above), across five major psychosocial domains: sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and social-sexual adjustment. Socio-sexual functioning is not included as a psychological domain during the childhood period, as well as scholastic performance and adaptation to school are not measured during the adulthood period. In addition to the 4 developmental subscales, the PAS-S also includes a section composed of 9 general items relating to educational level, the functioning achieved by the individual in school or work before onset of psychosis, as well as the establishment of independence, level of overall functioning, personal and social adaptation, degree of interest in life and energy level of the individual. The PAS-S scale includes 26-item which have a scoring range from 0 to 6, where "0" denotes normal adjustment and "6" severe impairment. The rater selects the number that corresponds most closely to the descriptive phrase nearest it. Not every aspect included in a descriptive phrase is necessary for the rating. The ratings received for each item in a subscale are summed and expressed as total obtained score. Scores for each of the subscales are calculated by dividing the total obtained score by the total possible score for that subscale. The possible score indicates the highest score obtainable by adding the maximum score for all items completed. The overall PAS-S score is calculated by averaging the scores obtained on each of the developmental subscales and on the general section. Ratings for both the subscales and the overall PAS-S score are expressed as decimal point numbers ranging from 0.0 to 1.0, where higher scores represented lower levels of premorbid adjustment. In this study we did not consider the general and adult subscales to calculate the overall PAS-S score because a significant number of our patients were under 18 years of age; the adult subscale not is relevant for these patients, and likewise several items on the general subscale either did not apply or were inappropriate for these young people (e.g. establishment of independence). Moreover, the general subscale is weighted more heavily in the overall score for young patients who have an early age of illness onset. This is because fewer developmental subscales can be completed in these patients, in relation to the age at onset of psychotic symptoms [7]. By another hand, consistent with past findings [16,18], which confirmed the existence of two factors, one reflecting academic adjustment (scholastic performance and adaptation to school) and the second reflecting more

general social adjustment (sociability and withdrawal; peer relationships and social–sexual adjustment), total average scores for these domains were calculated taking into account three age periods: childhood, early adolescence and late adolescence. Information on premorbid adjustment was gathered by a semi-structured interview performed by two researchers (licensed psychologists, AB and IB), who were trained to reliably administer the instrument. Also, PAS-S was completed using all available data, including clinical history data and interviews with patients and relatives. The scale adaptation methodology used was that of the translation procedure and transcultural adaptation. In this study, the version by Mastrigt and Addington [7] was chosen to be translated and adapted into Spanish, which includes the following modifications: a) minor changes which included definitions of some of the terms and anchors that enable to make better objective and reliable assessments of premorbid function; b) both homosexual and heterosexual relationships are scored equally (item 3 in the adulthood subscale; c) the end of the premorbid period is defined as 1 year before the onset of the positive psychotic symptoms, instead of the period ending 6 months before illness onset, indicated in the original version. Moreover, PAS-S included some other modifications based on cultural considerations: a) the item "Education", included in the general subscale, was adapted to the current Spanish education system; b) both married or living with regular partner are scored equally (item 3 in the adulthood subscale); c) the item "Establishment of independence", included in the general subscale, was not rated in patients under 18 years. The Mastrigt and Addington version [7] was translated by a bilingual translator (native Anglo-Saxon linguist with experience in the translation of biomedical texts). Thereafter, the translations were discussed with two of the investigators/psychologists (SO, AB) until reaching a consensus.An adaptation of the Spanish version of the Premorbid Adjustment Scale (PAS-S) may be consulted at http://cibersam.isp.ndsite.net/opencms/opencms/system/modules/es.oneclick.cibersambi/elements/jsp/busqueda/ficha.jsp?banner=bannerbusqueda.jpg&instrumento=213

- *Positive and Negative Syndrome Scale (PANSS)* [26], translated and validated in Spanish population [27]. The PANSS was developed in an attempt to provide a more comprehensive assessment of the symptoms of schizophrenia. It is widely used in clinical and research settings and is regarded as a reliable means of symptom assessment. This scale is the most widely used to determine levels of positive and negative psychotic symptoms. It includes 30 items which are divided into 3 subscales; positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items). PANSS rates may vary, according to the severity of symptoms, between 1 = absence of symptom and 7 = extreme presentation, with higher scores indicating higher psychopathology. Summary scores are obtained for each subscale (positive, negative and general psychopathology) and a total summary score can be obtained from the three subscales to rate global severity.

- *Global Assessment of Functioning Scale (GAF)* [28] is used to measure overall functioning (clinical/social), where 1 represents severe dysfunction and 100 represents good functioning. The GAF is a single-item rating of the lowest level of recent functioning which includes brief anchors at 10-point intervals. Higher scores indicate better functioning.

- The Spanish version of the *Life Skills Profile (LSP)* [29] is used to assess social functioning in situations and tasks of everyday life in the previous month. This questionnaire consists of 39 items. Each item is scored on a 4-point ordinal rating (from: 1, no difficulty to 4, extreme difficulty). A higher score means greater disability and worse functioning.

- The *Disability Assessment Schedule (DAS-sv)*, short version [30], translated and validated in Spanish population [31]. The DAS-sv is a semi-structured interview with an informant and with the patient to elicit responses to a number of questions over the last month in four areas of functioning: self care, occupation, family and social disability. Guiding questions and descriptions of anchor points for the assessment lead to the rating of a dysfunction on a six points scale from: 0, no dysfunction to 5, maximum dysfunction. Ratings are based on clinical judgment as result of different sources of information. A higher score means greater disability and worse functioning.

2.3. Statistical analysis

The Cronbach's alpha was performed to assess the internal consistency of PAS-S and subscales PAS-S. Due to the reduced number of items of each subscale, Cronbach's alphas of childhood (4 items), early adolescence (5 items) and late adolescence (5 items) subscales are compared to the Cronbach's alpha of total scale (14 items) using the Spearman-Brown prophecy formula. Thereby, it is possible to estimate the subscales' reliability in case that they were extended to 14 items, assuming that added items are parallels with current items.

Pearson's correlations were performed between the two domains of the PAS-S and with the total scale. In order to assess the convergent validity, a Pearson's correlation analysis between the PANSS and PAS-S was performed. In order to

explore the discriminant validity, a Pearson's correlation analysis between the LSP, DAS and GAF was performed. A linear regression analysis was carried out to assess the predictivity of PAS-S for the present symptoms (PANSS).

All the analyses were carried out using the SPSS statistical software package (version 17.0).

3. Results

A total of 140 people were assessed. 55% of the sample (n=77) was composed of people experiencing a first psychotic episode and the rest were people with schizophrenia (n=63, 45%). In the first-episode psychosis, the distribution of the subsample by diagnoses are the following: schizophrenia (n=10; 13.2%); schizophreniform disorder (n=13; 17.1%); schizoaffective disorder (n=1; 1.3%); brief psychotic disorder (n=1; 1.3%); substance-induced psychotic disorder (n=3; 3.9%); bipolar disorder with psychotic features (n=12; 15.8%); major depression with psychotic features (n=9; 11.8%); and psychotic disorder not otherwise specified (n=27; 35.5%). Table 1 describes the socio-demographic characteristics of the sample separately for each population group and for total sample.

Descriptive characteristics of the PAS-S subscales for first-episode psychosis group and schizophrenia group, as well as for overall sample, are shown in Table 2. In all cases, scores increased numerically (indicating worsening premorbid functioning) across the childhood, early adolescence, and late adolescence age periods. Regarding the data obtained from PAS-S factors, higher scores are found in academic PAS-S, in each population group analyzed. Similar results are obtained in total PAS-S when the sample is analyzed separately or jointly.

The Cronbach's alpha of the PAS-S scale, excluding the adult and general subscale items, was 0.85.

Table 1
Socio-demographic characteristics of the sample.

	FEP (n=77) n (%)	SCH (n=63) n (%)	Total sample (n=140) n (%)
Gender			
Male	42 (54.5)	42 (66.7)	84 (60.0)
Female	35 (45.5)	21 (33.3)	56 (40.0)
Marital status			
Single	70 (90.9)	51 (81.0)	121 (86.4)
Married	5 (6.5)	7 (11.1)	12 (8.6)
Other	2 (2.6)	5 (7.9)	7 (5.0)
Occupational status			
Active	27 (36.0)	12 (20.0)	39 (28.9)
Student	39 (52.0)	2 (3.3)	41 (30.4)
Domestic work	2 (2.7)	1 (1.7)	3 (2.2)
Incapacity	6 (8.0)	29 (48.3)	35 (25.9)
Other	1 (1.3)	16 (26.7)	17 (12.6)
Age (mean, SD)	20.44 (6.74)	39.21 (11.68)	28.89 (13.17)

FEP: First-episode psychosis; SCH: Schizophrenia; n: number of patients; SD: standard deviation.

Table 2
Descriptive statistics for the PAS-S subscales and PAS-S factors (mean, SD)*.

	FEP	SCH	Total sample
Childhood subscale	0.26 (0.183)	0.27 (0.184)	0.26 (0.183)
Early adolescence subscale	0.31 (0.167)	0.28 (0.184)	0.30 (0.175)
Late adolescence subscale	0.36 (0.198)	0.30 (0.215)	0.33 (0.207)
Adulthood subscale	0.33 (0.233)	0.37 (0.224)	0.35 (0.228)
General subscale	0.37 (0.195)	0.41 (0.176)	0.39 (0.188)
Social PAS-S	0.26 (0.220)	0.27 (0.202)	0.26 (0.211)
Academic PAS-S	0.42 (0.194)	0.34 (0.206)	0.39 (0.202)
Total PAS-S score	0.33 (0.155)	0.33 (0.151)	0.33 (0.153)

PAS-S: Premorbid Adjustment Scale-Spanish; SD: standard deviation; FEP: First-episode psychosis; SCH: schizophrenia.

* Higher scores indicate lower levels of premorbid adjustment (score range: from 0.0 to 1.0).

The Cronbach's alpha for the childhood subscale was 0.69; for the early adolescence subscale it was 0.68; and for the late adolescence subscale it was 0.68. Values higher in internal consistency were obtained when Spearman Brown formula was applied in these three subscales: childhood subscale (0.89); early adolescence (α=0.89); late adolescence (α=0.91). Internal consistency data were also calculated for the adult subscale (α=0.90) and general subscale (α=0.75).

Moreover, Cronbach's alpha coefficients are also obtained to PAS-S factors: social PAS-S (α=0.89) and academic PAS-S (α=0.84). Similar results to Cronbach's alpha of the PAS-S scale were achieved in both domains. When Spearman Brown correction was applied to these coefficients, higher values were obtained: social PAS-S (α=0.93); academic PAS-S (α=0.92).

Different levels of association between the PAS-S factors and total PAS-S were found. The correlation between social PAS-S and total PAS-S was very high ($r=0.85$, $p<0.001$); while for academic PAS-S and total PAS-S it was moderated ($r=0.53$, $p<0.001$). The correlation between academic PAS-S and social PAS-S was 0.22 ($p<0.01$).

In relation to the results obtained through of correlation analysis between the scores of each age period evaluated using the PAS-S scale, statistically significant correlations were observed between all measures, with a significance value less than 0.001. Scores in consecutive age periods (i.e., childhood and early adolescence (r=0.646), and early adolescence and late adolescence (r=0,567)) were more strongly correlated than those in the non-consecutive age periods (i.e., childhood and late adolescence (r=0.328)). Correlation coefficients between childhood, early adolescence, late adolescence and adulthood subscales ranged from r=0.328 and r=0.646.

In relation to convergent validity between symptoms and premorbid social adjustment, there was a relationship between negative symptoms and premorbid social adjustment ($r=0.20$, $p<0.05$) and total PAS-S ($r=0.22$, $p<0.05$). There was no relationship between positive symptoms and PAS-S (discriminant validity). Moreover, there was a correlation between academic PAS-S and general subscale of the PANSS ($r=0.19$, $p<0.05$) (Table 3). In the linear

Table 3
Convergent and discriminant validity between PAS-S and clinical and social functioning (r).

	Social PAS-S	Academic PAS-S	Total PAS-S
PANSS scale			
Positive PANSS	−0.059	0.159	−0.093
Negative PANSS	0.199*	−0.009	0.221*
General PANSS	0.154	0.188*	0.101
DAS scale			
Personal care DAS	0.185*	0.188*	0.294***
Occupational functioning DAS	0.238**	0.172	0.233**
Family functioning DAS	0.094	0.040	0.205*
Social functioning DAS	0.258***	0.000	0.257***
GAF scale	−0.124	−0.209*	−0.121
Total LSP score	−0.091	0.186	−0.056

PAS-S: Premorbid Adjustment Scale-Spanish; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning Scale; DAS: Disability Assessment Schedule; LSP: Life Skills Profile; r: Pearson's correlation coefficient.

* $p<0.05$.
** $p<0.01$.
*** $p<0.005$.

regression analysis, only social PAS-S (beta=0.17; $p<0.016$) and age (beta=8.54; $p=0.001$) predicted negative PANSS (adjusted $r^2=0.11$) ($F=8.17$; $p<0.001$). Neither social PAS-S nor academic PAS-S predicted positive or general symptoms.

Convergent validity was shown between total PAS-S and all DAS subscales. Social PAS-S was related to personal care disability, occupational disability and social functioning disability. Academic PAS-S showed discriminant validity with most of the variables of social functioning, it was only correlated with personal care disability and overall functioning (GAF) ($p<0.05$-0.001). PAS-S not showed association with total LSP scale (discriminant validity) (Table 3).

4. Discussion

The current study, in line with those by previous authors [7,21,24] supports the validity and use of the PAS-S in the Spanish population, as it obtains good psychometric properties. In our sample, using Cronbach's alpha, the estimated reliability for the scale and subscales was between 0.67 and 0.90. The childhood and adolescence subscales obtained the lowest scores. It could be due to the reduced number of items that make up each subscale. Applying the Spearman Brown formula to correct the effect produced by item reduction, higher results were obtained in all PAS-S subscales compared to the total PAS-S scale. In the German validation study [21], internal consistency scores were between 0.81 and 0.93, with the lowest score in the early adolescence subscale. In the Israeli validation study [24], results on reliability demonstrated Cronbach's alpha scores between 0.72 and 0.79 for the childhood and adolescence subscales. Lastly, in the Mexican validation study [22], the internal consistency (Cronbach's alpha) of the instrument was 0.76.

Over the last decade, premorbid functioning has not been considered a unitary construct, but as one that can be divided into at least two distinct domains, namely academic and social functioning. For this reason, we calculated the Cronbach's alpha coefficients separately, for both academic and social domains, given that heterogeneity of content item artificially reduces alpha coefficient. Compared to total PAS-S, higher scores in internal consistency were found in the PAS-S factors, indicating that the included items in each domain were assessing the same construct. A study conducted by Allen et al. [16] found that the correlation between two domains was 0.31, suggesting that they share a relatively small proportion of variance and, hence, premorbid adjustment could be considered multidimensional. In our study, the correlation between different domains was 0.23, so these domains could be considered independently. Furthermore, previous studies suggest that the social and academic domains are associated with different clinical variables [14,16].

We found a higher association between the social domain and total PAS-S than between the academic domain and total PAS-S. This could be due to the different number of items in each domain: the social domain is calculated through 8 items related to sociability and withdrawal, peer relationships and social-sexual adjustment. However, the academic domain is only represented by 6 items related to scholastic performance and adaptation to school. The academic domain is more poorly represented compared to the social domain in terms of the total PAS-S score.

As regards associations between subscales, we analyzed the correlations between the PAS-S subscales which assess premorbid adjustment throughout the patient's life (excluding the general section). The results showed predominantly moderate correlations between subscales, with the lowest score between childhood and late adolescence subscales and the highest score between childhood and early adolescence subscales. Monte et al. [14] showed results in the same direction, although the values of the correlation coefficients were slightly higher. In the German validation study [21], higher scores were obtained: the lowest score was between childhood and adulthood subscales and the highest score was between early and late adolescence subscales.

Consistent with several previous reports [1,14,18,32], we found overall premorbid adjustment to be related to the amount of negative symptoms at follow-up after onset of illness. Indeed, premorbid social functioning was associated to negative psychotic symptoms and was a good predictor of this psychopathological dimension at follow-up. Preventive interventions designed to target negative symptoms are indicated in adolescents with prominent deterioration in the social domain.

Likewise, following with the results about the convergent validity of the PAS-S, our analysis showed associations between social and total PAS-S with disability. The

association between poor premorbid functioning (especially in the area of social relationships) and poor outcome has been demonstrated by a large number of controlled studies thirty years ago. Currently, similar results have been found in other studies [14], so that premorbid social functioning was associated with the poorer social engagement aspect of social functioning. In this way, deficiencies in premorbid adjustment could reflect vulnerability to psychotic symptoms, as has been postulated by the neurodevelopment theory: non-specific functional deficits which are nevertheless significant could emerge prior to the start of the disease. For this reason, a large number of studies have aimed at the analysis of events preceding the onset of the psychotic episode, and the study of early phases of the disease [33-35].

In the past decade, some studies have already demonstrated the presence of functional changes prior to the start of the prodromic and psychotic phases and found deterioration in the premorbid phase in patients with schizophrenia [36]. In a subsequent study, Strous et al. [37] suggested that prior to the start of acute psychosis, there are specific precursors reflected in the premorbid functioning which could explain later manifestation of the disease. Thus, the premorbid functioning measures could be indicative of increased risk for the development of psychotic illness, which would manifest itself in a subtle form before the appearance of first psychotic symptoms. For this reason, it seems truly important to assess functioning across different age groups to prevent or detect these symptoms.

In relation to the discriminant validity of the PAS-S, our analysis showed absence of correlation between positive psychotic symptoms and social PAS-S, academic PAS-S or total PAS-S. Likewise, absence of correlation is observed between academic PAS-S with negative symptoms. Similarly, McClellan et al. [17] found significant associations between negative symptoms and social PAS-S but not with academic PAS-S. Nevertheless, academic PAS-S was related with other clinical variables, specifically with general symptoms. In this same direction, Monte et al. [14] concluded that the severity of general psychopathology symptoms was predicted by late adolescent academic functioning.

The **advantages of the scale** lie in its simplicity and its adaptability to a variety of information sources. It can be rated on the basis of personal interviews, family information, or chart histories, and is therefore of value for a variety of research purposes. This scale allows assessment of premorbid functioning across different age ranges and detection of possible changes in functioning, in both adult and adolescence patients. Furthermore, it may serve as a possible predictor in patients who could develop psychotic symptoms. Dragt et al. [38] demonstrated that environmental characteristics and social adjustment are predictive of transition to a psychosis in subjects at ultra high risk. These characteristics should be implemented in a model for prediction of psychosis, although more studies are needed to confirm this aspect.

Finally, to note several limitations of the scale: a) the premorbid period, as defined by Cannon-Spoor et al. [6], ends 6 months before the first admission to hospital or the onset of florid psychotic symptoms. However, Mastrigt & Addington [7] recommended that the end of the premorbid period should be taken as 1 year before that date. However, nowadays, there is much debate about determining the end of premorbid period or, in other words, to establish the onset of prodromal symptoms. There are researches which shows that the duration of the prodromal period is greater than 1 year, considering the presence of negative and nonspecific symptoms [39]; b) adult and general subscales must be reviewed, because the most common modifications to the PAS reported in the literature are not included in them; c) another common modification in the literature is related to the sociosexual section [7,40]: these items need to be updated and adapted to each cultural context; d) clearly, premorbid functioning must be assessed retrospectively, which may lead to inaccurate reporting, especially in chronic patients. It is also possible that relatives will give a description of the premorbid period influenced by the present experience with psychosis.

In conclusion, the Spanish version of the Premorbid Adjustment Scale showed appropriate psychometric properties in patients experiencing a first episode of psychosis and who have a chronic evolution of the illness. Moreover, each domain of the PAS-S (social and academic premorbid functioning) showed a differential relationship to other characteristics such as psychotic symptoms, disability or social functioning after onset of illness. Social PAS-S showed associations more similar to total PAS-S than academic PAS-S. Social PAS-S and total PAS-S were associated with specific psychotic symptoms (negative symptoms) and academic PAS-S with non-specific symptoms (general symptoms). Regarding social functioning, social PAS-S and total PAS-S showed significant associations in most of the discussed measures in contrast to academic PAS-S.

Acknowledgments

Acknowledgements are directed towards all patients and their relatives for their participation in the study and towards the clinical team at Sant Joan de Déu who collaborated. This project received financial help from the Fondo de Investigaciones Sanitarias de España (FIS PI05/1115); from the Instituto de Salud Carlos III de España, Centro de Investigación en Red de Salud Mental (CIBERSAM), from Caja Navarra and Fundació Marató de TV3 de Catalunya.

References

[1] Haim R, Rabinowitz J, Bromet E. The relationship of premorbid functioning to illness course in schizophrenia and psychotic mood disorders during two years following first hospitalization. J Nerv Ment Dis 2006;194:791-5.

[2] Rabinowitz J, De Smedt G, Harvey PD, Davidson M. Relationship between premorbid functioning and symptom severity as assessed at first episode of psychosis. Am J Psychiatry 2002;159:2021-6.
[3] Palmer BW, Heaton RK, Paulsen JS, Kuck J, Braff D, Harris MJ, et al. Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 1997;11:437-46.
[4] Rabinowitz J, Harvey PD, Eerdekens M, Davidson M. Premorbid functioning and treatment response in recent-onset schizophrenia. Br J Psychiatry 2006;189:31-5.
[5] Rabinowitz J, Haim R, Reichenberg A, Weiser M, Kaplan Z, Davidson M, et al. Association between functioning in adolescence prior to first admission for schizophrenia and affective disorders and patterns of hospitalizations thereafter. Schizophr Res 2005;73:185-91.
[6] Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982;8:470-84.
[7] Mastrigt S, Addington J. Assessment of premorbid function in first-episode schizophrenia: modifications to the Premorbid Adjustment Scale. J Psych Neurosc 2002;27(2):92-101.
[8] Wittman P, Steinberg DL. Follow-up objective evaluation. Elgin State Hospital Papers 1944;5:216-27.
[9] Phillips L. Case history data and prognosis in schizophrenia. J Nerv Ment Dis 1953;117:515-25.
[10] Gittelman-Klein R, Klein DF. Premorbid asocial adjustment and prognosis in schizophrenia. J Psychiatric Res 1969;7:35-53.
[11] Goldstein MJ. Premorbid adjustment survey. In: Kokes RF, Strauss JS, & Klorman R, editors. Premorbid adjustment in schizophrenia. Part II. Measuring premorbid adjustment: The instruments and their development, 3. Schizophr Bull; 1977. p. 186-213.
[12] Kantor R, Wallner J, Winder C. Process and reactive schizophrenia. J Consult Psychology 1953;17:157-62.
[13] Allen DN, Frantom LV, Strauss GP, Kammen DP. Differential patterns of premorbid academic and social deterioration in patients with schizophrenia. Schizophr Res 2005;75(2–3):389-97.
[14] Monte RC, Goulding SM, Compton MT. Premorbid functioning of patients with first-episode nonaffective psychosis: a comparison of deterioration in academic and social performance, and clinical correlates of Premorbid Adjustment Scale scores. Schizophr Res 2008;104(1–3):206-13.
[15] Strauss GP, Allen DN, Miski P, Buchanan RW, Kirkpatrick B, Carpenter WT. Differential patterns of premorbid social and academic deterioration in deficit and nondeficit schizophrenia. Schizophr Res 2012;135(1–3):134-8.
[16] Allen DN, Kelley ME, Miyatake RK, Gurklis JA, van Kammen DP. Confirmation of a two-factor model of premorbid adjustment in males with schizophrenia. Schizophr Bull 2001;27:39-46.
[17] McClellan J, Breiger D, McCurry C, Hlastala SA. Premorbid functioning in early-onset psychotic disorders. J Am Acad Child Adolesc Psych 2003;42(6):666-72.
[18] Norman RMG, Malla AK, Manchanda R, Townsend L. Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains. Acta Psychiatr Scand 2005;112:30-9.
[19] Debowska G, Grzywa A, Kucharska-Pietura K. Insight in paranoid schizophrenia – its relationship to psychopathology and premorbid adjustment. Comp Psychiatry 1998;39:255-60.
[20] Larsen TK, Johannessen JO, Opjordsmoen S. First-episode schizophrenia with long duration of untreated psychosis: pathways to care. Br J Psychiatry 1998;172:45-52.
[21] Krauss H, Marwinski K, Held T, Rietschel M, Freyberger HJ. Reliability and validity of the premorbid adjustment scale (PAS) in a German sample of schizophreniac and schizoaffective patients. Eur Arch Psychiatry Clin Neurosci 1998;248:277-81.
[22] Lopez M, Rodriguez S, Apiquian R, Paez F, Nicolini H. Translation study and validation of the Premorbid Adjustment Scale for Schizophrenia. Salud Mental 1996;19:24-9.
[23] Alvarez E, Garcia-Ribera C, Torrens M, Udina C, Guillamat R, Casas M. Premorbid Adjustment Scale as a prognostic predictor for schizophrenia. Br J Psychiatry 1987;150:411.
[24] Brill N, Reichenberg A, Wieser M, Rabinowitz J. Validity of the Premorbid Adjustment Scale. Schizophr Bull 2008;34(5):981-3.
[25] American Psychiatric Association. DSM-IV-TR. Diagnostic and statistical manual of mental disorders. Washington: APA; 2000.
[26] Kay SR, Fizbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13(2):261-76.
[27] Peralta V, Cuesta MJ. Validation of positive and negative symptom scale (PANSS) in a sample of Spanish schizophrenia patients. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1994;22:171-7.
[28] Endincott J. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766-71.
[29] Bulbena A, Fernández de Larrinoa P, Domínguez Al. Spanish adaptation of the Life Skills Profile. Profile of activities of daily living. Structure and factorial composition. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1992;20:51-60.
[30] Janca A, Kastrup M, Katschnig H, López-Ibor JJ, Mezzich JE, Sartorius N. The World Health Organization Short Disability Assessment Schedule (WHO DAS-S): a tool for the assessment of difficulties in selected areas of functioning of patients with mental disorders. Soc Psychiatry Psychiatr Epidemiol 1996;31: 349-54.
[31] Mas-Expósito L, Amador-Campos JA, Gómez-Benito J, Lalucat-Jo L. The World Health Organization Short Disability Assessment Schedule: a validation study in patients with schizophrenia. Compr Psychiatry 2012;53:208-16.
[32] Malla AK, Norman RMG, Manchanda R, Townsend L. Symptoms, cognition, treatment adherence and functional outcome in first episode psychosis. Psychol Med 2002;32(6):1109-19.
[33] Guerra A, Fearon P, Sham P, Jones P, Lewis S, Mata I, et al. The relationship between predisposing factors, premorbid function and symptom dimensions in psychosis: an integrated approach. Eur Psychiatry 2002;17(6):311-20.
[34] Schmael C, Georgi A, Krumm B, Buerger C, Deschner M, Nöthen MM, et al. Premorbid adjustment in schizophrenia. An important aspect of phenotype definition. Schizophr Res 2007;92(1–3):50-62.
[35] MacBeth A, Gumley A. Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. Acta Psychiatr Scand 2008;117:85-99.
[36] Haas GL, Sweeney JA. Premorbid and onset features of first-episode schizophrenia. Schizophr Bull 1992;18(3):373-86.
[37] Strous RD, Alvir JM, Robinson D, Gal G, Sheitman B, Chakos M, et al. Premorbid functioning in schizophrenia: relation to baseline symptoms, treatment response, and medication side effects. Schizophr Bull 2004;30(2):265-78.
[38] Dragt S, Nieman DH, Veltman D, Becker HE, van de Fliert R, de Haan L, et al. Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk. Schizophr Res 2011; 125(1):69-76.
[39] Häfner H, Maurer K. The prodromal phase of psychosis. In: & Miller T, et al, editor. Early Intervention in Psychotic Disorders. Dordrecht, Netherlands: Kluwer Academic; 2001. p. 71-100.
[40] Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 1992;49:615-23.

STUDY 2: Three-factor model of premorbid adjustment in a sample with chronic schizophrenia and first-episode psychosis

A. Barajas[a,b, c, d, e], J. Usall[b], I. Baños[b,d], I. Baños[b,d], M.Dolz[c], V. Villalta-Gil[b,d], M. Vilaplana[b], J. Autonell[b], B. Sánchez[c], J.A. Cervilla[b,f], A. Foix[b], J.E. Obiols[e], J.M. Haro[b], GENIPE group[1], S. Ochoa[b]

[a] Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain
[b] Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain
[c] Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[d] Fundació Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[e] Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
[f] Departamento de Medicina legal, Toxicología y Psiquiatría, Instituto de Neurociencias, Facultad de Medicina, Universidad Granada, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Granada, Spain

[1] GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, Dachs I, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Miquel L, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

Schizophrenia Research 2013; 151: 252 –258

Schizophrenia Research 151 (2013) 252–258

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Three-factor model of premorbid adjustment in a sample with chronic schizophrenia and first-episode psychosis

Ana Barajas [a,b,c,d,e,*], Judith Usall [b], Iris Baños [b,d], Montserrat Dolz [c], Victoria Villalta-Gil [b,d], Miriam Vilaplana [b], Jaume Autonell [b], Bernardo Sánchez [c], Jorge A. Cervilla [b,f], Alexandrina Foix [b], Jordi E. Obiols [e], Josep Maria Haro [b], GENIPE group [1], Susana Ochoa [b,*]

[a] Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain
[b] Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain
[c] Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[d] Fundació Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[e] Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
[f] Departamento de Medicina legal, Toxicología y Psiquiatría, Instituto de Neurociencias, Facultad de Medicina, Universidad Granada, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Granada, Spain

ARTICLE INFO

Article history:
Received 26 March 2013
Received in revised form 2 September 2013
Accepted 25 October 2013
Available online 17 November 2013

Keywords:
Premorbid functioning
Incipient psychosis
Psychotic disorders
Academic domain
Social domain
Socio-sexual domain

ABSTRACT

Background: The dimensionality of premorbid adjustment (PA) has been a debated issue, with attempts to determine whether PA is a unitary construct or composed of several independent domains characterized by a differential deterioration pattern and specific outcome correlates.
Aims: This study examines the factorial structure of PA, as well as, the course and correlates of its domains.
Method: Retrospective study of 84 adult patients experiencing first-episode psychosis (FEP) (n = 33) and individuals with schizophrenia (SCH) (n = 51). All patients were evaluated with a comprehensive battery of instruments including clinical, functioning and neuropsychological variables. A principal component analysis accompanied by a varimax rotation method was used to examine the factor structure of the PAS-S scale. Paired t tests and Wilcoxon rank tests were used to assess the changes in PAS domains over time. Bivariate correlation analyses were performed to analyse the relationship between PAS factors and clinical, social and cognitive variables.
Results: PA was better explained by three factors (71.65% of the variance): Academic PA, Social PA and Socio-sexual PA. The academic domain showed higher scores of PA from childhood. Social and clinical variables were more strongly related to Social PA and Socio-sexual PA domains, and the Academic PA domain was exclusively associated with cognitive variables.
Conclusion: This study supports previous evidence, emphasizing the validity of dividing PA into its sub-components. A differential deterioration pattern and specific correlates were observed in each PA domains, suggesting that impairments in each PA domain might predispose individuals to develop different expressions of psychotic dimensions.

1. Introduction

Behavioural changes have classically been described before the onset of schizophrenia (SCH), with patients being classified according to good or poor premorbid functioning. However, scientific studies have found that the impairments are not only behavioural, but also relational and cognitive, implying a multidimensional concept. As a result, premorbid functioning or premorbid adjustment (PA) has been defined as the psychosocial functioning in educational, occupational, social and interpersonal relation areas before evidence of characteristic positive symptoms (Cannon-Spoor et al., 1982).

The dimensionality of PA has been a debated issue, with attempts to determine whether PA is a unitary construct or composed of several domains partially independent from each other. Initially, Mukherjee et al. (1991), using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor

* Corresponding authors at: Parc Sanitari Sant Joan de Déu. CIBERSAM, C/Antoni Pujades, 42. CP 08830, Sant Boi de Llobregat, Spain. Tel.: +34 93 640 63 50; fax: +34 93 630 53 19.
E-mail addresses: ana.barajas@chmcorts.com (A. Barajas), sochoa@pssjd.org (S. Ochoa).

[1] GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, Dachs I, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Miquel L, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.10.027

et al., 1982), suggested that PA could be explained by two dimensions: social and academic. Krauss et al. (1998), in an attempt to avoid the interdependence of the original PAS subscales, found five independent dimensions which explained 70% of the total variance: (a) interpersonal relationships in childhood and early adolescence; (b) interpersonal relationships in late adolescence and adulthood; (c) scholastic performance and adaptation in school; (d) self-assertion; and (e) prodromal change. Subsequently, Allen et al. (2001) and Norman et al. (2005) provided evidence for at least two domains of PA in SCH, distinguishing between academic premorbid adjustment (Academic PA) and social premorbid adjustment (Social PA). These domains have presented a specific and differential pattern of correlations with clinical and cognitive variables: the Academic PA domain has been specifically associated with intellectual and cognitive deficits (Allen et al., 2001; Larsen et al., 2004; Rund et al., 2007); whilst the Social PA domain has been specifically associated with symptom-related variables, such as negative symptoms (Allen et al., 2001; McClellan et al, 2003; Larsen et al., 2004; Jeppesen et al., 2008; Ruiz-Veguilla et al., 2008; Strauss et al., 2012). However, it is not clear whether this specificity really exists because there are studies which indicate that both domains share associations with specific correlates: neuropsychological deficits (Silverstein et al., 2002; González-Blanch et al., 2008); general psychopathology symptoms (Monte et al., 2008); negative symptoms (Norman et al., 2005; Petersen et al., 2008; Brill et al., 2009; Chang et al., 2011); years of formal education (Allen et al., 2005); and age of onset of prodromal symptoms (Monte et al., 2008).

Several studies have used the PAS scale to investigate the course of Academic PA and Social PA across development periods (childhood, early adolescence and late adolescence) in both chronic (Allen et al., 2005) and acute psychotic spectrum disorders (Monte et al., 2008). Similar findings were found in these studies indicating that whilst increasing deterioration across age periods was present for both domains, there was a significant difference in deterioration during late adolescence, with greater impairment in Academic PA.

In summary, the characterisation of the period prior to the onset of overt psychotic symptoms might contribute to broaden the understanding of clues to aetiology, course and prognosis of psychotic spectrum disorders. Accordingly, the proposed aims in this study were as follows: a) to examine the factor model of PA and the course of its domains; b) to study associations between PA domains and clinical, social and cognitive correlates after the onset of psychosis; c) to describe similarities and differences in relation to the course and correlates of PA domains in two subsamples (FEP and chronic SCH).

2. Method

2.1. Sample

In the present study, we used a data set from two Spanish studies which included patients with chronic SCH and FEP. The inclusion criteria for the FEP subsample were: two or more psychotic symptoms (delusions, hallucinations, disorganized speech, catatonic or disorganized behaviour and negative symptoms); age between 18 and 65; first psychiatric visit to any centre participating in the study; less than 6 months since first contact with mental health services; and less than a year since onset of symptoms. The set of diagnoses that include the concept of FEP is as follows: schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; substance-induced psychotic disorder; bipolar disorder with psychotic features; major depression with psychotic features; and psychotic disorder not otherwise specified. The inclusion criteria for the chronic SCH subsample were: (a) primary diagnosis of schizophrenia (DSM-IV-TR criteria) (American Psychiatric Association, 2000); (b) age between 18 and 65; (c) to live in the catchment areas of the participating Community Mental Health Centres; and (d) to have had at least one outpatient visit during the 6 months prior to the beginning of the study. Patients with intellectual disabilities, traumatic brain injury or dementia were excluded from the study.

All selected individuals were informed of the objectives and methodology of this study by their psychiatrist or researcher and they signed the required informed consent form. The study design was approved by the Ethics and Research Committee of the *Parc Sanitari Sant Joan de Déu* and it was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. Instruments

All patients were evaluated with a battery of instruments to assess a set of sociodemographic, clinical, functioning and neuropsychological variables. This battery included a range of psychometric instruments: a) the Premorbid Adjustment Scale—Spanish [PAS-S, (Cannon-Spoor et al., 1982; Barajas et al., 2013)], this being the focus of the present investigation. This scale assesses the degree to which a person has successfully attained certain developmental goals at various life stages preceding the initial onset of psychosis symptoms. Functioning is assessed across four age periods or subscales: childhood (up to the age of 11), early adolescence (ages 12–15), late adolescence (ages 16–18) and adulthood (ages 19 and over); and across five major psychosocial domains: sociability and withdrawal; peer relationships; scholastic performance; adaptation to school; and social–sexual adjustment. The PAS-S also includes a section composed of 9 general items which together adult subscale were not considered for the statistical analysis. In this study, the PAS-S subscale scores are expressed as decimals ranging from 0.0 to 1.0, where higher scores represent lower levels of premorbid adjustment; b) the Global Assessment of Functioning Scale [GAF (Endicott, 1976)] was used to measure overall functioning (clinical/social), where 1 represents severe dysfunction and 100 represents good functioning; c) the Spanish version of the Life Skills Profile [LSP (Bulbena et al., 1992)] was used to assess social functioning in everyday-life situations and tasks in the previous month. A higher score means greater disability and worse functioning; d) the Disability Assessment Schedule—short version [DAS-sv (Janca et al., 1996; Mas-Expósito et al., 2011)] was used to explore four areas of functioning: self-care; occupation; family; and social disability. A higher score means greater disability and worse functioning; and e) the Positive and Negative Syndrome Scale [PANSS (Kay et al., 1987; Peralta and Cuesta, 1994)] was used to determine levels of positive and negative psychotic symptoms. A higher score means higher psychopathology severity. In addition, all patients completed a comprehensive neuropsychological test battery after being stable for at least eight weeks on medication. All cognitive measures were grouped into the six ability areas: a) Sustained attention was composed of two measures of the Continuous Performance Test—II [CPT-II (Conners, 1999)]: CPT-hit reaction time block change and CPT-hit standard error block change; b) Selective attention was estimated from three CPT measures (omissions, commissions and detectability), part A of Trail Making Test [TMT (Army Individual Test Battery, 1944; Reitan and Wolfson, 1993)], and interference measure of the Stroop Word–Color Test [SWCT (Golden, 1978)]; c) Working Memory was calculated using the Wechsler Adult Intelligence Scale III [WAIS-III (Wechsler, 1999)] Spanish version (Seisdedos et al., 1999) through three subtests: Letter and Number, Digit and Arithmetic; d) Verbal Learning and Memory was estimated through the *Test Aprendizaje Verbal España-Complutense* (Complutense Spanish Verbal Learning Test) [TAVEC (Benedet and Alejandre, 1998)]; e) Executive Functioning was composed of TMT-B and scores of the three Stroop trials (Word; Color and Word–Color); and f) Estimated Premorbid IQ was obtained by vocabulary subtest (WAIS-III), as suggested previously (Miralbell et al., 2010). All direct scores were transformed into a T-score (mean 50; SD = 10) and the mean of the scores according to each cognitive domain was calculated.

The neurocognitive battery was administered by two trained psychologists (IB, AB) over two sessions lasting approximately 1 h each.

2.3. Statistical analysis

Normal distribution of all variables was explored using the Kolmogorov–Smirnov test. A principal component analysis (PCA) accompanied by a Varimax rotation method, which seeks independent factors (Nunnally, 1978; Jolliffe, 1986) was used to examine the factor structure of the PAS-S scale. Preliminary analyses were first carried out using the Kaiser–Meyer–Olkin measure (KMO) and Bartlett's test of sphericity to determine the sampling adequacy [values above limit of 0.50 (Field, 2009)] and the adequacy of the relationship between the variables that we hoped to include in the analysis (p-value had to be less than 0.5) respectively. Based on Kaiser's criterion (Kaiser, 1960), we extracted all factors with eigenvalues greater than 1. PCA was performed for two and three factors. The analyses that follow were carried out across the three-factor model. Paired t tests and Wilcoxon rank tests were used to assess the changes in PAS domains over age periods in total sample or in split sample (FEP vs. SCH). Bivariate correlation analyses were performed to analyse the relationship between PAS factors and clinical, social and cognitive variables. We did not perform multiple comparison corrections due mainly to the exploratory nature of this study (Bender and Lange, 2001). All the analyses were carried out using the SPSS statistical software package (version 18.0).

3. Results

3.1. Socio-demographic and clinical data

A total of 84 people were assessed, of whom 66.7% (n = 56) were men. The mean age of the patients was 34.51 ± 11.96 years. A total of 39.3% of the sample (n = 33) was composed of people experiencing FEP and the rest were people with chronic SCH. When the sample was split according to diagnosis, most patients were men in both the FEP (n = 20; 60.6%) and SCH (n = 36; 70.6%) subsamples. The mean ages were 26.15 ± 6.83 years in the FEP subsample and 39.94 ± 11.41 years in the patients with chronic SCH.

The breakdown of the diagnoses in the FEP subsample was as follows: SCH (n = 4; 12.5%); schizophreniform disorder (n = 4; 12.5%); schizoaffective disorder (n = 1; 3.1%); substance-induced psychotic disorder (n = 1; 3.1%); bipolar disorder with psychotic features (n = 4; 12.5%); major depression with psychotic features (n = 3; 9.4%); and psychotic disorder not otherwise specified (n = 15; 46.9%). In one subject, diagnosis could not be specified.

In relation to cognitive measures statistically significant differences were found between FEP vs. SCH subsamples ($mean_{FEP}$ vs. $mean_{SQZ}$, p-value): TAVEC-immediate memory (37.76 vs. 28.42, p = 0.001); TAVEC-long-term memory (34.10 vs. 31.36, p = 0.034); CPT-omissions (57.23 vs. 94.24, p = 0.010); TMT-A (65.80 vs. 35.0, p < 0.001); TMT-B (81.64 vs. 37.75, p < 0.001); Stroop Color (35.25 vs. 29.88, p = 0.017); Stroop Word Color (39.16 vs. 32.57, p = 0.010); Stroop Word Color interference (50.38 vs. 46.82, p = 0.046); WAIS-III digit subtest (45.73 vs. 40.73, p = 0.025), showing better performance in the FEP group.

3.2. Premorbid general data

PA scores on the PAS-S were distributed as follows: childhood 0.26 ± 0.18 (score range 0.00–0.88); early adolescence 0.28 ± 0.18 (score range 0.00–0.77); and late adolescence 0.31 ± 0.20 (score range 0.00–0.83). When the sample was split, FEP group PA scores were: childhood 0.24 ± 0.18 (score range 0.00–0.67); early adolescence 0.29 ± 0.16 (score range 0.00–0.73); and late adolescence 0.32 ± 0.18 (score range 0.00–0.70). In the SCH group, PA scores were: childhood 0.28 ± 0.18 (score range 0.00–0.88); early adolescence 0.27 ± 0.19 (score range 0.00–0.77); and late adolescence 0.31 ± 0.21 (score range 0.00–0.83). No significant differences were found between groups.

Table 1
Two-factor loading principal component analysis of PAS-S with varimax rotation.

Item	Factor 1 (social)	Factor 2 (academic)
Childhood		
Sociability and withdrawal	0.83	
Peer relations	0.83	
Scholastic performance		0.71
Adaptation to school		0.50
Early adolescent		
Sociability and withdrawal	0.92	
Peer relations	0.86	
Scholastic performance		0.88
Adaptation to school		0.78
Socio-sexual functioning	0.45	
Late adolescent		
Sociability and withdrawal	0.86	
Peer relations	0.77	
Scholastic performance		0.89
Adaptation to school		0.77
Socio-sexual functioning	0.43	

3.3. Factor structure of the PAS-S scale

A PCA was conducted on the 14 items of the PAS-S scale with orthogonal rotation (varimax). The Kaiser–Meyer–Olkin measure verified the sampling adequacy for the analysis, KMO = 0.65, and all KMO values for individual items were >0.57. Bartlett's test of sphericity X^2 (91) = 483.60, p < 0.001, indicated that correlations between items were sufficiently large for PCA. An initial analysis was run to obtain eigenvalues for each component in the data. Two components explained only 58.24% with factor loadings of each of the relevant PAS-S items shown in Table 1. Three components had eigenvalues over Kaiser's criterion of 1 and, in combination, explained 71.65% of the variance. The scree plot showed inflexions that would justify retaining 3 components. Table 2 shows the factor loadings of three-factor model after rotation.

All variables had a normal distribution, except for the following: PAS socio-sexual; PAS early adolescence socio-sexual; PAS late adolescence socio-sexual; PAS social childhood; PAS academic childhood; PAS social early adolescence; selective attention domain; and LSP total score. As the sample was split according to FEP or chronic course of illness, the PAS socio-sexual domain and its components showed non-parametric distribution, as did LSP total score in the FEP group and selective attention domain in the SCH group.

Table 2
Three-factor loading principal component analysis of PAS-S with varimax rotation.

Item	Factor 1 (social)	Factor 2 (academic)	Factor 3 (socio-sexual)
Childhood			
Sociability and withdrawal	**0.89**		
Peer relations	**0.87**		
Scholastic performance		**0.72**	
Adaptation to school	0.50	**0.55**	
Early adolescent			
Sociability and withdrawal	**0.88**		
Peer relations	**0.77**		0.41
Scholastic performance		**0.86**	
Adaptation to school		**0.79**	
Socio-sexual functioning			**0.74**
Late adolescent			
Sociability and withdrawal	**0.76**		0.43
Peer relations	**0.75**		
Scholastic performance		**0.87**	
Adaptation to school		**0.77**	
Socio-sexual functioning			**0.79**

Factor loadings > 0.50 are highlighted in bold. Values ≤ 0.40 are not displayed in table.

3.4. Course of PAS-S factors over age periods

The course of each PA domain from childhood to late adolescence is presented in Fig. 1. An analysis of repeated measures (Wilcoxon signed-rank test and paired *t*-test) was used to examine the development of each domain in the three-factor model of PA across age periods (Table 3).

The Academic PA domain showed higher scores of PA than the other domains and significantly lower scores in childhood than in the other aged periods of this domain. Additionally, early and late adolescence academic functioning differed significantly. The Social PA domain showed higher scores than the Socio-sexual PA domain in each age range. Progressively higher scores in social functioning were found from childhood to late adolescence but the differences between each period were not significant. The Socio-sexual PA domain showed that early adolescence socio-sexual functioning was significantly better than late adolescence socio-sexual functioning.

When the sample was split according to chronicity of illness, there were no significant differences in the Social PA domain over time in both the FEP group as the SCH group. Regarding the Socio-sexual PA domain, significant differences were observed only in the SCH group. Finally, the Academic PA domain showed significant differences over time in both groups, except a trend difference found between early adolescence and late adolescence in SCH group (Table 3).

3.5. Correlates of the PAS-S factors

Table 4 presents evidence regarding correlates on each of the PAS-S factors. In overall sample, we observed the following specific associations between PA domains and outcome variables: Academic PA domain with cognitive variables (learning and verbal memory and estimated premorbid); and Socio-sexual PA domain with clinical variables (negative PANSS). Other significant correlations were found: both Social PA and Socio-Sexual PA domains were associated with positive PANSS.

When the sample was divided according to illness progression (FEP vs. SCH group), the FEP subsample showed a similar pattern of correlates associated with PAS-S factors as the total sample, adding a significant correlation between Social PA domain and social variables (DAS and LSP scales). In the SCH subsample, there were no significant associations between the three PA domains and clinical or social outcomes, but cognitive variables (executive functioning and estimated premorbid IQ) were associated with PAS-S factors (Social PA and Academic PA domains respectively).

4. Discussion

The multidimensionality of PA has been analysed by a number of studies in an attempt to show that PA is better explained using a construct comprising several domains; mainly two (Social PA and Academic PA domains) (Mukherjee et al., 1991; Allen et al., 2001, 2005, 2013), or even five (Krauss et al., 1998). As shown in these studies, the present study provides evidence of PA dimensionality, although a different factor model was identified. Our analysis revealed that PA was better explained by three factors, splitting the classic social factor into two components, Social PA and Socio-sexual PA domains. These results have both methodological and theoretical implications. From a methodological standpoint, a difference of 13.41% in the variance was not explained if a two-factor model was chosen, and three-factor model reduces the number of variables analysed (five in the original scale), thereby decreasing error associated with making multiple comparisons. From a theoretical standpoint, the importance of distinguishing between these domains and examining them at each age level, rather than using an average score, is clearly demonstrated by the differential pattern of deterioration and specific correlates shown in each domain.

4.1. Academic PA domain

As in previous studies (Allen et al., 2005; Monte et al., 2008), our results indicate a pattern of deterioration in Academic PA across age periods. However, in contrast to the aforementioned studies that found a pronounced deterioration in a later period, we observed a more evident impairment between childhood and early adolescence. This pattern remained when the sample was analysed according to the course of the illness (FEP vs. SCH).

Previous research found associations between neuropsychological functioning and both Social PA and Academic PA domains (Silverstein et al., 2002; Norman et al., 2005; González-Blanch et al., 2008), indicating that cognition is distinctly associated with early social and academic functioning. However, other studies have shown an exclusive association between poor Academic PA and neurocognitive performance: working memory/fluency and verbal learning (Rund et al., 2004, 2007). Our results show that only the Academic PA was

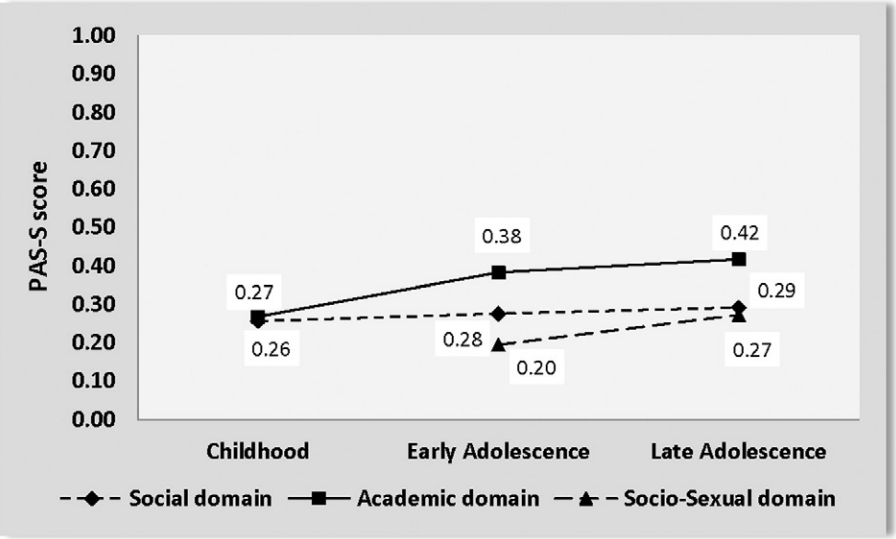


Fig. 1. Patterns of deterioration for PA factors over time in total sample.

Table 3
Course of the PAS-S factors: a comparison between different aged periods [mean, (SD)[a]].

	Childhood–early adolescence	Childhood–late adolescence	Early adolescence–late adolescence
Factor 1 (social)			
FEP	0.25–0.26 (0.25–0.23)	0.25–0.28 (0.25–0.22)	0.26–0.28 (0.23–0.22)
SCH	0.26–0.29 (0.25–0.25)	0.25–0.30 (0.26–0.25)	0.27–0.30 (0.25–0.25)
Total sample	0.26–0.28 (0.25–0.24)	0.25–0.29 (0.25–0.24)	0.26–0.29 (0.24–0.24)
Factor 2 (academic)			
FEP	0.22–0.41 (0.20–0.31)****	0.19–0.45 (0.16–0.27)****	0.35–0.45 (0.27–0.27)**
SCH	0.28–0.37 (0.19–0.23)***	0.18–0.37 (0.18–0.27)***	0.28–0.37 (0.23–0.27)
Total sample	0.25–0.38 (0.20–0.27)****	0.19–0.42 (0.17–0.27)****	0.32–0.42 (0.26–0.27)***
Factor 3 (socio-sexual)			
FEP	–	–	0.14–0.22 (0.25–0.29)
SCH	–	–	0.21–0.32 (0.27–0.33)*
Total sample	–	–	0.18–0.27 (0.26–0.32)**

PAS-S: Premorbid Adjustment Scale—Spanish; SD: standard deviation.
[a] Higher scores indicate lower levels of premorbid adjustment (score range: from 0.0 to 1.0).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.005$.
**** $p < 0.001$.

related exclusively to cognitive correlates (learning and verbal memory and premorbid IQ).

Taking these findings into account, Academic PA, in addition to premorbid IQ, could be considered as an indirect measure of the cognitive competence before the onset of psychotic illness. This issue has become increasingly relevant since the emergence of evidence suggesting that some cognitive deficits are present premorbidly. It has been observed in a number of studies that individuals who later develop SCH demonstrate decline in their academic performance from childhood to adolescence (Cannon et al., 2002; Fuller et al., 2002; Zammit et al., 2004). With this in mind, and supporting the concept of a continuum of neurocognitive function in psychotic spectrum disorders, it is possible that the factors that precipitate the transition from premorbid to prodromal stage are not necessarily distinct from those involved in the transition to psychosis. In fact, cognitive impairments were found in recent studies of neuropsychological functioning at ultra-high risk subjects (Lencz et al., 2005; Niendam et al., 2006; Eastvold et al., 2007; Simon et al., 2007; Jahshan et al., 2010; Woodberry et al., 2010; Kim et al., 2011). The study of premorbid cognitive performance could therefore make it possible to identify potential premorbid markers for the transition to prodromal stage or full-threshold psychosis.

4.2. Social PA domain

The course of the Social PA factor across development periods showed a softer pattern of impairment in relation to the Academic PA domain, as indicated in previous studies (Allen et al., 2005; Monte et al., 2008), but worse than the Socio-sexual PA domain. Our results also showed a stable pattern of impairment, suggesting that the onset of social functioning deficits had already begun in childhood. Previous studies have indicated similar results with SCH (Cannon et al., 1997; Strauss et al., 2012) and FEP (Larsen et al., 2004; Allen et al., 2005; Monte et al., 2008) samples. Because these social impairments are present as early as childhood, low social drive may be a very early indicator of the neurodevelopmental abnormalities that later go on to

Table 4
Bivariate correlation coefficients between PAS-S factors and clinical, disability and cognitive variables [r(p)].

Variables	Factor 1 (social)[a]			Factor 2 (academic)[a]			Factor 3 (socio-sexual)[b]		
	FEP	SCH	TOTAL	FEP	SCH	TOTAL	FEP	SCH	TOTAL
Clinical variables									
Positive PANSS[a]	**−0.429 (0.014)***	−0.095 (0.564)	**−0.234 (0.049)***	0.141 (0.440)	−0.110 (0.503)	0.036 (0.766)	−0.323 (0.072)	−0.053 (0.751)	**−0.270 (0.024)***
Negative PANSS[a]	0.296 (0.106)	0.155 (0.347)	0.206 (0.086)	−0.002 (0.993)	0.199 (0.225)	0.069 (0.568)	**0.383 (0.033)***	0.176 (0.291)	**0.362 (0.002)*****
General PANSS[a]	0.033 (0.857)	−0.101 (0.542)	−0.054 (0.656)	0.225 (0.215)	0.086 (0.601)	0.153 (0.203)	0.338 (0.058)	0.196 (0.238)	0.209 (0.082)
Disability variables									
Total DAS[a]	**0.378 (0.043)***	0.082 (0.622)	0.226 (0.063)	0.182 (0.344)	0.183 (0.266)	0.149 (0.226)	0.053 (0.785)	0.288 (0.079)	0.224 (0.069)
Total GAF[a]	−0.177 (0.332)	−0.248 (0.128)	−0.204 (0.088)	−0.071 (0.701)	−0.163 (0.322)	−0.130 (0.281)	−0.050 (0.787)	−0.231 (0.162)	−0.065 (0.594)
Total LSP[b]	**−0.457 (0.017)***	−0.005 (0.976)	−0.166 (0.186)	0.074 (0.714)	0.079 (0.638)	0.099 (0.431)	−0.123 (0.540)	−0.316 (0.057)	−0.174 (0.169)
Cognitive variables									
Sustained attention[a]	0.045 (0.810)	0.012 (0.940)	0.016 (0.892)	−0.149 (0.423)	−0.011 (0.944)	−0.048 (0.684)	−0.045 (0.809)	−0.146 (0.364)	−0.168 (0.157)
Selective attention[b]	0.198 (0.277)	−0.176 (0.231)	−0.083 (0.464)	0.342 (0.056)	−0.067 (0.715)	0.005 (0.967)	−0.067 (0.715)	−0.015 (0.923)	−0.132 (0.246)
Learning & verbal memory[a]	0.116 (0.549)	0.147 (0.334)	0.099 (0.401)	**−0.598 (0.001)*****	−0.173 (0.256)	**−0.354 (0.002)*****	−0.001 (0.998)	0.179 (0.245)	0.037 (0.753)
Executive functioning[a]	−0.017 (0.927)	**0.327 (0.025)***	0.027 (0.812)	**0.414 (0.018)***	−0.146 (0.326)	0.160 (0.158)	0.040 (0.827)	0.220 (0.141)	−0.164 (0.151)
Working memory[a]	−0.161 (0.378)	0.178 (0.265)	0.032 (0.791)	−0.268 (0.139)	−0.079 (0.623)	−0.148 (0.213)	0.019 (0.917)	0.173 (0.287)	−0.004 (0.970)
Estimated premorbid IQ[a]	−0.269 (0.137)	0.166 (0.305)	−0.063 (0.597)	**−0.409 (0.020)***	**−0.432 (0.005)****	**−0.393 (0.001)*****	−0.260 (0.150)	0.015 (0.926)	**−0.236 (0.048)***

PAS-S: Premorbid Adjustment Scale—Spanish; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning Scale; DAS: Disability Assessment Schedule; LSP: Life Skills Profile; r: Pearson's correlation coefficient for normally distributed variables (a) or Spearman's correlation coefficient for variables not normally distributed (b).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.005$.

be expressed as a different sub-type of psychosis phenotype (Read et al., 2001; Birchwood, 2003).

Previous research has demonstrated that the Social PA domain is strongly associated with symptom-related variables (Allen et al., 2001; Rabinowitz et al., 2002; Silverstein et al., 2002; Monte et al., 2008). Our analysis showed an association between severity of positive symptoms and Social PA in the overall sample and the FEP group. However, previous findings exploring associations with social PA domain showed that impaired sociability correlated with severe negative symptoms (Addington et al., 2003; Strous et al., 2004; Jeppesen et al., 2008; Monte et al., 2008), suggesting developmental continuity from premorbid social impairment to negative symptoms (Petersen et al., 2008). Nevertheless, it must be taken into account that in these studies the Social PA domain also included socio-sexual items.

Finally, it is known that deficits in social functioning before the onset of the FEP are often prognostic of later social functioning (Davidson et al., 1999; Häfner et al., 1999; Addington and Addington, 2005). Our results also point in this direction, since we identified a specific correlation between the Social PA domain and the outcome variable of functioning (DAS score) in the FEP subsample, indicating continuity between premorbid and morbid social impairment. Thus, future preventive efforts may be critical in the premorbid periods to minimise or prevent further social disability that has already begun to develop by the time of symptom onset.

4.3. Socio-sexual PA domain

The Socio-sexual domain assesses social competence in intimate relationships and interest in maintaining close ties, which may involve sexual activity, during adolescence. As in the Rabinowitz et al. (2002) study, we observed that the Socio-sexual PA domain was the best preserved area in comparison with other PA domains, both in patients with brief or chronic course of psychotic symptoms. However, the main interest of this finding lies in the recognition of specific clinical correlates to Socio-sexual PA domains. In previous studies, negative symptoms have been related to the classic premorbid social functioning domain, which included social and socio-sexual areas. In our study, negative symptoms were associated exclusively with the Socio-sexual PA domain. From a dimensional approach, our results suggest that the Socio-sexual PA domain could be considered as a good predictor of transition to psychosis in subjects initiating the illness with negative symptoms. A poorer Socio-sexual PA domain in individuals at high clinical risk for psychosis could alert us to the need for intervention in order to avoid progression of the deterioration in this kind of social competence.

Lastly, some limitations of our study are: a) the SCH subsample did not include patients with affective psychosis, in contrast to the FEP subsample. This could have influenced the results in both Social PA and Socio-sexual PA in the FEP subsample, being less deteriorated than the Academic PA domain in psychotic mood disorders (Tarbox et al., 2012). However, we must take into account that, like patients included in SCH subsample, all patients included in the FEP subsample had experienced two or more psychotic symptoms; b) academic functioning was not assessed through a systematic study of school records or interviews with teachers; c) the retrospective design of the PAS raises the possibility of recall bias; however, the predictive and concurrent validity of the PAS are well supported (Brill et al., 2008); d) the small sample sizes in analyses using FEP or SCH subsamples may have reduced statistical power, thus potentially increasing the occurrence of type II errors; e) in the scientific literature, the lack of consensus on the tests used to measure different cognitive domains makes it difficult to compare findings; f) it is impossible to eliminate the effect of pharmacological treatment and this could introduce some variability in performance in some of the tests, inhibiting cognitive decline or even improving cognition over time (Lieberman et al., 2001).

In conclusion, this study supports previous evidence in considering PA as a multi-component construct, specifically three-domain model, and establishes the importance of differentiating between capacity to form intimate socio-sexual ties and other kinds of social relationships. We found evidence of a differential pattern of development in each domain, with a steeper decline occurring for the Academic PA domain. Lastly, exclusive and differential relationships were observed between each of the PA domains and the outcome variables (such as, Academic PA domain with cognitive functioning, Social PA domain with social variables, and Socio-sexual PA domain with negative symptoms), suggesting that the heterogeneity of the psychotic spectrum begins early, long before the onset of psychosis. From a dimensional approach to psychosis, PA could be understood as a risk factor modulating expression of psychotic symptoms, whereby impairments in each PA domain might predispose individuals to develop different expressions of psychotic dimensions in relation to the particular impaired domain.

On the other hand, results of this study could contribute to improve our knowledge of the R-DoC (Research Domain Criteria), a new way of classifying mental disorders based on dimensions (Insel et al., 2010), specifically in two domains: cognitive and social process systems. Thereby, Academic PA domain could be considered as an indirect measure, among other behavioural analysis units, to study cognitive domain, in particular attention, perception and declarative memory constructs; and Social and Socio-sexual PA domains could be considered as units of analysis to study social process domain, in particular social communication and perception and understanding of self/other constructs. Studies based on R-DoC criteria, by using PA domains as analysis units in cognitive and social process domains, could allow progress towards knowledge of new strategies for early detection and psychosocial interventions adapted to needs of patients and focusing on disturbed constructs, not on diagnosis.

Future research should be directed at increasing our knowledge about the relationship between premorbid impairments and prodromal symptoms, since the emergence of prodromal symptoms is more proximal to the onset of psychosis syndrome. This might help to plan preventive interventions adapted to the specific needs of each individual, whilst making it easier to identify specific premorbid risk factors. Moreover, a detailed examination of patterns of premorbid deterioration in relation to prodromal and psychotic symptoms at the onset of psychosis could lead to better understanding in terms of predictive power in relation to the transition to psychosis.

Role of funding sources

This work was supported by Fondo de Investigaciones Sanitarias de España (FIS PI05/1115), Instituto de Salud Carlos III de España, Centro de Investigación en Red de Salud Mental (CIBERSAM), Caja Navarra and Fundació Marató de TV3 de Catalunya.

Contributors

Authors S.O., J.U., M.D. and B.S. were involved in the design of the GENIPE study (about FEP). S.O., J.U., M.D., J.A.C. and J.M.H. were involved in the design of the NEDENA study (about chronic SCH). S.O. and A.B. performed statistical analyses and data processing steps. Data collection was performed by I.B., A.B., V.V.-G. and M.V. A.B. wrote the first draft of the manuscript. Subsequent drafts of the manuscript were edited by all authors, who have contributed to and approved the final manuscript.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgements

Acknowledgements are directed towards all patients and their relatives for their participation in the study and towards all the coordinating clinicians and staff from the psychiatric inpatient and outpatient units at Sant Joan de Déu who collaborated.

References

Addington, J., Addington, D., 2005. Patterns of premorbid functioning in first episode psychosis: relationship to 2-year outcome. Acta Psychiatr. Scand. 112, 40–46.

Addington, J., van Mastrigt, S., Addington, D., 2003. Patterns of premorbid functioning in first-episode psychosis: initial presentation. Schizophr. Res. 62, 23–30.

Allen, D.N., Kelley, M.E., Miyatake, R.K., Gurklis, J.A., van Kammen, D.P., 2001. Confirmation of a two-factor model of premorbid adjustment in males with schizophrenia. Schizophr. Bull. 27, 39–46.
Allen, D.N., Frantom, L.V., Strauss, G.P., van Kammen, D.P., 2005. Differential patterns of premorbid academic and social deterioration in patients with schizophrenia. Schizophr. Res. 75 (2–3), 389–397.
Allen, D.N., Strauss, G.P., Barchard, K.A., Vertinski, M., Carpenter, W.T., Buchanan, R.W., 2013. Differences in developmental changes in academic and social premorbid adjustment between males and females with schizophrenia. Schizophr. Res. 146 (1-3), 132–137 (http://dx.doi.org/10.1016/j.schres.2013.01.032).
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision). American Psychiatric Association, Washington, DC.
Army Individual Test Battery, 1944. Manual of Directions and Scoring. War Department, Adjutant General's Office, Washington, DC.
Barajas, A., Ochoa, S., Baños, I., Dolz, M., Villalta-Gil, V., Vilaplana, M., et al., 2013. Spanish validation of the Premorbid Adjustment Scale (PAS-S). Compr. Psychiatry 54 (2), 187–194.
Bender, R., Lange, S., 2001. Adjusting for multiple testing — when and how? J. Clin. Epidemiol. 54, 343–349.
Benedet, M.J., Alejandre, M.A., 1998. TAVEC: Test de Aprendizaje Verbal España-Complutense. TEA Ediciones, Madrid.
Birchwood, M., 2003. Pathways to emotional dysfunction in first episode psychosis. Br. J. Psychiatry 182, 373–375.
Brill, N., Reichenberg, A., Weiser, M., Rabinowitz, J., 2008. Validity of the premorbid adjustment scale. Schizophr. Bull. 34 (5), 981–983.
Brill, N., Levine, S.Z., Reichenberg, A., Lubin, G., Weiser, M., Rabinowitz, J., 2009. Pathways to functional outcomes in schizophrenia: the role of premorbid functioning, negative symptoms and intelligence. Schizophr. Res. 110, 40–46.
Bulbena, A., Fernández de Larrinoa, P., Domínguez, Al, 1992. Spanish adaptation of the Life Skills Profile. Profile of activities of daily living. Structure and factorial composition. Actas Luso Esp. Neurol. Psiquiatr. Cienc. Afines 20, 51–60.
Cannon, M., Jones, P., Gilvarry, C., Rifkin, L., McKenzie, K., Foerster, A., et al., 1997. Premorbid social functioning in schizophrenia and bipolar disorder: similarities and differences. Am. J. Psychiatry 154, 1544–1550.
Cannon, M., Caspi, A., Moffitt, T.E., Harrington, H., Taylor, A., Murray, R.M., et al., 2002. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch. Gen. Psychiatry 59, 449–456.
Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J., 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr. Bull. 8 (3), 470–484.
Chang, W.C., Hui, C.L.M., Tang, J.Y.M., Wong, G.H., Lam, M.M., Chan, S.K., et al., 2011. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr. Res. 133, 22–28.
Conners, K., 1999. Continuous Performance Test II. Psychological Assessment Resources, Odessa, FL.
Davidson, M., Reichenberg, A., Rabinowitz, J., Weiser, M., Kaplan, Z., Mark, M., 1999. Behavioural and intellectual markers for schizophrenia in apparently healthy male adolescents. Am. J. Psychiatry 156, 1328–1355.
Eastvold, A.D., Heaton, R.K., Cadenhead, K.S., 2007. Neurocognitive deficits in the (putative) prodrome and first episode psychosis. Schizophr. Res. 93 (1–3), 266–277.
Endicott, J., 1976. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33, 766–771.
Field, A.P., 2009. Discovering Statistics Using SPSS: and Sex and Drugs and Rock' n' Roll, third ed. Sage, London.
Fuller, R., Nopoulos, P., Arndt, S., O'Leary, D., Ho, B.-C., Andreasen, N.C., 2002. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. Am. J. Psychiatry 159, 1183–1189.
Golden, C.J., 1978. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Stoeltnig Company, Chicago.
González-Blanch, C., Crespo-Facorro, B., Álvarez-Jiménez, M., Rodríguez-Sánchez, J.M., Pelayo-Terán, J.M., Pérez-Iglesias, R., et al., 2008. Pretreatment predictors of cognitive deficits in early psychosis. Psychol. Med. 38 (5), 737–746.
Häfner, H., Loffler, W., Maurer, K., Hambrecht, M., An Der Heiden, W., 1999. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. Acta Psychiatr. Scand. 100, 105–118.
Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., et al., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167 (7), 748–751.
Jahshan, C., Heaton, R.K., Golshan, S., Cadenhead, K.S., 2010. Course of neurocognitive deficits in the prodrome and first episode of schizophrenia. Neuropsychology 24 (1), 109–120.
Janca, A., Kastrup, M., Katschnig, H., López-Ibor, J.J., Mezzich, J.E., Sartorius, N., 1996. The World Health Organization Short Disability Assessment Schedule (WHO DAS-S): a tool for the assessment of difficulties in selected areas of functioning of patients with mental disorders. Soc. Psychiatry Psychiatr. Epidemiol. 31, 349–354.
Jeppesen, P., Petersen, L., Thorup, A., Abel, M.B., Øhlenschlaeger, J., Christensen, T.Ø., et al., 2008. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. Psychol. Med. 38, 1157–1166.
Jolliffe, I.T., 1986. Principal Component Analysis. Springer-Verlag, New York.
Kaiser, H.F., 1960. The application of electronic computers to factor analysis. Educ. Psychol. Meas. 20, 141–151.
Kay, S.R., Fizbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Kim, H.S., Shin, N.Y., Jang, J.H., Kim, E., Shim, G., Park, H.Y., et al., 2011. Social cognition and neurocognition as predictors of conversion to psychosis in individuals at ultra-high risk. Schizophr. Res. 130, 170–175.
Krauss, H., Marwinski, K., Held, T., Rietschel, M., Freyberger, H.J., 1998. Reliability and validity of the Premorbid Adjustment Scale (PAS) in a German sample of schizophrenic and schizoaffective patients. Eur. Arch. Psychiatry Clin. Neurosci. 248, 227–281.
Larsen, T.K., Friis, S., Haahr, U., Johannessen, J.O., Melle, I., Opjordsmoen, S., et al., 2004. Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. Br. J. Psychiatry 185, 108–115.
Lencz, T., Smith, C.W., McLaughlin, D., Auther, A., Nakayama, E., Hovey, L., et al., 2005. Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol. Psychiatry 59, 863–871.
Lieberman, J.A., Perkins, D., Belger, A., Chakos, M., Jarskog, F., Boteva, K., et al., 2001. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol. Psychiatry 50 (11), 884–897.
Mas-Expósito, L., Amador-Campos, J.A., Gómez-Benito, J., Lalucat-Jo, L., 2011. The World Health Organization Short Disability Assessment Schedule: a validation study in patients with schizophrenia. Compr. Psychiatry 53 (2), 208–216.
McClellan, J., Breiger, D., McCurry, C., Hlastala, S.A., 2003. Premorbid functioning in early-onset psychotic disorders. J. Am. Acad. Child Adolesc. Psychiatry 42 (6), 666–672.
Miralbell, J., Soriano, J.J., López-Cancio, E., Arenillas, J.F., Dorado, L., Barrios, M., et al., 2010. Vascular risk factors and cognitive performance in patients 50 to 65 years-old. Neurologia 25 (7), 422–429.
Monte, R.C., Goulding, S.M., Compton, M.T., 2008. Premorbid functioning of patients with first-episode nonaffective psychosis: a comparison of deterioration in academic and social performance, and clinical correlates of Premorbid Adjustment Scale scores. Schizophr. Res. 104 (1–3), 206–213.
Mukherjee, S., Reddy, R., Schnur, D.B., 1991. A developmental model of negative syndromes in schizophrenia. In: Greden, J., Tandon, R. (Eds.), Negative Schizophrenic Symptoms: Pathophysiology and Clinical Implications. American Psychiatric Press, Washington DC, pp. 173–178.
Niendam, T.A., Bearden, C.E., Johnson, J.K., McKinley, M., Loewy, R., O'Brien, M., et al., 2006. Neurocognitive performance and functional disability in the psychosis prodrome. Schizophr. Res. 84, 100–111.
Norman, R.M.G., Malla, A.K., Manchanda, R., Townsend, L., 2005. Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains. Acta Psychiatr. Scand. 112, 30–39.
Nunnally, J., 1978. Psychometric Theory. McGraw Hill, New York.
Peralta, V., Cuesta, M.J., 1994. Validation of Positive and Negative Symptom Scale (PANSS) in a sample of Spanish schizophrenia patients. Actas Luso Esp. Neurol. Psiquiatr. Cienc. Afines 22, 171–177.
Petersen, L., Throup, A., Øqhlenschlaeger, J., Christensen, T.Ø., Jeppesen, P., et al., 2008. Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. Can. J. Psychiatry 53 (10), 660–670.
Rabinowitz, J., De Smedt, G., Harvey, P.D., Davidson, M., 2002. Relationship between premorbid functioning and symptom severity as assessed at first episode of psychosis. Am. J. Psychiatry 159, 2021–2026.
Read, J., Perry, B., Moskowitz, A., Connolly, J., 2001. The contribution of early traumatic to schizophrenia in some patients: a traumagenic neurodevelopmental model. Psychiatry 64, 319–345.
Reitan, R.M., Wolfson, D., 1993. The Helstead–Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Neuropsychology Press, Tucson, AZ.
Ruiz-Veguilla, M., Cervilla, J.A., Barrigón, M.L., Ferrín, M., Gutiérrez, B., Gordo, E., et al., 2008. Neurodevelopmental markers in different psychopathological dimensions of first episode psychosis: the ESPIGAS study. Eur. Psychiatry 23, 533–540.
Rund, B.R., Melle, I., Friis, S., Larsen, T.K., Midbøe, L.J., Opjordsmoen, S., et al., 2004. Neurocognitive dysfunction in first-episode psychosis: correlates with symptoms, premorbid adjustment, and duration of untreated psychosis. Am. J. Psychiatry 16, 466–472.
Rund, B.R., Melle, I., Friis, S., Johannessen, J.O., Larsen, T.K., Midbøe, L.J., et al., 2007. The course of neurocognitive functioning in first-episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. Schizophr. Res. 91, 132–140.
Seisdedos, N., Corral, S., Cordero, A., de la Cruz, M.V., Hernández, M.V., Pereña, J., 1999. WAIS III Escala de Inteligencia de Wechsler para Adultos III. Manual Técnico. TEA Ediciones, Madrid.
Silverstein, M.L., Mavrolefteros, G., Close, D., 2002. Premorbid adjustment and neuropsychological performance in schizophrenia. Schizophr. Bull. 28, 157–165.
Simon, A.E., Cattapan-Ludewig, K., Zmilacher, S., Arbach, D., Gruber, K., Dvorsky, D.N., et al., 2007. Cognitive functioning in the schizophrenia prodrome. Schizophr. Bull. 33 (3), 761–771.
Strauss, G.P., Allen, D.N., Miski, P., Buchanan, R.W., Kirkpatrick, B., Carpenter, W.T., 2012. Differential patterns of premorbid social and academic deterioration in deficit and nondeficit schizophrenia. Schizophr. Res. 135 (1–3), 134–138.
Strous, R.D., Alvir, J.M.J., Robinson, D., Gal, G., Sheitman, B., Chakos, M., et al., 2004. Premorbid functioning in schizophrenia: relation to baseline symptoms, treatment response, and medication side effects. Schizophr. Bull. 30 (2), 265–278.
Tarbox, S.I., Brown, L.H., Haas, G.L., 2012. Diagnostic specificity of poor premorbid adjustment: comparison of schizophrenia, schizoaffective disorder, and mood disorder with psychotic features. Schizophr. Res. 141 (1), 91–97.
Wechsler, D., 1999. Wechsler Adult Intelligence Scale—Third Edition (WAIS-III). Administration and Scoring Manual. The Psychological Corporation, San Antonio, TX.
Woodberry, K.A., Seidman, L.J., Giuliano, A.J., Verdi, M.B., Cook, W.L., McFarlane, W.R., 2010. Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. Schizophr. Res. 123, 188–198.
Zammit, S., Allebeck, P., David, A.S., Dalman, C., Hemmingsson, T., Lundberg, I., et al., 2004. A longitudinal study of premorbid IQ Score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. Arch. Gen. Psychiatry 61 (4), 354–360.

5.2. About prodomal phase:

STUDY 3: Predictive capacity of prodromal symptoms in first-episode psychosis of recent-onset

A. Barajas[a,b,c,d,e], T. Pelaez[b], O. González[b], J. Usall[b], R. Iniesta[d], M. Arteaga[b], C. Jackson[f], I. Baños[d], B. Sánchez[c], M. Dolz[c], J.E. Obiols[e], J.M. Haro[b], GENIPE group[g], S. Ochoa[b]

[a] Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain
[b] Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain
[c] Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[d] Fundació Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[e] Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
[f] Birmingham Early Intervention Service, Birmingham and Solihull Mental Health Foundation Trust, Birmingham, UK

[1] GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, Dachs I, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Miquel L, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

Under review for publication in Comprehensive Psychiatry (see annex)

STUDY 4: Gender differences in individuals at high-risk of psychosis: A comprehensive literature review

A. Barajas[a,b,c], S. Ochoa[c], J.E. Obiols[b], Ll. Lalucat-Jo[a]

[a] Department of Research, Centre d'Higiene Mental Les Corts, Network Group for Research in Women's Mental Health (NGRWMH), 08029 Barcelona, Spain

[b] Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, 08193 Cerdanyola del Vallès, Spain

[c] Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Network Group for Research in Women's Mental Health (NGRWMH), Sant Boi de Llobregat, 08830 Barcelona, Spain

The Scientific World Journal 2015; http://dx.doi.org/10.1155/2015/430735

Hindawi Publishing Corporation
The Scientific World Journal
Volume 2015, Article ID 430735, 13 pages
http://dx.doi.org/10.1155/2015/430735

Review Article

Gender Differences in Individuals at High-Risk of Psychosis: A Comprehensive Literature Review

Ana Barajas,[1,2,3] Susana Ochoa,[3] Jordi E. Obiols,[2] and Lluís Lalucat-Jo[1]

[1]*Department of Research, Centre d'Higiene Mental Les Corts, Network Group for Research in Women's Mental Health (NGRWMH), 08029 Barcelona, Spain*
[2]*Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, 08193 Cerdanyola del Vallès, Spain*
[3]*Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Network Group for Research in Women's Mental Health (NGRWMH), Sant Boi de Llobregat, 08830 Barcelona, Spain*

Correspondence should be addressed to Ana Barajas; ana.barajas@chmcorts.com

Received 31 July 2014; Revised 7 December 2014; Accepted 8 December 2014

Academic Editor: Vittorio Di Michele

Introduction. To date, few studies have focused on the characterization of clinical phenomenology regarding gender in population at high-risk of psychosis. This paper is an attempt to summarize the findings found in the scientific literature regarding gender differences in high-risk populations, taking into account parameters studied in populations with schizophrenia and other psychotic disorders, such as incidence, clinical expression, duration of untreated illness (DUI), social functioning, and cognitive impairment prior to full-blown psychosis development. *Method*. Studies were systematically searched in PubMed. Studies using gender variable as a control variable were excluded. 12 studies met inclusion criteria. *Results*. Most of the studies found a differential pattern between women and men as regards clinical, social, and cognitive variables in the prodromal phase, with worse performance in men except in cognitive functioning (more severe negative symptoms, worse social functioning, and longer DUI in men). Similar conversion rates over time were found between men and women. *Conclusions*. Many of the studies analyzed suggest that differences between men and women in the expression of psychosis extend across a continuum, from the subclinical forms of illness to the debut of psychosis. However, the small number of studies and their significant methodological and clinical limitations do not allow for firm conclusions.

1. Introduction

Gender differences in the clinical expression and outcome of schizophrenia and first-episode psychosis have long been recognized in the literature on schizophrenia and other psychoses [1–5]. Thereby, men and women experience psychosis differently and often require different intervention methods regarding doses and/or types of medications, staging of interventions, and array of treatments offered [6–8]. These studies have meant an advance in the adaptation and improvement of therapeutic strategies targeting this population. Taking into account gender differences found from the dimensional perspective of psychosis, it would be reasonable to consider different expression of the illness from early phases of psychosis, even before the illness appears. Then, learning whether gender differences in clinical presentation and general functioning are present prior to the development of psychosis is an issue of high priority because it could have implications in intervention strategies, making it possible to maximize the impact of these treatments taking gender into account.

In the last two decades, scientific and clinical interest has been focused on early identification of psychosis and intervening as soon as possible to improve the illness prognosis. In this sense, new intervention strategies have focused on people with signs of incipient psychosis, presenting with potentially prodromal symptoms, who have principally been categorized into three clusters of subjects: young people with attenuated positive symptoms, as revealed by dedicated interviews [9]; people with diagnosable transient psychotic symptoms, not

stabilized in a syndrome yet [10, 11]; and a third category of people with genetic risk (first degree relatives of subjects with psychosis), or meeting the criteria for schizotypal personality disorder, who are showing symptoms of deterioration [12]. This clinical syndrome has been termed an at-risk mental state [13], and operationalized criteria—the ultra-high risk (UHR) [14] or clinical high-risk (HR) criteria [15]—have been developed to identify the syndrome. These criteria have been adopted and adapted in a number of other settings around the world [9]. However, this new approach has not taken into account the gender variable, due in part to the lack of research on this topic. To date, only a few studies have focused on the characterization of clinical phenomenology regarding gender in population at high-risk of psychosis.

This paper attempts to summarize the findings in the scientific literature regarding gender differences in high-risk populations, taking into account parameters studied in populations with schizophrenia and other psychotic disorders, such as incidence, clinical expression, duration of untreated illness (DUI), social functioning, and cognitive impairment prior to full-blown psychosis development.

In this review we will try to discuss the following hypothesis: if gender-related factors are equally meaningful over the entire psychosis continuum, it is reasonable to expect that gender differences could also be already identified in subclinical psychosis. It would then be presumed that the same (continuous) development pattern by gender exists from gestation of psychosis until the psychosis threshold. Alternatively, if the hypothesized gender differences are not found, we would have to assume that there are different patterns in how symptoms develop in men and women, with exponential and differential effects starting only when the psychosis threshold is reached.

2. Method

2.1. Inclusion and Exclusion Criteria. Studies analyzing gender differences in high-risk populations for psychosis were considered. Those examining determined outcome measures, such as incidence, clinical expression, duration of untreated illness (DUI), social functioning, and cognitive impairment, were selected. Studies using gender variable as a control variable, in which the main aim was not to examine gender differences in the parameters above indicated, were excluded.

2.2. Search Strategy and Study Selection. PubMed was consulted twice using the following search terms and Boolean operators up to May 31, 2014: (1) a specific search using *high-risk* AND *psychosis* AND (*gender* OR *sex*) AND (*epidemiology* OR *incidence* OR *transition* OR *symptoms* OR *clinical* OR *duration of untreated illness* OR *DUI* OR *social functioning* OR *disability* OR *cognitive functioning* OR *cognitive impairment* OR *cognition* OR *neurocognition*), and (2) a general search using *high risk* AND *psychosis* AND (*gender* OR *sex*). No additional filters regarding the publication date of the articles were used.

The general and specific PubMed searches together generated 258 hits. After removing double hits and screening title and abstract according to the inclusion and exclusion criteria mentioned above, 20 potentially relevant papers were retrieved for more detailed evaluation. These studies were screened on meeting the inclusion criteria and subsequently 12 studies were excluded after reading the full texts, due to irrelevant subject, qualitative methodology, or descriptive nature. Four studies cited in articles selected across PubMed, fulfilling inclusion criteria, were also included. Finally, 12 studies met the inclusion criteria, which are included in Table 1 and in the references list of this paper [16–27].

2.3. Data Extraction. Eligible studies were independently screened by two researchers (S. Ochoa and A. Barajas) to verify the fulfillment of the criteria. The following variables were extracted to generate Table 1: (1) author and publication data, (2) participant characteristics, (3) outcome variables, and (4) main findings. Studies were grouped according to whether outcome measures were related to the following topics: epidemiology, clinical expression, social functioning, and cognitive functioning. For each topic, a general conclusion was extracted in order to summarize the main findings about gender differences in high-risk populations for psychosis.

3. Results

3.1. Epidemiology: Incidence of Transition to Psychosis. Historically, gender differences in schizophrenia cases have been associated with almost all aspects of the disease, including incidence and prevalence ([28–32], see Table 2). The epidemiological characteristics of a disorder can provide important clues in the search for etiology and are essential in the development of evidence-based treatment models. No gender differences in prevalence of schizophrenia have been found in recent studies. Nevertheless, the most replicated result of incidence studies is a higher rate in males versus females in patients with schizophrenia or/and schizophrenia-like psychosis. It is possible that the stricter the diagnostic criteria for schizophrenia, the greater the exclusion for women, resulting in a higher proportion of men diagnosed. However, other authors have attributed this discrepancy in gender differences between incidence and prevalence to clinical variables: a higher suicide rate in men with schizophrenia compared with women [5] or a higher trend to briefer episodes of psychosis, with more complete resolution, in women [33].

According to the continuum hypothesis [34], gender-related factors as identified in full-blown psychosis would be equally meaningful over the entire psychosis continuum and we should expect that "true" gender differences could also be identified in subclinical psychosis. However, to date it is unknown whether gender differences in the epidemiology of schizophrenia extend to those subjects who are at high-risk of developing psychosis. Only a few studies have addressed this question, and they have presented inconsistent results. In a recent study, as part of the North American Prodrome Longitudinal Study (NAPLS) [21], gender differences in the antecedents and course of the prodrome to psychosis in clinical high-risk adolescents and young adults were analyzed. No gender differences were found in conversion rates at

Table 1: Overview of gender differences in high-risk population for psychosis, according to outcome measures: results and main conclusions.

	Study	Sample characteristics	Outcome measures	Key finding	Main conclusion
Epidemiology	Amminger et al., 2006 [16]	86 individuals considered to be at UHR for schizophrenia	Transition to psychosis	The rate of conversion to nonaffective psychosis was not higher among males than females. Female gender was a significant predictor of conversion to affective psychosis at 2-year follow-up.	Inconsistent results were found: some studies did not show gender differences and others indicated a greater risk for conversion to psychosis in men. More studies analyzing gender differences regarding transition to psychosis are needed.
	Nordentoft et al., 2006 [17]	79 patients diagnosed with schizotypal disorder	Transition to psychosis	Males versus females had a fourfold risk [RR: 4.47, CI: 1.30–15.33] for conversion to schizophrenia at 1-year follow-up.	
	Lemos-Giráldez et al., 2009 [18]	61 participants meeting criteria for UHR of psychosis	Transition to psychosis	The conversion rate to psychosis was 22.95% in the three-year follow-up period without gender statistical gender differences (22.5% men versus 23.8% women).	
	Goldstein et al., 2011 [19]	159 parents with psychoses and 114 comparable, healthy control parents. 203 HR and 147 control offspring.	Transmission to psychosis	Risk of psychosis in offspring was a function of the sex of parent and offspring. The male : female ratio for affected offspring differed significantly between affected mothers and fathers.	
	Ziermans et al., 2011 [20]	72 adolescents putatively at UHR for psychosis	Transition to psychosis	15.6% of UHR adolescents converted to psychosis at 2-year follow-up, with a higher proportion of men (13.8%).	
	Walder et al., 2013 [21]	276 CHR NAPLS participants	Transition to psychosis	CHR participants who converted to psychosis (70, 34%) at some point over a 2.5-year follow-up period did not significantly differ in gender distribution.	
Clinical expression	Willhite et al., 2008 [22]	68 UHR patients assessed at baseline, six and twelve months later	Symptoms	Males appeared to have more severe negative symptoms when data from all three time points were examined.	Differences by gender were modest or absent under many variables that were classified as typical of schizophrenia in the past. More negative symptoms in men versus females are the most replicated result in some of the CHR population studies, as in studies of patients with a psychotic spectrum disorder.
	Lemos-Giráldez et al., 2009 [18]	61 participants meeting criteria for UHR of psychosis	Symptoms and recovery pattern	No gender differences in symptom or functioning levels at the three follow-up time points (at baseline, at 1-year and at 3-year follow-up) were found. Males experienced faster and longer deterioration when psychotic symptoms arise.	
	Corcoran et al., 2011 [23]	56 young people at CHR for psychosis	Negative symptoms	As for gender, male patients only had significantly more negative symptoms than females.	
	Cocchi et al., 2014 [24]	106 patients at UHR of psychosis	Age at onset and DUI	No gender differences were found in age of onset, DUI, symptom severity, or level of functioning.	
Social functioning	Willhite et al., 2008 [22]	68 UHR patients assessed at baseline, six and twelve months later.	Functioning and social support	Males were rated as having marginally lower functioning than females over the three follow-up time points. Males reported less positive social support than their female counterparts and felt they received marginally more criticism than females.	Most studies indicated gender differences in premorbid and psychosocial functioning, being worse in men. Social dysfunction in adolescence might be a good predictor of transition to psychosis.
	Lemos-Giráldez et al., 2009 [18]	61 participants meeting criteria for UHR of psychosis	Social functioning	No gender differences in functioning levels at the three follow-up time points (at baseline, at 1-year and at 3-year follow-up) were found.	
	Salokangas et al., 2013 [25]	244 young help-seeking CHR patients	Psychosocial state	At baseline, males' psychosocial situation was poorer than that of females, but at follow-up there was no longer any gender difference in psychosocial outcome. There was also no gender difference in global outcome.	
	Tarbox et al., 2013 [26]	270 CHR individuals in the NAPLS	Premorbid functioning	In the full CHR sample, male participants had worse social functioning in early and late adolescence. Early adolescent social dysfunction significantly predicted conversion to psychosis.	
	Walder et al., 2013 [21]	276 CHR NAPLS participants	Premorbid adjustment and social and role functioning	Baseline social and role functioning are more impaired in CHR males than females (though not in early childhood adjustment).	

Table 1: Continued.

	Study	Sample characteristics	Outcome measures	Key finding	Main conclusion
Cognitive functioning	Walder et al., 2008 [27]	37 youth at HR for psychosis	Neurocognitive performance	AHRP+ females performed worse than same-gender AHRP− on several neurocognitive measures. There were no significant differences between male converters and nonconverters. AHRP− males performed worse than their HR female counterparts on a variety of neurocognitive measures. AHRP+ females performed worse than their HR male counterparts on a measure of verbal memory.	Neurocognitive performance in CHR shows a differential gender effect that varies by risk status. It suggests the importance of considering sexually differentiated patterns of cognitive decline in prodromal subjects.

CHR: clinical high-risk; NAPLS: North American Prodrome Longitudinal Study; HR: high-risk; UHR: ultrahigh risk; RR: relative risk; CI: confidence interval; AHRP+: at high-risk for psychosis who converted; AHRP−: at high-risk for psychosis who did not convert.

Table 2: Overview of gender differences in psychosis spectrum disorder studies: controversial results and main conclusions.

	Study	Sample characteristics*	Outcome measures	Key finding**	Main conclusion
Epidemiology	Castle et al., 1993 [28]	470 first-contact patients with nonaffective functional psychosis	Incidence	The ratio of male to female incidence rates rose progressively when RDC (1.2), DSM-III-R (1.3), DSM-III (2.2), and Feighner (2.5) criteria for schizophrenia were applied. Schizophrenia was most common in young males and least common in older males, with females occupying an intermediate position.	Gender differences in incidence rates were found in patients with schizophrenia and schizophrenia-like psychosis, being higher in males. However, no gender differences were found in terms of prevalence. These results may depend on the stringency of the diagnostic criteria applied (i.e., age cut-off or a narrower definition of schizophrenia in terms of symptomatology and duration of symptoms): the broader the criteria the less significant the gender differences in incidence or prevalence.
	Aleman et al., 2003 [29]	38 publications on "incidence of schizophrenia" published during the period between January 1980 and September 2001	Incidence	The incidence risk ratios for men developing schizophrenia relative to women were 1.42 (95% [CI], 1.30–1.56) when all studies were included in the analysis (49 effect sizes). This risk remained significantly higher in men after controlling for potentially confounding factors (i.e. age bias, criterion bias, and hospital bias).	
	Saha et al., 2005 [30]	A total of 1,721 prevalence estimates from 188 studies	Prevalence	No significant differences in prevalence of schizophrenia were found between males and females. For the male: female estimate ratio (based on 57 ratios), the median value was 1.11, and the 10% and 90% quantiles were 0.50 to 1.70.	
	Perälä et al., 2007 [31]	248 subjects, 30 years or older, with a diagnosis of any psychotic disorder	LTP	The LTP was 3.06% for any psychotic disorder, and regarding gender it was 3.11% for men vs. 3.01% for women. In particular, in relation to schizophrenia diagnosis no gender differences were observed in the prevalence data.	
	McGrath et al., 2008 [32]	For the incidence analysis, 158 studies that generated 1,458 rates For the prevalence analysis, 188 studies that provided 1,721 prevalence estimates	Incidence and prevalence	The distribution of incidence rates differed significantly between males and females, and the median (10, 90 percent quantiles) rate ratio for male : female estimates was 1.4 (0.9, 2.4). The gender difference identified in the incidence rates is not reflected in prevalence estimates (the median lifetime prevalence estimates for males were 3.7 per 1,000 vs. 3.8 per 1,000 for females)	
Clinical expression	Lindström and Von Knorring, 1994 [40]	140 patients with schizophrenic syndromes	Positive, negative, excited, anxious/depressive, and cognitive symptoms	No gender differences were found in the 5-factor model of schizophrenia, including positive, negative, excited, anxious/depressive and cognitive factors.	No consensus exists regarding gender differences in the clinical expression of psychosis. This could be due to clinical and/or methodological factors. Studies showing gender differences obtained discordant results. However, the most replicated findings suggest that mood symptoms are common in women with schizophrenia or FEP, while negative symptoms tend to be more predominant in men.
	Szymanski et al., 1995 [41]	54 patients with first-episode schizophrenia	Affective and positive symptoms	Females displayed significantly less illogical thinking, but more anxiety, inappropriate affect and bizarre behavior than the men.	
	Gur et al., 1996 [42]	272 patients with schizophrenia	Negative and positive symptoms	A greater severity of negative symptoms in men and identical severity of positive symptoms for men and women in all age groups were observed.	
	Hayashi et al., 2002 [43]	308 patients with DSM-IV schizophrenia	Positive, negative, excited, anxious/depressive, and cognitive symptoms	In a five-factorial structure model of PANSS the factors and component symptoms were common across gender.	

Table 2: Continued.

	Study	Sample characteristics*	Outcome measures	Key finding**	Main conclusion
	Morgan et al., 2008 [44]	1090 cases of affective and nonaffective psychosis	Positive, affective, and negative symptoms	In schizophrenia specifically, women were significantly less likely than men to report having hallucinations, delusions or poor concentration currently, and more likely to report at least one serious episode of dysphoria over a lifetime. Within all groups, women were less likely than men to experience negative symptoms.	
	Cotton et al., 2009 [45]	661 patients with first episode psychosis	Depressive symptoms	Females were more likely to have depressive symptoms while males experienced more severe psychopathology.	
	Barajas et al., 2010 [46]	53 consecutive cases with a first psychotic episode	Negative symptoms and insight	In the group of younger patients, men showed more negative symptoms and poorer insight than women. No gender differences were observed in the clinical expression of the episode in the older group of patients.	
	Galderisi et al., 2012 [47]	276 patients with spectrum disorders of schizophrenia	Negative symptoms	Female patients, as compared with males, showed fewer negative symptoms.	
Social functioning	Häfner et al., 1993 [59]	267 first-admitted patients with nonaffective functional psychosis	Premorbid and social and occupational functioning	Males had lower social role functioning than females prior to first admission, and of those patients who achieved adequate role functioning, males had greater deterioration in social and occupational functioning after onset.	Better social functioning appears to be a particular strength of women with psychosis spectrum disorders compared to men. However, not all studies confirm this finding. Methodological issues could explain these discrepancies (i.e., sample size, lack of sample representativeness, and measures used to assess social functioning).
	Andia et al., 1995 [60]	85 outpatients with schizophrenia	Psychosocial functioning	Women exhibited better psychosocial functioning (better educated and more often married, living independently, and employed).	
	Usall et al., 2002 [61]	200 outpatients with schizophrenia (DSM-IV criteria)	General functioning and disability	Gender influenced significantly on DAS (occupational and personal care) and GAF, with men showing worse functioning.	
	Grossman et al., 2008 [62]	97 patients with schizophrenia and other psychotic disorders	Global functioning	Women showed significantly better global functioning at 3 of the 6 follow-ups (the 2-, 7.5-, and 10-year follow-ups).	
	Cotton et al., 2009 [45]	661 patients with first episode psychosis	Premorbid and social functioning	There were no gender differences in premorbid functioning (measured by the GAF). Males experienced lower levels of functioning, being less likely to be working/studying, and more likely to be living with their family.	
	Bottlender et al., 2010 [64]	177 patients with life-time diagnoses belonging to the schizophrenic, schizoaffective, or affective spectrum (ICD-10 criteria)	Social disability	No gender differences were found in social disability using DAS scale.	
	Vila-Rodriguez et al., 2011 [63]	231 community-dwelling individuals with schizophrenia	Social functioning	Women scored higher in social functioning (LSP). While men's social functioning is affected by positive symptoms, women's social functioning is impaired by disorganized symptoms.	
	Galderisi et al., 2012 [47]	295 stabilized patients with schizophrenia, schizoaffective, or delusional disorder	Social functioning	No significant effect of gender was observed on any index of social functioning.	

Table 2: Continued.

	Study	Sample characteristics*	Outcome measures	Key finding**	Main conclusion
Cognitive functioning	Goldberg et al., 1995 [73]	Four independent schizophrenic cohorts: two groups of inpatients with chronic courses at a research hospital ($N = 191$), one group of consecutive admissions to a private psychiatric hospital ($N = 57$), and one group of schizophrenic twins from discordant monozygotic pairs ($N = 20$)	Neuropsychological performance	Not one comparison significantly favored women, and few were even significantly different by gender.	The inconsistencies in the results may be due mainly to methodological questions (i.e., samples of convenience including not representative male and female patients, analysis not controlling clinical variables, lack of normal comparison group, or lack of consensus in measures used).
	Lewine et al., 1996 [69]	195 patients with schizophrenia or schizoaffective disorder	Neuropsychological functioning	Women performed significantly more poorly than men in verbal memory, spatial memory, and visual processing.	
	Purcell et al., 1998 [70]	159 patients with schizophrenia or schizoaffective disorder	VIQ and PIQ	Significantly more men than women with schizophrenia exhibited a VIQ > PIQ pattern.	
	Moriarty et al., 2001 [74]	205 geriatric patients with lifelong poor-outcome schizophrenia	Cognitive impairment	No gender differences in cognitive functioning were found.	
	Bozikas et al., 2010 [71]	96 schizophrenia patients	Basic cognitive abilities	The effect of gender was significant for verbal learning and memory, wherein women outperformed men.	
	Vaskinn et al., 2011 [72]	154 participants with schizophrenia and 106 participants with bipolar I disorder	Neurocognitive performance	Women performed better than men for all neuropsychological tests (except attention and working memory).	

*Sample characteristics of the participants with a psychotic spectrum disorder **key finding regarding gender differences.

RDC: research diagnostic criteria; DSM: diagnostic and statistical manual of mental disorder; CI: confidence interval; LTP: lifetime prevalence; PANSS: positive and negative syndrome scale; DAS: disability assessment scale; GAF: global assessment functioning; ICD: international classification of diseases; VIQ: substantial verbal intelligence quotient; PIQ: performance intelligence quotient.

2.5 years follow-up (26.5% women; 24.5% men). In the same sense, Lemos-Giráldez et al. [18]. found that the conversion rate to psychosis was 22.95% in the three-year follow-up period without statistical gender differences (22.5% men versus 23.8% women). In addition, in a study with help-seeking adolescents at ultrahigh risk (UHR) for psychosis, Ziermans et al. [20] showed that at the end of the follow-up period (2 years) 15.6% of UHR adolescents had experienced a psychotic transition, with a higher proportion of men. Furthermore, Nordentoft et al. [17] found that, among young adults with a diagnosis of schizotypal disorder, men had a fourfold greater risk for conversion to schizophrenia one-year after enrollment when compared to women. However, the findings of this study may not be directly comparable to the entire UHR population, which includes a wider definition of psychosis risk. To date, it is unclear if at-risk-mental-state in men is associated with a higher risk of progression to schizophrenia than in women. Amminger et al. [16] found that the rate of conversion to nonaffective psychosis was not higher among men than women. They explained this result in relation to the greater weight of positive psychotic symptoms in the UHR criteria definition, which might be more effective in detecting "true" prodromal cases among women than men because they focus on positive attenuated symptoms, with minimal attention to negative symptoms. This interpretation is supported by Maric et al. [35], who reported that, in a general population sample, subclinical positive psychotic symptoms were more prevalent in women, whilst subclinical negative psychotic symptoms were more prevalent in men. Some epidemiological investigations that took a more general approach concerning subclinical psychosis have detected no gender differences [36, 37]. Van Os et al. [34] found slightly increased odds ratios for men in a meta-analysis of epidemiological studies focusing on subclinical psychosis. These results referred only to prevalence rates whereas the incidence rate in that meta-analysis was minimally higher for women. Spauwen et al. [38] analyzed a representative Dutch population sample (aged 17 to 28), with their main focus being on possible gender differences before and after the age of 21. They found that the incidence of subclinical psychotic experiences was higher in men aged 17 to 21 but then became similar to that of women when those men reached 22 to 28 years of age.

On the other hand, Goldstein et al. [19] demonstrated that there are sex-specific patterns of transmission of psychosis. Among fathers with psychoses most offspring who developed psychosis were female (15.2% females versus 3.1% males); in contrast, among mothers with psychosis 18.8% of their male offspring developed psychosis compared with 9.5% of their daughters. So that risk of psychosis among the offspring of parents with psychosis was dependent on the gender variable. These results show the importance of considering sexual differentiation in the concept of psychosis risk.

Finally, it is important to note that more women than men seek help for psychological or medical problems [39]. Taking this into account, additional strategies of detection and different criteria are needed to determine real incidence rates in risk mental states of psychosis.

The disparity found between these findings, as in the schizophrenia studies, could be due to clinical and/or methodological factors: the lack of consensus among the studies in defining a patient at high-risk for psychosis, as well as the lack of differential detection strategies according to gender, could be some possible explanations. In this sense, in epidemiological terms, it is not possible to confirm continuity in gender differences between subthreshold psychosis and frank psychosis.

In relation to the lack of consensus on the definition of risk criteria for psychosis, they could be based on expression differential between women and men as regards clinical, social, and cognitive variables in the prodromal phase. We will now turn to a summary of studies that have analyzed the differences in clinical, functional, and cognitive expression by gender in individuals at risk of psychosis.

3.2. Clinical Expression and DUI. Gender differences in symptom expression have important implications for several reasons. For example, symptom presentation likely plays an important role in determining treatment regimens and understanding gender differences in treatment response. To date, the results in psychosis spectrum disorder studies regarding this area are inconclusive ([40–47], see Table 2). A number of factors may account for this, including medication status (higher doses of typical antipsychotics contributing to negative symptomatology), diagnostic stringency (use of stricter criteria excluding women with affective symptoms), age at onset (negative symptoms are more prominent in younger men than in younger women), and sampling bias (inadequate sample size or overrepresentation of men). Nevertheless, the most replicated findings, in samples of patients with psychotic spectrum disorders, suggest that affective symptoms are more common in women while negative symptoms tend to be more predominant in men. These findings have also been found in some studies analyzing gender differences in UHR samples. Willhite et al. [22] found that, prior to the expression of full-blown psychosis, young men were rated as having more severe negative symptoms than women when baseline and follow-up time points (6- and 12-month) were jointly considered. This result is consistent with the large literature in the field, in both studies of individuals at-risk for psychosis [23] and studies about psychotic disorders spectrum [1, 48, 49], indicating that the differences between men and women in clinical presentation extend across the continuum of psychosis. Men with UHR for psychosis had more "typical" symptoms of schizophrenia than women. However, there was no effect of gender for ratings on the other symptom dimensions using the Structured Interview for Prodromal Syndromes (SIPS). In another study analyzing individuals with UHR for psychosis by gender [16] it was found that female gender was one of the independent significant predictors of affective psychosis, which is in accordance with the higher prevalence of affective disorders in women [50]. These findings suggest that underlying gender differences may predate the onset of psychosis. This could reflect the fact that men and women are vulnerable to different "types" of psychotic disorders or

that psychosis develops differently in men and women. In contrast, other studies of individuals with UHR for psychosis did not find gender differences in the expression of symptoms [18, 24]. As already mentioned in the previous section, methodological and clinical variables could influence the discrepancy of the results found, similarly to what occurs in schizophrenia and first-episode psychosis studies.

In relation to onset of illness, in the ABC first-episode sample with a broad definition of schizophrenia, Häfner [51], showed that the disorder manifests itself clearly later in women than men, from the first sign of the illness. Women's mean age at first symptom was 25.4 years, 2.9 years higher than men's age. On the other hand, women in general are more help seeking and have a more positive attitude towards taking medication than men [52]. Further, women tend to express their emotions more readily and behave in a relatively unobtrusive way. Thus, women patients may be more likely to be misdiagnosed, for example, with a mood disorder [53]. Also, it is widely accepted that women have better access to social networks and social support [54]. This behaviour pattern together with a later onset of first symptoms of illness could indicate a shorter duration of untreated illness in women. However, Cocchi et al. [24] and previous studies [16, 18] with UHR samples did not find significant differences by gender in DUI, which was shorter in women than in men in most samples. This discrepancy may be a consequence of faster and longer deterioration in men when symptoms arise [18]. Additionally, in the general population age-related gender differences in maturational processes have been observed, in particular, a significantly greater loss of cerebral grey matter in boys compared to girls [55], which may represent the underlying mechanism of men showing an earlier age of onset of psychosis than women in subclinical samples. An alternative explanation may be found in the differential exposure to estrogens which may play a protective role by decreasing the risk for and the severity of psychotic disorders in women [56]. Despite the results about DUI being replicated in UHR samples, we must take into account that a high percentage of the sample will not transition to psychosis. So the implications of these findings in the continuum of psychosis should be treated with caution. These findings should be compared with studies about UHR individuals who convert to psychosis.

Regarding the association between clinical symptoms and social functioning found in psychotic disorders [57, 58], there are studies with UHR samples which confirm that this association is already present before the onset of psychosis [22, 23]. Because UHR patients may experience different combinations of symptoms according to gender these differences may contribute to different functional outcomes. Based on these results, developing targeted intervention to decrease the severity of symptoms would improve the general functioning and quality of life for patients.

3.3. Social Functioning. In general, psychosis spectrum disorder studies analyzing premorbid and social functioning show better performance in women ([45, 59–63], see Table 2). We have not found studies reporting worse social functioning in women. However, there are studies reflecting the absence of gender differences in this area ([47, 64], see Table 2). Methodological issues might explain these discrepancies (i.e., small sample size, lack of sample-gender representativeness, or measures used to assess social functioning). Similar conclusions can be drawn from studies with patients at high-risk for psychosis. Willhite et al. [22] investigated gender differences in functioning and social support in individuals at UHR for developing a psychotic disorder, showing that men had marginally lower functioning than women over the three time points (at baseline, 6- and 12-month follow-up). Differences in other psychosocial factors may also contribute to better functioning in women UHR patients. Women reported higher levels of social support at baseline: women were more likely to say that their friends and family members "appreciate them" and that they feel they can "open up" to their friends and family members, while men report marginally higher levels of criticism than women. These results would support the importance of psychosocial interventions for this population. However, subsequently, mixed results have been obtained, from studies that contradict these results [18] as well as those that confirm them [25].

In relation to premorbid functioning, most studies in psychotic disorder samples have found gender differences, this being worse in men than in women [44, 46, 65]. Contrary to expectation, the NAPLS study [21] found that early childhood academic, social, and total adjustments were comparable by gender. It is possible that impairment at this age may be too subtle to be detected, being more evident from adolescence.

On the other hand, there are suggestions that deficits in social functioning are often predictors of later social functioning [66]. Besides, prior findings have indicated that social and role (school/work) functioning are key predictors of conversion among UHR youth [67, 68]. Therefore, prevention strategies could be improved with a more comprehensive approach that involves developmentally earlier functional deficits. However, it has been suggested that social functioning as a predictor of psychosis onset may be stronger for men than women [22, 26]. These findings are corroborated in Walder et al. [21]; specifically, poorer baseline social functioning and positive prodromal symptoms predict greater conversion risk among men. So, to understand the early development of psychosis it is essential to consider sexually differentiated predictors. It may be helpful to improve risk identification using algorithms that take into account the gender variable. To date a global assessment of functioning (GAF) score of 50 or below has been used in the risk criteria, but gender variable was not considered.

There is some agreement among the results found in the scientific literature about full-blown psychosis and the UHR studies regarding social and role functioning. These results support the continuum hypothesis in the development of psychosis, taking into account a differential expression of social functioning according to gender from premorbid phases, which is worse in men. Nevertheless, broader samples with more equal distribution by gender are essential for more rigorous investigation.

3.4. Cognitive Functioning. Although studies analyzing cognitive function in patients with psychosis spectrum disorders have reported gender differences on neuropsychological testing ([69–72], see Table 2), these differences have not been tested in all studies ([73, 74], see Table 2) and their nature is controversial. As indicated in previous sections, these discrepancies could be partly related to methodological issues. Among studies showing gender differences, the finding most often replicated indicates higher levels of cognitive functioning in women.

Over the past several years, under the assumption that the prodromal period is marked by disruptions in the normal brain maturation processes having an impact on neurocognition, there has been an accumulation of data examining cognition in those at elevated risk for psychosis [75–77], which have confirmed that cognitive deficits are already present before the first episode. These studies report widespread cognitive deficits intermediate to healthy control and first-episode psychosis samples. However, these studies have several methodological limitations (i.e., small samples, lack of power to detect differences, and a limited longitudinal framework, among others) that make it difficult to generalize the results. In this sense more research about cognition functioning is required, also taking into account gender factor from the incipient phases of psychosis. To date, scarce research has been performed in this direction. To our knowledge, the study of Walder et al. [27] is the only one to consider this issue as a main objective. It is a longitudinal study of 37 adolescents at high-risk for psychosis, which showed that women who convert performed worse on several neurocognitive measures than same-gender subjects who do not convert. There were no significant differences between men converters and nonconverters. In the group who converts, women showed worse performance than their high-risk male counterparts on a measure of verbal memory, unlike the results found with schizophrenia patients [71]. The low number of women converters did not allow for valid conclusions on gender differences. Nevertheless, these results suggest the importance of considering sexually differentiated patterns of cognitive decline in prodromal individuals. Furthermore, sexually differentiated neurohormonal fluctuations are present during adolescence and early adulthood and may play an integral role in the transition to psychosis [78].

More studies are needed to explore a possible continuity of cognitive decline according to gender from subthreshold phases of psychosis up to its onset. Future longitudinal research, overcoming the previous methodological limitations and aimed at tracking at-risk cohorts from premorbid periods until clinical high-risk to psychosis onset, will help clarify the existence of neurocognitive profiles in predicting conversion risk based on gender differences.

4. Conclusions

In conclusion, although the extent of gender differences in individuals with UHR for psychosis is reduced mainly due to the small number of studies published to date and their limitations (see Section 5), in this section we will try to summarize the most relevant findings and their clinical and research implications.

(i) Inconsistent results were found in relation to transition to psychosis: some studies did not show gender differences and others indicated a greater risk for conversion to psychosis in men. It might be suggested that differential precipitating factors exist according to gender which are involved in conversion to psychosis and their identification should be useful in clinical practice.

(ii) Men at-risk for psychosis have more severe negative symptoms than women before full-blown psychosis, being more difficult to detect them across current risk criteria for psychosis focused on positive attenuated symptoms. In addition, developing targeted intervention to decrease the severity of negative symptoms during prodromal phase, more severe in men, would improve the general functioning and quality of life for patients since earlier phases of psychosis.

(iii) Female gender is one of the independent significant predictors of affective psychosis. It highlights the importance of considering sexually differentiated high-risk criteria to improve the identification of possible risk cases with different diagnoses in the continuum of psychosis.

(iv) Significant gender differences have not been found in DUI, although it is shorter in women than in men in most of the studies. It is likely that more women seek help for psychological or medical problems than men. Additional detection strategies, especially targeted at males, should be developed, not only to improve the quality of research but also above all to prevent the development of more severe forms of the disease.

(v) Men show lower functioning and social support than women before full-blown psychosis. Also, social functioning is a stronger predictor of psychosis onset in men than women. Psychosocial interventions targeted at this population would be helpful to improve the prognosis of the illness.

(vi) The limited scientific evidence about cognitive impairment in prodromal phase according to gender has indicated a differential sex effect that varies by risk status. However, the lack of studies does not allow us to generalize from the results. It is necessary to broaden our knowledge in this area and so be able to implement the findings in clinical practice.

In summary, many of the studies analyzed suggest that differences between men and women in the expression of psychosis extend across a continuum, from the subclinical forms of illness to the debut of psychosis, mainly in aspects of clinical expression (such as more negative symptoms in men) and social functioning (such as premorbid and psychosocial functioning, worse in men). However, the small number of studies and their significant methodological and clinical limitations do not allow for firm conclusions.

5. Limitations and Future Directions

We must be cautious when considering the extracted conclusions of this comprehensive review about gender differences in individuals at high-risk for psychosis due to the limitations of the studies analyzed. The main clinical and methodological limitations of the studies included in this review are the following: (a) the limited sample size with unequal distribution of participants at baseline by gender, (b) a strict age range, (c) the exclusion of people with substance dependence, (d) the lack of standardized instruments to measure some variables (e.g., DUI), (e) the use of diagnostic criteria for the UHR which require the presence of symptoms in excess, and (f) the large attrition rates. Taking into account these limitations, it is possible that the samples of these studies are not representative of the population of all UHR cases and may obscure or reduce the extent of gender-related differences found. Also, the methodological variability of these studies limits the generalizability of their findings. Nevertheless, something to keep in mind is that gender differences might be less evident in UHR samples than in samples of people diagnosed with psychotic disorders because only a minority of UHR people develops full-blown psychosis [79].

More research is needed to overcome the limitations mentioned in order to deepen our knowledge about this topic. Future researchers should be focused on (a) improving detection algorithms for risk of psychosis, due to differential expression of subclinical forms of psychosis according to gender; according to the results found, there is a need to include negative symptoms in the risk criteria, which may help to identify more young men at risk for psychosis; (b) analyzing other variables or risk factors by gender such as substance use, family history, stress, or obstetric complications; (c) using gender as a covariable in future research about effectiveness of interventions in prodromal phase; (d) studying gender differences in the precipitating factor for psychosis; (e) analyzing different pattern of cognitive impairment by gender; and (f) identifying protector factors delaying conversion by gender. Further elucidation of differential pattern by gender during the prodrome to psychosis is critical to understanding illness etiology and generating more powerful predictive models that would be maximally sensitive and specific. This may aid in development of individually tailored treatments, with consideration of the effects of gender, which may target different neurobiological systems and/or use alternative cognitive/behavioral approaches with optimal effect. Gender-sensitive services are a first step toward individual-specific personalized care, as men and women may differentially benefit from certain approaches to intervention.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] A. Leung and P. Chue, "Sex differences in schizophrenia, a review of the literature," *Acta Psychiatrica Scandinavica, Supplement*, vol. 101, no. 401, pp. 3–38, 2000.

[2] A. Køster, M. Lajer, A. Lindhardt, and B. Rosenbaum, "Gender differences in first episode psychosis," *Social Psychiatry and Psychiatric Epidemiology*, vol. 43, no. 12, pp. 940–946, 2008.

[3] K. M. Abel, R. Drake, and J. M. Goldstein, "Sex differences in schizophrenia," *International Review of Psychiatry*, vol. 22, no. 5, pp. 417–428, 2010.

[4] S. Ochoa, J. Usall, J. Cobo, X. Labad, and J. Kulkarni, "Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review," *Schizophrenia Research and Treatment*, vol. 2012, Article ID 916198, 9 pages, 2012.

[5] M. V. Seeman, "Women and psychosis," *Women's Health*, vol. 8, no. 2, pp. 215–224, 2012.

[6] J. Kulkarni, A. de Castella, P. B. Fitzgerald et al., "Estrogen in severe mental illness: a potential new treatment approach," *Archives of General Psychiatry*, vol. 65, no. 8, pp. 955–960, 2008.

[7] S. Smith, "Gender differences in antipsychotic prescribing," *International Review of Psychiatry*, vol. 22, no. 5, pp. 472–484, 2010.

[8] J. Usall, E. Huerta-Ramos, R. Iniesta et al., "Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial," *The Journal of Clinical Psychiatry*, vol. 72, no. 11, pp. 1552–1557, 2011.

[9] K. A. Olsen and B. Rosenbaum, "Prospective investigations of the prodromal state of schizophrenia: assessment instruments," *Acta Psychiatrica Scandinavica*, vol. 113, no. 4, pp. 273–282, 2006.

[10] A. E. Simon, D. N. Dvorsky, J. Boesch et al., "Defining subjects at risk for psychosis: a comparison of two approaches," *Schizophrenia Research*, vol. 81, no. 1, pp. 83–90, 2006.

[11] L. J. Phillips, P. D. McGorry, H. P. Yuen et al., "Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis," *Schizophrenia Research*, vol. 96, no. 1–3, pp. 25–33, 2007.

[12] B. A. Cornblatt, T. Lencz, C. W. Smith, C. U. Correll, A. M. Auther, and E. Nakayama, "The schizophrenia prodrome revisited: a neurodevelopmental perspective," *Schizophrenia Bulletin*, vol. 29, no. 4, pp. 633–651, 2003.

[13] A. R. Yung, P. D. McGorry, C. A. McFarlane, H. J. Jackson, G. C. Patton, and A. Rakkar, "Monitoring and care of young people at incipient risk of psychosis," *Schizophrenia Bulletin*, vol. 22, no. 2, pp. 283–303, 1996.

[14] A. R. Yung, L. J. Phillips, H. P. Yuen, and P. D. McGorry, "Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features," *Schizophrenia Research*, vol. 67, no. 2-3, pp. 131–142, 2004.

[15] B. A. Cornblatt, T. Lencz, C. W. Smith et al., "Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents," *The Journal of Clinical Psychiatry*, vol. 68, no. 4, pp. 546–557, 2007.

[16] G. P. Amminger, S. Leicester, A. R. Yung et al., "Early-onset of symptoms predicts conversion to non-affective psychosis in ultra-high risk individuals," *Schizophrenia Research*, vol. 84, no. 1, pp. 67–76, 2006.

[17] M. Nordentoft, A. Thorup, L. Petersen et al., "Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment," *Schizophrenia Research*, vol. 83, no. 1, pp. 29–40, 2006.

[18] S. Lemos-Giráldez, O. Vallina-Fernández, P. Fernández-Iglesias et al., "Symptomatic and functional outcome in youth at ultra-high risk for psychosis: a longitudinal study," *Schizophrenia Research*, vol. 115, no. 2-3, pp. 121–129, 2009.

[19] J. M. Goldstein, S. Cherkerzian, L. J. Seidman et al., "Sex-specific rates of transmission of psychosis in the New England high-risk family study," *Schizophrenia Research*, vol. 128, no. 1–3, pp. 150–155, 2011.

[20] T. B. Ziermans, P. F. Schothorst, M. Sprong, and H. van Engeland, "Transition and remission in adolescents at ultra-high risk for psychosis," *Schizophrenia Research*, vol. 126, no. 1–3, pp. 58–64, 2011.

[21] D. J. Walder, C. W. Holtzman, J. Addington et al., "Sexual dimorphisms and prediction of conversion in the NAPLS psychosis prodrome," *Schizophrenia Research*, vol. 144, no. 1–3, pp. 43–50, 2013.

[22] R. K. Willhite, T. A. Niendam, C. E. Bearden, J. Zinberg, M. P. O'Brien, and T. D. Cannon, "Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder," *Schizophrenia Research*, vol. 104, no. 1–3, pp. 237–245, 2008.

[23] C. M. Corcoran, D. Kimhy, M. A. Parrilla-Escobar et al., "The relationship of social function to depressive and negative symptoms in individuals at clinical high risk for psychosis," *Psychological Medicine*, vol. 41, no. 2, pp. 251–261, 2011.

[24] A. Cocchi, A. Lora, A. Meneghelli et al., "Sex differences in first-episode psychosis and in people at ultra-high risk," *Psychiatry Research*, vol. 215, no. 2, pp. 314–322, 2014.

[25] R. K. R. Salokangas, D. H. Nieman, M. Heinimaa et al., "Psychosocial outcome in patients at clinical high risk of psychosis: a prospective follow-up," *Social Psychiatry and Psychiatric Epidemiology*, vol. 48, no. 2, pp. 303–311, 2013.

[26] S. I. Tarbox, J. Addington, K. S. Cadenhead et al., "Premorbid functional development and conversion to psychosis in clinical high-risk youths," *Development and Psychopathology*, vol. 25, no. 4, pp. 1171–1186, 2013.

[27] D. J. Walder, V. Mittal, H. D. Trotman, A. L. McMillan, and E. F. Walker, "Neurocognition and conversion to psychosis in adolescents at high-risk," *Schizophrenia Research*, vol. 101, no. 1–3, pp. 161–168, 2008.

[28] D. J. Castle, S. Wessely, and R. M. Murray, "Sex and schizophrenia: effects of diagnostic stringency, and associations with premorbid variables," *British Journal of Psychiatry*, vol. 162, pp. 658–664, 1993.

[29] A. Aleman, R. S. Kahn, and J.-P. Selten, "Sex differences in the risk of schizophrenia: evidence from meta-analysis," *Archives of General Psychiatry*, vol. 60, no. 6, pp. 565–571, 2003.

[30] S. Saha, D. Chant, J. Welham, and J. McGrath, "A systematic review of the prevalence of schizophrenia," *PLoS Medicine*, vol. 2, no. 5, article e141, 2005.

[31] J. Perälä, J. Suvisaari, S. I. Saarni et al., "Lifetime prevalence of psychotic and bipolar I disorders in a general population," *Archives of General Psychiatry*, vol. 64, no. 1, pp. 19–28, 2007.

[32] J. McGrath, S. Saha, D. Chant, and J. Welham, "Schizophrenia: a concise overview of incidence, prevalence, and mortality," *Epidemiologic Reviews*, vol. 30, no. 1, pp. 67–76, 2008.

[33] A. Castagnini and G. E. Berrios, "Acute and transient psychotic disorders (ICD-10 F23): a review from a European perspective," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 259, no. 8, pp. 433–443, 2009.

[34] J. Van Os, R. J. Linscott, I. Myin-Germeys, P. Delespaul, and L. Krabbendam, "A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder," *Psychological Medicine*, vol. 39, no. 2, pp. 179–195, 2009.

[35] N. Maric, L. Krabbendam, W. Vollebergh, R. De Graaf, and J. Van Os, "Sex differences in symptoms of psychosis in a non-selected, general population sample," *Schizophrenia Research*, vol. 63, no. 1-2, pp. 89–95, 2003.

[36] J. Scott, D. Chant, G. Andrews, and J. McGrath, "Psychotic-like experiences in the general community: the correlates of CIDI psychosis screen items in an Australian sample," *Psychological Medicine*, vol. 36, no. 2, pp. 231–238, 2006.

[37] N. J. Wiles, S. Zammit, P. Bebbington, N. Singleton, H. Meltzer, and G. Lewis, "Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British National Psychiatric Morbidity Survey," *British Journal of Psychiatry*, vol. 188, no. 6, pp. 519–526, 2006.

[38] J. Spauwen, L. Krabbendam, R. Lieb, H.-U. Wittchen, and J. Van Os, "Sex differences in psychosis: normal or pathological?" *Schizophrenia Research*, vol. 62, no. 1-2, pp. 45–49, 2003.

[39] A. M. Möller-Leimkühler, "Barriers to help-seeking by men: a review of sociocultural and clinical literature with particular reference to depression," *Journal of Affective Disorders*, vol. 71, no. 1–3, pp. 1–9, 2002.

[40] E. Lindström and L. Von Knorring, "Symptoms in schizophrenic syndromes in relation to age, sex, duration of illness and number of previous hospitalizations," *Acta Psychiatrica Scandinavica*, vol. 89, no. 4, pp. 274–278, 1994.

[41] S. Szymanski, J. A. Lieberman, J. M. Alvir et al., "Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients," *The American Journal of Psychiatry*, vol. 152, no. 5, pp. 698–703, 1995.

[42] R. E. Gur, R. G. Petty, B. I. Turetsky, and R. C. Gur, "Schizophrenia throughout life: sex differences in severity and profile of symptoms," *Schizophrenia Research*, vol. 21, no. 1, pp. 1–12, 1996.

[43] N. Hayashi, Y. Igarashi, M. Yamashina, and K. Suda, "Is there a gender difference in a factorial structure of the positive and negative syndrome scale? A test by structural equation modeling," *Psychopathology*, vol. 35, no. 1, pp. 28–35, 2002.

[44] V. A. Morgan, D. J. Castle, and A. V. Jablensky, "Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders," *Australian and New Zealand Journal of Psychiatry*, vol. 42, no. 1, pp. 74–82, 2008.

[45] S. M. Cotton, M. Lambert, B. G. Schimmelmann et al., "Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis," *Schizophrenia Research*, vol. 114, no. 1–3, pp. 17–24, 2009.

[46] A. Barajas, I. Baños, S. Ochoa et al., "Gender differences in incipient psychosis," *The European Journal of Psychiatry*, vol. 24, no. 3, pp. 176–194, 2010.

[47] S. Galderisi, P. Bucci, A. Üçok, and J. Peuskens, "No gender differences in social outcome in patients suffering from schizophrenia," *European Psychiatry*, vol. 27, no. 6, pp. 406–408, 2012.

[48] J. Usall, S. Ochoa, S. Araya, and M. Márquez, "Gender differences and outcome in schizophrenia: a 2-year follow-up study in a large community sample," *European Psychiatry*, vol. 18, no. 6, pp. 282–284, 2003.

[49] L. S. Grossman, M. Harrow, C. Rosen, and R. Faul, "Sex differences in outcome and recovery for schizophrenia and other psychotic and nonpsychotic disorders," *Psychiatric Services*, vol. 57, no. 6, pp. 844–850, 2006.

[50] D. G. Blazer, R. C. Kessler, K. A. McGonagle, and M. S. Swartz, "The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey," *American Journal of Psychiatry*, vol. 151, no. 7, pp. 979–986, 1994.

[51] H. Häfner, "Schizophrenia: do men and women suffer from the same disease?" *Revista de Psiquiatria Clinica*, vol. 29, no. 6, pp. 267–292, 2002.

[52] P. M. Galdas, F. Cheater, and P. Marshall, "Men and health help-seeking behaviour: literature review," *Journal of Advanced Nursing*, vol. 49, no. 6, pp. 616–623, 2005.

[53] Z. Folnegovic and V. Folnegović-Smalc, "Schizophrenia in Croatia: age of onset differences between males and females," *Schizophrenia Research*, vol. 14, no. 1, pp. 83–91, 1994.

[54] C. Gayer-Anderson and C. Morgan, "Social networks, support and early psychosis: a systematic review," *Epidemiology and Psychiatric Sciences*, vol. 22, no. 2, pp. 131–146, 2013.

[55] M. D. de Bellis, M. S. Keshavan, S. R. Beers et al., "Sex differences in brain maturation during childhood and adolescence," *Cerebral Cortex*, vol. 11, no. 6, pp. 552–557, 2001.

[56] A. Riecher-Rössler and H. Häfner, "Gender aspects in schizophrenia: bridging the border between social and biological psychiatry," *Acta Psychiatrica Scandinavica, Supplement*, vol. 102, no. 407, pp. 58–62, 2000.

[57] D. Weinberg, G. Shahar, L. Davidson, T. H. McGlashan, and S. Fennig, "Longitudinal associations between negative symptoms and social functioning in schizophrenia: the moderating role of employment status and setting," *Psychiatry*, vol. 72, no. 4, pp. 370–381, 2009.

[58] M. Brüne, D. Schaub, G. Juckel, and R. Langdon, "Social skills and behavioral problems in schizophrenia: the role of mental state attribution, neurocognition and clinical symptomatology," *Psychiatry Research*, vol. 190, no. 1, pp. 9–17, 2011.

[59] H. Häfner, A. Riecher-Rössler, W. A. der Heiden, K. Maurer, B. Fätkenheuer, and W. Löffler, "Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia," *Psychological Medicine*, vol. 23, no. 4, pp. 925–940, 1993.

[60] A. M. Andia, S. Zisook, R. K. Heaton et al., "Gender differences in schizophrenia," *The Journal of Nervous and Mental Disease*, vol. 183, no. 8, pp. 522–528, 1995.

[61] J. Usall, J. M. Haro, S. Ochoa, M. Márquez, and S. Araya, "Influence of gender on social outcome in schizophrenia," *Acta Psychiatrica Scandinavica*, vol. 106, no. 5, pp. 337–342, 2002.

[62] L. S. Grossman, M. Harrow, C. Rosen, R. Faull, and G. P. Strauss, "Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery," *Comprehensive Psychiatry*, vol. 49, no. 6, pp. 523–529, 2008.

[63] F. Vila-Rodriguez, S. Ochoa, J. Autonell, J. Usall, and J. M. Haro, "Complex interaction between symptoms, social factors, and gender in social functioning in a community-dwelling sample of schizophrenia," *Psychiatric Quarterly*, vol. 82, no. 4, pp. 261–274, 2011.

[64] R. Bottlender, A. Strauß, and H.-J. Möller, "Social disability in schizophrenic, schizoaffective and affective disorders 15 years after first admission," *Schizophrenia Research*, vol. 116, no. 1, pp. 9–15, 2010.

[65] R. M. G. Norman, A. K. Malla, R. Manchanda, and L. Townsend, "Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains," *Acta Psychiatrica Scandinavica*, vol. 112, no. 1, pp. 30–39, 2005.

[66] J. Addington, D. Penn, S. W. Woods, D. Addington, and D. O. Perkins, "Social functioning in individuals at clinical high risk for psychosis," *Schizophrenia Research*, vol. 99, no. 1–3, pp. 119–124, 2008.

[67] S. Dragt, D. H. Nieman, D. Veltman et al., "Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk," *Schizophrenia Research*, vol. 125, no. 1, pp. 69–76, 2011.

[68] B. A. Cornblatt, R. E. Carrión, J. Addington et al., "Risk factors for psychosis: impaired social and role functioning," *Schizophrenia Bulletin*, vol. 38, no. 6, pp. 1247–1257, 2012.

[69] R. R. J. Lewine, E. F. Walker, R. Shurett, J. Caudle, and C. Haden, "Sex differences in neuropsychological functioning among schizophrenic patients," *The American Journal of Psychiatry*, vol. 153, no. 9, pp. 1178–1184, 1996.

[70] D. W. Purcell, R. R. J. Lewine, J. Caudle, and L. R. Price, "Sex differences in verbal IQ-performance IQ discrepancies among patients with schizophrenia and normal volunteers," *Journal of Abnormal Psychology*, vol. 107, no. 1, pp. 161–165, 1998.

[71] V. P. Bozikas, M. H. Kosmidis, A. Peltekis et al., "Sex differences in neuropsychological functioning among schizophrenia patients," *Australian and New Zealand Journal of Psychiatry*, vol. 44, no. 4, pp. 333–341, 2010.

[72] A. Vaskinn, K. Sundet, C. Simonsen, T. Hellvin, I. Melle, and O. A. Andreassen, "Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder," *Neuropsychology*, vol. 25, no. 4, pp. 499–510, 2011.

[73] T. E. Goldberg, J. M. Gold, E. F. Torrey, and D. R. Weinberger, "Lack of sex differences in the neuropsychological performance of patients with schizophrenia," *American Journal of Psychiatry*, vol. 152, no. 6, pp. 883–888, 1995.

[74] P. J. Moriarty, D. Lieber, A. Bennett et al., "Gender differences in poor outcome patients with lifelong schizophrenia," *Schizophrenia Bulletin*, vol. 27, no. 1, pp. 103–113, 2001.

[75] W. J. Brewer, S. J. Wood, L. J. Phillips et al., "Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis," *Schizophrenia Bulletin*, vol. 32, no. 3, pp. 538–555, 2006.

[76] K. A. Hawkins, R. S. E. Keefe, B. K. Christensen et al., "Neuropsychological course in the prodrome and first episode of psychosis: findings from the PRIME North America Double Blind Treatment Study," *Schizophrenia Research*, vol. 105, no. 1–3, pp. 1–9, 2008.

[77] L. J. Seidman, A. J. Giuliano, E. C. Meyer et al., "Neuropsychology of the prodrome to psychosis in the NAPLS Consortium: relationship to family history and conversion to psychosis," *Archives of General Psychiatry*, vol. 67, no. 6, pp. 578–588, 2010.

[78] E. F. Walker, D. J. Walder, and F. Reynolds, "Developmental changes in cortisol secretion in normal and at-risk youth," *Development and Psychopathology*, vol. 13, no. 3, pp. 721–732, 2001.

[79] M. B. De Koning, O. J. N. Bloemen, T. A. M. J. Van Amelsvoort et al., "Early intervention in patients at ultra high risk of psychosis: benefits and risks," *Acta Psychiatrica Scandinavica*, vol. 119, no. 6, pp. 426–442, 2009.

5.3. About psychotic phase:

STUDY 5: Gender differences in incipient psychosis

A. Barajas[a,b,c,d], I. Baños[b], S. Ochoa[b], J. Usall[b], E. Huerta[b], M.Dolz[c], B. Sánchez[c], V. Villalta-Gil[b], A. Foix[b], J.E. Obiols[d], J.M. Haro[b], GENIPE group[1]

[a] Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain
[b] Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain
[c] Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[d] Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain

[1] GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, De Miquel L, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

The European Journal of Psychiatry 2010; 24(3): 176 –194

Eur. J. Psychiat. Vol. 24, N.° 3, (176-194)
2010

Keywords: First episode; Gender differences; Incipient psychosis; Neurodevelopmental; Age of onset.

Gender differences in incipient psychosis

Ana Barajas[*,**]
Iris Baños[**]
Susana Ochoa[**]
Judith Usall[**]
Elena Huerta[**]
Montserrat Dolz[***]
Bernardo Sánchez[***]
Victoria Villalta[**]
Alexandrina Foix[**]
Jordi Obiols[****]
Josep María Haro[**]
GRUPO GENIPE

* Department of Research. Centre de Higiene Mental Les Corts, Barcelona

** Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM)

*** Hospital Sant Joan de Déu de Barcelona, Esplugues de Llobregat. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM)

**** Psychopathology and Neuropsychology Research Unit, Department of Clinical and Health Psychology, Faculty of Psychology, Autonomous University of Barcelona, Bellaterra, Barcelona

SPAIN

ABSTRACT – *Background and Objectives*: To describe gender differences in a group of patients with first-episode psychotic in different aspects: socio-demographic features, characteristics of the phases prior to disease onset (premorbid and prodromic periods), clinical manifestation of psychotic symptoms and possible corresponding cognitive alterations after disease onset, using the age at onset of first psychotic episode as a control variable.

Methods: Longitudinal study of 53 consecutive cases with a first psychotic episode. Inclusion criteria: two or more psychotic symptoms; age between 7 to 65 years old; first consultation to the medical center of study; less than 6 months since the first contact to the medical service; and less than a year of symptoms' evolution. The methodologic assess-

ment includes: a socio-demographic questionnaire and an extensive battery of tests to assess premorbid/prodromic, clinical and cognitive characteristics. We perform mean differences tests to analyze continuous variables (non-parametric U-Mann-Whitney and t-Student test) and chi-square test for categorical variables (SPSS 16.0).

Results: In the group of patients under 18 years, men showed higher scores in adjustment premorbid (U = 54.0, p = 0.050), more neurological soft signs (U = 31.0 p = 0.003), more negative psychotic symptoms (U = 48.5, p = 0.051) and worse insight (U = 30.0, p = 0.003) than women (after 8 weeks of psychotic episode onset).

Conclusions: We found gender differences in most of the variables analyzed when age at onset was controlled. These differences should be taken into account to learn more about the different types of onset of the disease, its prevention and possible improvements in therapeutic approach. Our findings suggest that younger men with an earlier onset of psychotic episode have more alterations in the stages prior to the onset of the disease supporting the neurodevelopmental hypothesis for gender differences.

Received: 2 January 2009
Revised: 14 May 2010
Accepted: 14 May 2010

Introduction

"… Gender differences are an ideal window through which to look at the interplay of biological and psychosocial factors"[1].

The study of gender differences in the psychotic spectrum disorders has given rise to a number of models which have been grouped in two different dimensions: clinical/psychosocial and neurobiological[2,3]. The first refers to the expression of symptoms and social behaviour in schizophrenic patients. Males show a higher frequency of negative psychotic symptoms, whilst females, have a higher probability of showing affective symptoms[4,5]; usually, women with schizophrenia are more active and have a wider social network than affected men, who, in turn, are more passive and have social difficulties[6,7]. The neurobiological dimension could include four hypotheses regarding gender differences in schizophrenia: a) the estrogen hypothesis postulates a protective effect by estrogens in the development of schizophrenia in women which could explain certain gender differences in the manifestation of the disease[8]. In women, estrogens could retard schizophrenia development up to menopause, which would explain its late onset[9]; b) different sub-types of schizophrenia: postulates the existence of two distinct schizophrenias, masculine and feminine[10], corresponding to different forms of expression of specific psychotic symptoms according to the gender of the patient rather than the existence two types of schizophrenic endophenotypes which are clearly differentiated. Castle *et al.*[11], performed a study on a sample of patients with a first psychotic episode and identified three groups: a neurodevelopmental type (predominantly male), a schizoaffective type (almost entirely female) and a paranoid type (with equal sex ratio); c) early and late developmental models: both models postulate changes in the neurological development which predispose the appearance of schizophrenia, but in accordance with the early neurodevelopmental model, these anomalies start at the prenatal and neonatal stages[12]. On the other hand, the late neurodevelopmental

model supports the hypothesis that these occur later in life, particularly during adolescence[13]; d) and brain lateralization: this model attributes gender differences in schizophrenia to the differential hemispheric organization of the male and female brain since the latter is more symmetrically organized (less lateralized) than the male brain[14].

These models do not necessarily contradict each other since they explain distinct aspects and periods in the disease progression. Häfner *et al*.[15,16], stated that the combination of both clinical/psychosocial and neurobiological models could explain gender differences in the expression of schizophrenia. Both clinicians and researchers have observed that males and females do not manifest psychotic spectrum disorders in the same way, since both differ in multiple aspects. In general, women tend to have a more benign form with less deterioration at presentation of schizophrenia.

Socio-demographic Variables

A consistent finding in the literature is the difference between men and women at age of onset of schizophrenia: males have an earlier age of onset compared to females by 3 - 5 years[17,18], independently from the culture of the study group or the diagnostic classification used[3]. Castle *et al*.[19], mention 3 peaks in the age at onset of schizophrenia with distinct distributions between women and men: an early peak which was more prominent in males, a middle peak which was more frequent in females and a third, late onset peak, which was nearly exclusively composed of females coinciding with the results from other studies[17,18,20]. Studies conducted on patients who presented a first psychotic episode[21,22] continue to corroborate this idea. However, these results do not agree with other studies which do not found differences in age at onset between genders[23,24].

Throughout the last decades, other sociodemographic variables and their relationship with gender have been taken into account to explain the observed variability in the manifestation of schizophrenia. Various studies have demonstrated that the age of women at primary hospitalization was higher than for men[25], that the development of the disease in women was less severe[26] and that premorbid competence was better in women than in men measured according to educational level, civil and work status[27].

Studies by Mueser *et al*.[28] and Rabinowitz *et al*.[29] showed a lower frequency in alcohol, cannabis and other substance abuse in women than in men. In a study from Rabinowitz *et al*.[29], in a sample of patients with a first psychotic episode, 17% of men and 6% of women had a moderate-severe grade of substance abuse.

Premorbid and prodromic variables

Classically, the premorbid period has been defined as the period preceding the start of clinical psychosis, whilst the prodromic period refers to the period in which the disease process starts in the absence of clear psychotic symptoms. Studies on the difference between genders during pre-psychotic periods have increased our knowledge regarding the variability in risk factors with respect to gender, the different characteristics in the transition process of psychosis and its later evolution and prognosis in both genders.

Numerous studies which have analyzed gender differences during the premorbid period in schizophrenic patients have shown a better premorbid adaptation in women than

in men[30-32], but their conclusions are not consistent[33,34]. Such differences could be explained by a higher probability in the presentation of altered patterns in neurodevelopment in men than in women[35].

Häfner *et al*.[9] explained that the better premorbid functioning (PF) in women with schizophrenia is due to social and academic factors: a later onset of the disease, an increased ability to maintain social relationships, to have finished their studies and to have an active life before the start of the first psychotic episode.

Studies in patients with a first psychotic episode have shown a possible relationship between the presence of Neurological Soft Signs (NSS) and the male gender[36]. NSS are minor ("soft") neurological abnormalities in sensory and motor performance identified by clinical examination. In a follow-up study by Madsen *et al*.[36], a significant increase in the number of neurological abnormalities was observed in a group of males five years after the onset of the first psychotic episode. Nevertheless, results from studies with schizophrenia patients were not consistent with respect to the differences in gender and NSS. These studies showed increased NSS in patients with schizophrenia when compared to a healthy control group, however there is little evidence regarding gender differences with respect to the mean NSS demonstrated by patients[37,38].

In a study by Häfner[39], which analyzed prodromic symptoms in a patient sample with a first psychotic episode, no gender differences were observed in the ten most frequent initial symptoms, except in worrying, which was significantly more frequent in women. In a sample of 231 patients with a first psychotic episode, Gutiérrez *et al*.[40] observed that the male group manifested the following prodromic symptoms with increased frequency: unusual perceptive experiences, deterioration in personal hygiene and psychosocial isolation. Nevertheless, due to difficulties in evaluating the prodromic period, as well as the variety of existing instruments, a number of inconsistencies in the methodology have been introduced in the scientific literature preventing a consensus in the study of prodromic symptoms.

Clinical Variables

The most reproducible data in the study of gender differences in the expression of psychotic symptoms has been the predominance of negative symptoms in men such as social withdrawal, blunted effect, poverty of speech and amotivation[35,41-43]. In contrast, studies have shown that women manifest more affective symptoms, atypical and cyclical forms of psychosis as well as a higher incidence in the diagnosis of paranoid and disorganized subtypes[4,44,45]. Szymanski *et al*.[45] observed less illogical thinking but more anxiety, inappropriate affect and bizarre behaviour in women than men with first psychotic episode. Shtasel *et al*.[46] showed that men with schizophrenia showed more negative symptoms than women, however there were no gender differences with respect to positive psychotic symptoms. The studies of Gur *et al*.[47] and Lindamer *et al*.[48], both studies confirmed that women experience less negative symptoms than men and that this is more evident in women who develop the disease later in life. Nevertheless, there are studies which did not demonstrate psychopathological differences between men and women suffering from schizophrenia[23,49,50].

Traditionally it was considered that women with schizophrenia had better insight which in turn allowed them to use mental health services more than men. However,

publications in the last years do not show any conclusive results regarding the relationship between gender and level of insight. On the other hand, a study with patients with a first psychotic episode, Mc Evoy *et al*.[51] demonstrated that multiple factors exist which contribute to having a good insight including late onset of the psychotic episode and female gender whilst earlier studies[52] go in the opposite direction and show that worse insight is associated with the female gender.

Cognitive function variables

Although a vast amount of work has been dedicated to study the cognitive function in schizophrenic patients, no consensus was reached with respect to gender differences. Some studies showed that men with schizophrenia have a greater cognitive deficit than women, especially in verbal processing; on the other hand; other studies conclude that women show worse cognitive function; whilst other studies failed to demonstrate any differences between the two groups.

Haas *et al*.[42] did not show any gender differences in cognitive functioning in patients with first psychotic symptoms, however, in patients with disease progression of 5 years or more, men showed a greater deficit in verbal tasks, which could indicate dysfunction in the left hemisphere. Various studies indicated that men with schizophrenia have more alterations in sustained attention, abilities in language, executive functions and intelligence than women[53,54]. Nevertheless, other studies did not show any gender differences in cognitive functions between patients[55,56]. On the other hand, others have found major alterations in the female group with schizophrenia on attention and conceptualization tasks[57] as well as on verbal memory, spatial memory and visual processing tasks[58].

Aim

The aim of this study was to describe gender differences in a group of patients with first-episode psychotic in different aspects: socio-demographic features, characteristics of the phases prior to disease onset (premorbid and prodromic periods), clinical manifestation of psychotic symptoms and possible corresponding cognitive alterations after disease onset, using the age at onset of first psychotic episode as a control variable.

Methods

Sample

Our sample was composed of patients with a first psychotic episode selected in a consecutive manner. The patients were recruited when they were consulting in an adult mental health services at *Sant Joan de Déu* or the infant-juvenile services at the *Hospital San Joan de Déu,* either in a hospital or in a community psychiatric services. These centers belong to the metropolitan area and outskirts of Barcelona, taking into account a reference population of approximately 800,000 persons.

The inclusion criteria were: two or more psychotic symptoms (delirious ideas, hallucinations, disorganized speech, catatonic or disorganized behaviour and negative symptoms); age between 7 and 65 years; first psychiatric visit in any centre participating in the study; less than 6 months since the first contact to the medical service; and less than a year of symptoms' evolution. Patients diagnosed with mental retardation, craneoencephalic trauma or dementia were excluded from the study.

All selected individuals were informed of the objectives and methodology of this study by their psychiatrist or researcher and signed the required informed consent. In cases where the patients were minors, the informed consent was obtained from their parents or carers.

The study was approved by the Ethics and Research Comittee of the "*Sant Joan de Déu"*.

Instruments of measurement

The socio-demographic characteristics of the sample (gender, mental health centre (community psychiatric services/ hospital), race, socioeconomic status, marital status, ages and level of education, and work status) including age at onset of illness, initial visit at a psychiatry services, history of substance abuse and family psychiatry history, were obtained via a clinical-sociodemographic questionnaire.

Information about premorbid and prodromic variables was collected using the following scales or interviews:

Premorbid Adjustment Scale (PAS)[59]. A 26-items scale, administrated by an researcher, which evaluates sociability and withdrawal, social relationships, adaptation to school and behavior at school in four periods: childhood, up to 11 years; early adolescence, 12-15 years; late adolescence, 16-18 years; and adult life, above 18 years; as well as social-sexual aspects after 15 years of age. The PAS also includes a section composed of 9 general items related to education, work, performance at work or at school, behaviour at school immediately before onset of psychosis, elevated level of independence on the family, high levels of social-personal adjustment, grade of interests in life and energy level. The total PAS score were in the range of 0.0 and 1.0, wherein higher scores represented lower levels of FP. The premorbid adjustment scale was completed using all available data, including clinical history data, interviews with patients and relatives. The scale was translated and its used was validated in the Spanish population[60].

The present study is based on the results obtained from the research of Norman *et al*.[31] which find two factors: one showing academic PF (adaptation to and behaviour at school) and the second one showing a social PF (sociability and withdrawal; poor relationships and social-sexual adjustment).

Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS)[61]: Structured interview which evaluates retrospectively the start of schizophrenia. The interview is composed of 5 sections for the collection of socio-demographic data relating to the patient, psychiatric symptoms starting from 12 years of age, prodromic symptoms and establishment of the disease as well as the quality of the information. In the present study, only the section comprising prodromic symptoms was used. This included 7 parts: perceptual disturbances (excluding hallucinations); hallucinations; subjective thought disturbances (i.e. thoughts being read, thought insertion); delusional ideas and delusions; cognitive deterioration; altered affect; behavioural and motor abnormalities; and dysfunctional language. The presence or absence of such symptoms was evaluated.

Neurological Evaluation Scale (NES)[37]: a 26-item scale with three main subscales: sensory integration (SI), motor coordination (MC), sequencing of complex motor acts (SCMA) and an extra subscale that evaluates short-term memory, frontal release signs, and eye movement abnormalities ("others" subscale). Each item is rated from 0 to 2: 0 (no abnormality), 1 (mild, but definite im-

pairment) and 2 (marked impairment). The higher the rating in total score, the higher the presence of neurological soft signs.

Information regarding clinical variables was obtained via the following scales or interviews:

Positive and Negative Syndrome Scale (PANSS)[62], translated and validated by Peralta and Cuesta[63]. This scale is the most widely used scale of psychotic symptom evaluation. It measures 30 symptoms on a scale of 1-7, with higher scores indicating higher psychopathology. In this study, in order to analyze the date we have used four dimensions described by Villalta *et al.*[64]: positive, negative, affective, and excitative.

At the moment of inclusion of the patient, a retrospective evaluation of the symptoms was carried out in those cases where the psychiatrist reported a previous more severe symptomatology. A second evaluation was carried out 8 weeks later since the onset of episode.

Clinical Global Impression- Schizophrenia scale (ICG-ESQ). Determine the severity of the disease (scale from 1 to 7, from normal to higher severity) and the grade of improvement (scale from 1 to 9, from major improvement to non applicable) in four groups of schizophrenia symptoms (positive, negative, cognitive and depressive). A global severity score of the disease is also determinaded. Its use has been validated for use in the spanish population with the same purpose as the present study[65].

Global Assessment of Functioning Scale (GAF)[66] is used to measure global functioning (clinical/social), where 0 represents severe dysfunction and 100 represents good functioning.

Scale for the Assessment of Unawareness of Mental Disorder (SUMD)[67]: a 20-item scale which assesses awareness of mental disorder, awareness of response to medication, awareness of social consequences of mental disorder, and awareness of specific symptoms of the illness. These items are rated according to a scale of 1 to 5, where a score of 1 is considered as being aware, a score of 3 is somewhat aware, and a score of 5 is unaware. For each symptom presented, a score is calculated based on the attribuition which the patient gave to the symptom (1 = Correct: symptom is due to a mental disorder; 3 = Partial: unsure, but can consider possibility that it is due to a mental disorder; 5= Incorrect: symptom is unrelated to a mental disorder). Higher scores on this scale indicate poor awareness.

Young Mania Rating Scale (YMRS)[68]: an 11-item scale which measures maniac symptoms. For adult patients the scale was administered by the researcher, whilst for adolescents, the self-administered version for parents (P-YMRS) was utilised. Some items were scored from 0-4 or 0-8 (in the case of items 5, 6, 8 and 9). The value of 0 means absence of symptoms whilst the highest value indicates the presence of the severe symptoms.

Cognitive assessment was performed by means of a neuropsychological battery designed to assess cognitive functions that the literature reports to be affected in psychotic disorders: attention, working memory, executive functioning and verbal memory. Table I summarises the neuropsychological tests which were used to measure each of these cognitive domains. To be able to calculate the total score for each of these domains, the direct score was transformed into a T-score (mean 50; SD = 10) and the mean of the scores according to each cognitive domain was calculated.

Statistical analysis

After verifying the hypothesis for normality using the Kolmogorov-Smirnov nonparametric test ($p < 0.05$) for all variables of the study, the gender differences were analyzed for each group of variables of interest.

Table I
Neuropsychological tests by cognitive domain

Cognitive domain	Neuropsychological tests
Attention	
	[a]CPT index's
	[b]Stroop Interference
	[c]Trail Making Test, part A
Working Memory	
	[d]WAIS-III/[e]WISC-IV: Digits (Forward & Backward)
	WAIS-III/WISC-IV: Number-Letter Sequencing
	WAIS-III/WISC-IV: Arithmetic
Verbal Memory	
	[f]TAVEC Immediately Verbal Memory
	TAVEC Short Term Verbal Memory
	TAVEC Long Term Verbal Memory
	TAVEC Recognition
Executive Function	
	Trail Making Test, part B
	Stroop Word
	Stroop Color
	Stroop Color-Word

[a] CPT: Continuous Performance Test.
[b] STROOP: Stroop Color and Word Test.
[c] TMT: Trail Making Test (part A & B).
[d] WAIS-III: Weschsler Adult Intelligence Scale, 3rd Edition.
[e] WISC-IV: Wechsler Intelligence Scale for Children, 4 th Edition.
[f] TAVEC: Spanish version of the California Verbal Learning Test.

The socio-demographic variables of patients were analyzed using a chi-square test for categorical variables and Student's test for continuous variables. For comparison of categorical variables with expected frequencies cells less than 5, the Fisher's exact test was used.

For the analysis of premorbid and prodromic variables, differences of the means were calculated for independent samples (Student's T-test) which allowed comparison the scores of PAS, NES and IRAOS with respect to gender.

Gender differences in clinical and cognitive variables were analyzed using differences of the means (Student's T-test) since all variables were quantitative and complied with the criteria for normality.

For the whole variables (socio-demographic, premorbid/prodromic, clinical and cognitive), a second analysis was carried out

taking into account the age at onset of the psychotic episode. For this part of the study, the sample was divided into adults (> = 18 years) and adolescents (<18 years). The data were analyzed using the non-parametric U-Mann-Whitney test.

Analyses were carried out using SPSS statistical software package (version 16.0). All statistical tests were two-tailed, with $p < 0.05$ considered statistically significant.

Results

Up to now, 53 patients with a first psychotic episode have been evaluated. Males compose 49.1% (n = 26) of the sample with a mean age of 20.21 years (SD = 6.2). Patients which started the psychotic episode at less than 18 years of age, comprise 52.8% (n = 28) of the sample with their mean age being 16.14 (SD = 1.2). The subgroup which had the first psychotic episode in adulthood had a mean age of 24.76 years (SD = 6.3).

Gender differences with respect to socio-demographic characteristics and substance abuse

Table II shows the gender differences and socio-demographic variables of the sample used in this study. Analysis of these results revealed significant differences only in two of the socio-demographic variables: failed school-course ($\chi^2(1) = 6.526$, p = 0.011) and work status (*Fisher's Exact Test* = 7.702, 0 = 0.050).

Women comprise 76.5% (n = 13) of the sample which did not fail any school-course, whilst from the repeater group, 61.1% (n = 22) are men. With respect to work status, 70% (n = 7) of patients who worked before the onset of the psychotic episode were men and from the patients who were unemployed 78.6% (n = 11) were women.

No significant differences were observed between the groups of men and women with respect to the time elapsed until they had contact with mental health services (t = 0.650, p = 0.519), although the average number of days was higher in men and than in women (114 days against 89 days respectively).

With respect to substance abuse, there were significant differences between the genders in the consumption of cannabis and hallucinogenic substances (Table III). Women composed 90% (n = 9) of sporadic consumers of cannabis, whilst 72.7% (n = 16) of daily consumers were men. In this sample there were no daily consumers of hallucinogenic substances, however 85.7% (n = 6) of sporadic consumers were men.

Patients belonging to families with previous psychotic disorders history comprise 28.3% (n = 13) of the sample, 17% (n = 9) of which are women. However, no significant differences were observed with respect to gender in family psychiatric history which includes disorders of the psychotic spectrum, affective disorders and others.

In a second analysis, no significant differences were observed between genders when the sample was divided into different age groups (<18 years: U = 88.0, p = 0.684; > = 18 years: U = 70.5, p = 0.720).

Gender difference in premorbid variables and prodromic symptoms

No significant gender differences were found in this sample either in global premorbid functioning or in its social and academic dimensions. However, when the effect

Table II
Gender differences in socio-demographic characteristics

	Male (n = 26) n(%)	Female (n = 27) n(%)	Statistical analysis t /χ^2 p-value
Mental Health Centre			
Out-patients	7(58.3%)	5 (41.7%)	χ^2 (1) = 0.534 p = 0.465
In-patients	19 (46.3%)	22 (53.7%)	
Socio-economic status (Hollingshead Scale)			
I	5 (45.5%)	6 (54.5%)	*Fisher's Exact Test* p = 0.788
II	5 (38.5%)	8 (61.5%)	
III	9 (50.0%)	9 (50.0%)	
IV	6 (60.0%)	4 (40.0%)	
V	1 (100%)	0 (0%)	
Race			
Caucasian	22 (50.0%)	22 (50.0%)	*Fisher's Exact Test* p = 0.746
Hispanic	3 (60.0%)	2 (40.0%)	
Others	1 (25.0%)	3 (75.0%)	
Marital status			
Single	24 (49.0%)	25 (51.0%)	*Fisher's Exact Test* p = 1.000
Married	2 (66.7%)	3 (33.3%)	
Separated/Divorcee	0 (0%)	1 (100%)	
Education (years)			
5-8 years	1 (16.7%)	5 (83.3%)	*Fisher's Exact Test* p =
9-12 years	15 (50.0%)	15 (50.0%)	
> 12 years	10 (58.8%)	7 (41.2%)	
Failed school-course			
Yes	22 (61.6%)	14 (38.9%)	χ^2 (1) = 6.526 p = 0.011*
No	4 (23.5%)	13 (76.5%)	
Level of Education			
Primary	1 (25.0%)	3 (75.0%)	*Fisher's Exact Test* p = 0.472
Secondary	14 (45.2%)	17 (54.8%)	
High School	6 (54.5%)	5 (45.5%)	
University	5 (71.4%)	2 (28.6%)	
Work Status			
Actively employed	7 (70.0%)	3 (30.0%)	*Fisher's Exact Test* p = 0.050
Unemployed	3 (21.4%)	11 (78.6%)	
Student	12 (50.0%)	12 (50.0%)	
Registered Sick	4 (80.0%)	1 (20.0%)	
Mean $\pm$ SD	**Mean $\pm$ SD**		
Age of onset	20.85 $\pm$ 6.40	19.59 $\pm$ 5.97	t = 0.738 p = 0.464

* p < 0.05 ; **p < 0.01; Bold values show significant tendencies.

Table III
Gender differences in substance misure

	Male (n = 26) n(%)	Female (n = 27) n(%)	Statistical analysis χ^2 p-value
Tobbaco			
Non-consumer	7 (38.9%)	11 (61.1%)	χ^2 (2) = 1.563 p = 0.458
Sporadic	11 (50.0%)	11 (50.0%)	
Diary	8 (61.5%)	5 (38.5%)	
Alcohol			
Non-consumer	9 (45.0%)	11 (55.0%)	*Fisher's Exact Test* p = 0.702
Sporadic	14 (48.3%)	15 (51.7%)	
Diary	3 (75.0%)	1 (25.0%)	
Cannabis			
Non-consumer	9 (42.9%)	12 (57.1%)	***Fisher's Exact Test* p = 0.003****
Sporadic	1 (10.0%)	9 (90.0%)	
Diary	16 (72.7%)	6 (27.3%)	
Cocaine			
Non-consumer	18 (43.9%)	23 (56.1%)	*Fisher's Exact Test* p = 0.134
Sporadic	8 (72.7%)	3 (27.3%)	
Diary	0 (0%)	1 (100%)	
Hallucinogenic Substance			
Non-consumer	20 (43.5%)	26 (56.5%)	***Fisher's Exact Test* p = 0.050**
Sporadic	6 (85.7%)	1 (14.3%)	
Diary	0 (0%)	0 (0%)	

* $p < 0.05$; **$p < 0.01$; Bold values show significant tendencies.

of age at onset of psychotic episode was taken into account, significant differences were revealed: in patients younger than 18 years, men showed higher PF scores than women in total PAS (U = 54.0, p = 0.050) (Table IV). In patients older than or equal to 18 years of age, women showed the highest scores, although this happened only in the social domain (U = 29.5, p = 0.018) (Table V). In patients younger than 18 years, significant differences in PF during early adolescent stage was observed (U = 38.0, p = 0.013), with males showing lower scores.

No significant differences between genders were observed in the presence of minor neurological signs (t = 0.394, p = 0.695). When the effect of age at onset of psychotic episode was taken into account, significant gender differences were observed: in the group younger than 18 years of age, men show higher number of minor neurological signs (U = 31.0, p = 0.003) and also higher total NES scores (U = 47.0, p = 0.056) (Table IV) than women; in patients 18 years and over, no significant differences were observed with respect to gender.

Table IV
Differences of gender in earlier onset of first psychotic episode (< 18 years)

	Male (n = 12) Mean ± SD	Female (n = 16) Mean ± SD	Statistical analysis p-value
Premorbid variables			
PAS			
Premorbid adaptation	0.42 ± 0.18	0.28 ± 0.16	**p = 0.050**
Premorbid social adaptation	0.37 ± 0.29	0.19 ± 0.20	p = 0.145
Premorbid school adaptation	0.50 ± 0.21	0.38 ± 0.19	p = 0.159
NES			
Nº of neurological soft signs	22.64 ± 0.12	18.06 ± 6.23	**p = 0.056**
Total score	14.36 ± 2.62	10.63 ± 3.10	**p = 0.003****
Prodromic variables			
IRAOS			
Perceptual disturbances	1.55 ± 1.29	2.83 ± 1.36	p = 0.130
Hallucinations	1.00 ± 0.89	2.25 ± 1.65	**p = 0.052**
Delusions	4.73 ± 2.45	5.44 ± 2.50	p = 0.292
Subjective thought disturbances	3.09 ± 1.97	3.88 ± 1.89	p = 0.271
Dysfunctional language	1.73 ± 1.01	1.94 ± 1.29	p = 0.609
Behavioural abnormalities	1.36 ± 0.81	1.44 ± 1.15	p = 0.958
Altered affect	2.55 ± 1.13	3.38 ± 1.36	p = 0.110
Clinical variables			
PANSS			
Positive	25.75 ± 7.92	25.69 ± 8.51	p = 1.000
Negative	27.42 ± 7.62	27.06 ± 12.20	p = 0.530
Afective	19.50 ± 4.98	17.19 ± 4.05	p = 0.235
Excitative	12.17 ± 4.91	14.31 ± 3.91	p = 0.154
PANSS (after 8 weeks)			
Positive	15.27 ± 5.41	13.75 ± 4.24	p = 0.455
Negative	25.18 ± 10.01	19.19 ± 8.06	**p = 0.051**
Afective	13.18 ± 3.49	10.94 ± 2.38	**p = 0.073**
Excitative	7.18 ± 1.89	9.19 ± 2.93	**p = 0.072**
CGI-SQZ			
Total score	4.50 ± 1.27	5.00 ± 1.51	p = 0.298
GAF			
Total score	34.00 ± 9.66	35.36 ± 15.00	p = 0.916
YOUNG			
Total score	17.40 ± 9.02	19.14 ± 12.69	p = 0.907
SUMD			
Total score	3.27 ± 1.41	3.14 ± 1.53	p = 0.834
Awareness of symptoms	2.95 ± 1.29	2.79 ± 1.31	p = 0.792
Attribution total score	3.77 ± 1.37	3.48 ± 1.96	p = 0.479
SUMD (after 8 weeks)			
Total score	2.57 ± 1.53	1.75 ± 1.14	p = 0.083
Awareness of symptoms	2.62 ± 1.25	1.22 ± 0.76	**p = 0.003****
Attribution total score	3.39 ± 1.65	2.76 ± 1.44	p = 0.188

* $p < 0.05$; **$p < 0.01$; Bold values show significant tendencies.

Analysis of prodromic symptoms showed significant differences in gender in hallucinations, with a higher presence in women (t = -2.36, p = 0.017). When age at the beginning of psychotic episode was taken into account, this tendency was maintained in the age group younger than 18 years but not in the older group (> = 18 years) (U = 49.5, p = 0.052) (Tables IV y V). In this group there were significant differences in dysfunctional language (U = 31.0, p = 0.027) and tendencies in the variables for "subjective thought disturbance" (U = 33.0, p = 0.66) and "behavioural and motor abnormalities" (U = 39.0, p = 0.79) with higher scores obtained for males (Table V).

Gender differences in clinical variables

No significant gender differences were observed with respect to the presence and severity of psychotic symptoms at the onset of the psychotic episode. However, when age at onset was taken into account, gender differences were observed: men < 18 years showed an increased severity in negative psychotic symptoms with respect to women, both in the acute phase (although significant differences were not observed: $\overline{X}_{\text{males}} = 15.63$; $\overline{X}_{\text{females}} = 13.66$; p = 0.530) and during the stable phase, showing a significant tendency (U = 48.5, p = 0.051) (Table IV). In the > = 18 years age group, a tendency in gender differences with respect to excitative symptoms was observed in the acute phase with men showing a higher score (U = 42.0, p = 0.055). On the Young scale, significant gender differences were observed only in the group > = 18 years, with males showing higher scores than women (U = 34.0, p = 0.014) (Table V).

As other clinical variables, gender differences were observed if age at onset of the disease was taken into account, regarding to the awareness of the disease. In the group which started the episode at an earlier age, awareness of the symptoms of the disease was worse in males (U = 30.0, p = 0.003) (Table IV). On the other hand, in the older age group the opposite result was observed, with women scoring lower on the subscale for symptom awareness of SUMD, although this difference was not significant (U = 42.5, p = 0.088) (Table V). No significant differences between genders were observed in the attribution of symptoms.

No other significant differences were observed between genders in the other clinical variables studied (GAF and CGI).

Gender differences in cognitive functioning

In the analysis of cognitive domains, significant gender differences were observed only with respect to verbal memory (t = 2.49, p = 0.017) with worse scores obtained by women. These differences were still observed after subdividing the sample into age groups according to age at onset of first psychotic episode.

Discussion

Gender differences with respect to psychotic disorders are an important factor in the understanding of the manifestation and development of the disease. Even though in the last decades this was an intensively studied aspect, controversial results were obtained from the different studies performed.

In line with Angermeyer *et al.*[27], we observed that women have a higher educational competence than men. On the other hand,

Table V
Differences of gender in adult onset of first psychotic episode (> = 18 years)

	Male (n = 14) Mean ± SD	Female (n = 11) Mean ± SD	Statistical analysis p-value
Premorbid variables			
PAS			
Premorbid adaptation	0.27 ± 0.13	0.37 ± 0.18	p = 0.147
Premorbid social adaptation	0.19 ± 0.17	0.38 ± 0.17	**p = 0.018***
Premorbid school adaptation	0.37 ± 0.23	0.42 ± 0.18	p = 0.480
NES			
Nº of neurological soft signs	13.54 ± 7.46	19.40 ± 9.97	p =0 .121
Total score	10.00 ± 4.95	12.30 ± 5.31	p = 0.297
Prodromic variables			
IRAOS			
Perceptual disturbances	1.80 ± 1.55	0.78 ± 0.03	p = 0.117
Hallucinations	0.82 ± 0.87	1.00 ± 0.63	p = 0.525
Delusions	4.83 ± 2.69	4.80 ± 1.93	p = 1.000
Subjective thought disturbances	4.00 ± 2.28	2.18 ± 1.94	**p = 0.066**
Dysfunctional language	2.25 ± 1.55	0.91 ± 1.30	**p = 0.027***
Behavioural abnormalities	1.33 ± 0.99	0.04 ± 0.81	**p = 0.079**
Altered affect	3.08 ± 1.44	3.00 ± 1.34	p = 0.849
Clinical variables			
PANSS			
Positive	24.00 ± 7.25	23.27 ± 3.32	p = 0.762
Negative	26.29 ± 7.50	26.55 ± 9.47	p = 0.956
Afective	15.50 ± 4.94	14.91 ± 5.50	p = 0.891
Excitative	15.36 ± 6.70	10.36 ± 4.78	**p = 0.055**
PANSS (after 8 weeks)			
Positive	15.46 ± 8.23	10.00 ± 5.53	p = 0.467
Negative	20.23 ± 7.97	20.36 ± 4.27	p = 0.663
Afective	12.92 ± 6.21	11.00 ± 4.17	p = 0.641
Excitative	8.46 ± 4.05	8.45 ± 4.41	p = 0.813
CGI-SQZ			
Total score	4.50 ± 1.20	4.11 ± 0.93	p = 0.482
GAF			
Total score	36.88 ± 10.33	37.56 ± 11.80	p = 0.845
YOUNG			
Total score	18.17 ± 4.92	10.00 ± 5.35	**p = 0.014***
SUMD			
Total score	3.67 ± 1.18	3.33 ± 1.41	p = 0.681
Awareness of symptoms	2.42 ± 0.33	2.47 ± 1.23	p = 0.732
Attribution total score	4.37 ± 0.87	4.27 ± 1.20	p = 1.000
SUMD (after 8 weeks)			
Total score	1.90 ± 1.19	2.42 ± 1.35	p = 0.280
Awareness of symptoms	1.66 ± 0.98	2.40 ± 0.91	p = 0.142
Attribution total score	2.96 ± 1.61	3.88 ± 1.28	p = 0.088

* $p < 0.05$; **$p < 0.01$; Bold values show significant tendencies.

our results do not coincide with these authors with respect to labour competence, with men being in a better situation before onset of the disease. In the last decades, several studies have been published supporting the hypothesis that no gender differences existed with respect to age at onset of schizophrenia[23,24]. Indeed our results are in line with these studies. One of the limitations that could account for this difference in results across the literature is the limited age range for inclusion in the studies, which would not permit a representative sample of the population as a whole. On the other hand, tobacco, alcohol and cannabis are frequently used by schizophrenia patients[69,70], as confirmed by the sample in this study. We observed a higher frequency of cannabis consumers among younger men with a first psychotic episode. This result has been described by other authors[71,72].

The gender differences observed in the premorbid clinical variables studied are due to the effect of age. These differences are in line with a model for neurodevelopment which indicates that subtle abnormalities could be observed already at PF, especially in early adolescence and a higher number of minor neurological symptoms in persons who later develop the disease. Such aspects would be more frequent in male patients who start a psychotic episode early.

As mentioned previously, there is considerable controversy regarding gender differences with respect to the presentation of symptoms in psychotic disorder spectrum. With respect to positive psychotic symptoms, a large number of studies have reached the conclusion that both men and women experience the same level of positive symptoms[23,46], although certain symptoms such as auditory hallucinations and persecutory delusions are more frequent in women[44]. The analysis regarding prodromic symptoms in our sample comes to similar conclusions, with women showing an early onset of the disease presenting a higher frequency of subclinical senso-perceptive disturbance. Instead, the group of younger men had worse dysfunctional language than women before the onset of psychotic episode.

When symptoms of the first psychotic episode were taken into account, our results were in line with studies that did not find psychopathological differences between men and women with schizophrenia[23,49,50]. However, the differences found refer to the course of the first episode and not to the expression of initial symptoms. The presence of a higher severity in negative psychotic symptoms and poor awareness of disease, after 8 weeks of evolution of the episode, in the group of males younger than 18 years could suggest the presence of a subpopulation which is more resistant to therapeutic interventions and with worse prognosis. Nevertheless, in line with the results from Cuesta & Peralta[52], women in our sample with a later onset of the disease show less awareness of symptoms.

Although a large number of articles has been dedicated to cognitive functioning in patients with schizophrenia, no consensus was reached regarding the observed gender differences. This is mostly due to the variability of instruments of measure utilised to evaluate the different cognitive domains. In line with results by Haas *et al*.[42], no significant differences in gender were observed in executive function, attention and working memory in patients with first psychotic episode. Without doubt, the differences in verbal memory, with men having better capacity, add more data to the divergent results found in the scientific literature. However, we are currently conducting a one year follow-up study of first psychotic episodes which will produce more data regarding questions that still need to be clarified in the literature.

Limitations

Some limitations of the present study are related to the measurement instruments used: Premorbid Adjustment Scale (PAS) and Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) are instruments for retrospective assessment, in which some information could be inaccurate as it relies on the patients' or family members' memory.

The size of the sample is another limitation for this study and does not permit the extrapolation of the data obtained to the general population. It also makes it difficult to stratify the sample to study and compare different groups (it is necessary to use non parametric tests).

The absence of a control group does not allow to performance a comparison between both populations, health people and patients with a psychotic episode in relation to the premorbid and prodromic variables.

Other limitation is related to patients that have an insidious onset of psychotic episode and not consult to mental health services included in our study. For this reason, not all the first psychotic episodes could be represented in our sample.

Finally, the absence of a control for pharmacological treatment group could influence the analysis of certain variables as well as the symptoms after 8 weeks of evolution of the episode or cognitive functioning. It is a factor which will be taken into account in future analyses. Nevertheless, this limitation is not considered to invalidate the overall conclusions which have been reached in this study.

Conclusion

The most relevant conclusions from our study are the following:

- Women have a higher educational competence than men. In return, men show a higher labour competence than women before onset of the disease.
- No significant differences in gender were observed with respect to onset of the psychotic episode.
- Men are more frequently daily consumers of cannabis whilst women are usually sporadic users.
- Males who started the psychotic episode earlier showed more alterations in premorbid functioning, especially in early adolescence, and a higher number of neurological soft signs.
- Women in early onset showed a higher frequency of senso-perceptive subclinical disturbance (hallucinations) in the prodromic phase.
- Males younger than 18 years show negative psychotic symptoms which are more severe and poorer awareness than females, after 8 weeks of onset the first psychotic episode.
- No gender differences were observed in executive functioning, attention and working memory, although this was different with respect to verbal memory with men having a higher performance.
- Age is an important variable to be considered in future studies about gender differences in psychotic disorders.

The conclusions are important in light of the idea that men and women suffering from schizophrenia show features, characteristics and pecularities typical of their gender. These characteristics should be taken into account to learn more about the different types of onset of the disease, its prevention and possible improvements in therapeutic approach with respect to gender. Finally, it is important to mention that a large part of

the discovered gender differences are within the context of a neurodevelopmental model and the existence of alterations in the stages prior to the onset of the disease which predispose its appearance.

Acknowledgements

We thank all patients and families for participating in the study as well as the clinical team at *Sant Joan de Déu* for their collaboration. This project received financial help from the Fondo de Investigaciones Sanitarias de España (FIS PI05/1115); from the Instituto de Salud Carlos III de España, Centro de Investigación en Red de Salud Mental (CIBERSAM) and from Caja Navarra.

References

1. Riecher-Rossler A, Häfner H. Gender aspects in schizophrenia: Bridging the border between social and biological psychiatry. Acta Psychiatr Scand Suppl. 2000; 102: 58-62.

2. Koster A, Lajer M, Lindhardt A, Rosenbaum B. Gender differences in first episode psychosis. Soc Psychiatry Psychiatr Epidemiol 2008; 43: 940-946.

3. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand Suppl 2000; 401: 3-38.

4. McGlashan TH, Bardenstein KK. Gender differences in affective, schizoaffective, and schizophrenic disorders. Schizophr Bull 1990; 16(2): 319-329.

5. Goldstein J, Link B. Gender and the expression of schizophrenia. J Psychiatr Res 1988; 22: 141-155.

6. Roy MA, Maziade M, Labbé A, Mérette C. Male gender is associated with deficit schizophrenia: a meta-analysis. Schizophr Res 2001; 47: 141-147.

7. Simonsen E, Friis S, Haahr U, Johannessen JO, Larsen TK, Melle I, et al. Clinical epidemiologic first-episode psychosis. 1 year outcome and predictors. Acta Psychiatr Scand 2007; 116: 54-61.

8. Seeman MV, Lang M. The role of estrogens in schizophrenia gender differences. Schizophrenia Bull 1990; 16(2): 185-194.

9. Häfner H, Riecher A, Maurer K, Löffler W, Munk-Jorgensen P, Strömgren E. How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. Psychological Med 1989; 19: 903-918.

10. Murray RM, Lewis SW, Reveley AM. Towards an etiological classification of schizophrenia. Lancet 1985; 4: 1023-1026.

11. Castle DJ, Sham PC, Wessely S, Murray RM. The subtyping of schizophrenia in men and women: A latent class analysis. Psychol Med 1994; 24: 41-51.

12. Murray RM, O'Callaghan E, Castle DJ, Lewis SW. A neurodevelopmental approach to the classification of schizophrenia. Schizophr Bull 1992; 18(2): 319-332.

13. Jerningan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. Brain 1991; 114: 2037-2049.

14. Flor-Henry P. Gender, hemispheric organization and psychopathology. Soc Sci Med 1978; 12B: 155-162.

15. Häfner H, An Der Heiden W, Behrens S, Gattaz WF, Hambretch M, Löffler W, et. al. Causes and consequences of the gender difference in age at onset of schizophrenia. Schizoph Bull 1998; 24(1): 99-113.

16. Häfner H, Maurer K, Loffler W, An Der Heiden W, Munk-Jorgensen P, Hambrecht M, et al. The ABC schizophrenia study: a preliminary overview of the results. Soc Psychiatry Psychiatr Epidemiol 1998; 33: 380-386.

17. Faraone SV, Chen WJ, Goldstein JM, Tsuang MT. Gender differences in age at onset of schizophrenia. Br J Psychiatry 1994; 164: 625-629.

18. Gureje O, Bamidele RW. Gender and schizophrenia: association with age at onset with antecedent, clinical and outcome feature. Aust N Z J Psychiatry 1998; 32: 415-423.

19. Castle DJ, Wessely S, Murray RM. Sex and schizophrenia: effects of diagnostic stringency and associations with premorbid variables. Br J Psychiatry 1993; 162: 658-662.

20. Ochoa S, Usall J, Villalta-Gil V, Vilaplana M, Márquez M, Valdelomar M, et. al. Influence of age at onset on social functioning in outpatients with schizophrenia. Eur J Psychiatry 2006; 20(3): 157-163.

21. Larsen TK, McGlashan TH, Moe LC. First-episode schizophrenia: I. Early course parameters. Schizophr Bull 1996; 22(2): 241-256.

22. Häfner H, Hambrecht M, Loffler W, Munk-Jorgensen P, Riecher-Rossler A. Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. Psychol Med 1998; 28: 351-365.

23. Addington D, Addington J, Patten S. Gender and affect in schizophrenia. Can J Psychiatry 1996; 41(5): 265-268.

24. Naqvi H, Khan MM, Faizi A. Gender differences in age of onset of schizophrenia. J Coll Physicians Surg Pak 2005; 15(6): 345-348.

25. Amminger GP, Resch F, Mutschlecher R, Fredrich MH, Ernst E. Premorbid adjustment and remission of positive symptoms in first-episode psychosis. Acta Paedopsychiatr 1997; 6(4): 212-216.

26. Childers SE, Harding CM. Gender, premorbid social functioning, and long-term outcome in DSM-III schizophrenia. Schizophr Bull 1990; 16(2): 309-318.

27. Angermeyer MC, Kuhn L, Goldstein J. Gender and the course of schizophrenia: Differences in treated outcomes. Schizophr Bull 1990; 16(2): 293-307.

28. Mueser KT, Bellack AS, Morrison RL, Wade JH. Gender, social competence and symtomatology in schizophrenia: A longitudinal analysis. J Abnorm Psychol 1990; 99: 138-147.

29. Rabinowitz J, Bromet EJ, Lavelle J, Carlson G, Kovasznay B, Schwartz JE. Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients. Psychol Med 1998; 28(6): 1411-1419.

30. Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L. First- episode schizophrenia: II. Premorbid patterns by gender. Schizophr Bull 1996; 22(2): 257-269.

31. Norman RMG, Malla AK, Manchanda R, Townsend L. Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains. Acta Psychiatr Scand 2005; 112: 30-39.

32. Rabinowitz J, Smedt G, Harvey PD, Davidson M. Relationship between premorbid functioning and symptom severity as assessed at first episode of psychosis. Am J Psychiatry 2002; 159(12): 2021-2026.

33. Addington J, Mastrigt S, Addington D. Patterns of premorbid functioning in first-episode psychosis: initial presentation. Schizophr Res 2003: 62(1-2): 23-30.

34. Silverstein ML, Mavrolefteros G, Close D. Premorbid adjustment and neuropsychological performance in schizophrenia. Schizophr Bull 2002; 28(1): 157-65.

35. Castle DJ, Murray RM. The neurodevelopmental basis of sex differences in schizophrenia. Psychol Med 1991; 21(3): 565-575.

36. Madsen AL, Vorstrup S, Rubin P, Larsen JK, Hemmingsen R. Neurological abnormalities in schizophrenic patients: a prospective follow-up study 5 years after first admission. Acta Psychiatr Scand 1999; 100: 119-125.

37. Buchanan RW, Heinrichs DW. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res 1989; 27: 335-350.

38. Rossi A, De Cataldo S, Di Michele V, Manna V, Ceccoli S, Stratta P, et al. Neurological soft signs in schizophrenia. Br J Psychiatry 1990; 157: 735-739.

39. Häfner H. Gender differences in schizophrenia. Psychoneuroendocrinology 2003; 28: 17-54.

40. Gutiérrez M, Segarra R, Eguiluz I, Ojeda N, Fernández C. 2 year follow-up of women with first episode schizophrenia or schizophreniphorm disorder treated with risperidone (in press).

41. Ring N, Tantum D, Montague L, Newby D, Balk D, Morris J. Gender differences in the incidence of definitive schizophrenia and atypical psychosis: Focus negative symptoms of schizophrenia. Acta Psychiatr Scand 1991; 84: 489-496.

42. Haas Gl, Sweeney JA, Hien DA, Golman D, Deck M. Gender differences in schizophrenia. Schizophr Res 1991; 4(3): 277.

43. Schultz SK, Miller DD, Oliver SE, Arndt S, Flaum M, Andreasen NC. The life course of schizophrenia: age and symptom dimensions Schizophr Res 1997; 23(1): 15-23.

44. Goldstein JM, Santangelo SL, Simpson JC, Tsuang MT. The role of gender in identifying subtypes of schizophrenia: A latent class analytic approach. Schizophr Bull 1990; 16: 263-275.

45. Szymanski S, Lieberman JA, Alvir JM, Mayerhoff D, Loebel A, Geisler S, et al. Gender differences in onset of illness, treatment response, course and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry 1995; 152(5): 698-703.

46. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Gur RC. Gender differences in the clinical expression of schizophrenia. Schizophr Res 1992; 7: 225-231.

47. Gur RE, Perry RG, Turetsky BI, Gur RC. Schizophrenia throughout life: sex differences in severity and profile of symptoms. Schizophr Res 1996; 21: 1-12.

48. Lindamer LA, Lohr JB, Harris JM, McAdams LA, Jeste DV. Gender-related clinical differences in older patients with schizophrenia. J Clin Psychiatry 1999; 60: 61-67.

49. Hayashi N, Igarashi Y, Yamashina M, Suda K. Is there a gender difference in a factorial structure of the positive and negative syndrom scale. Psychopathology 2002; 35: 28-35.

50. Usall J, Ochoa S, Araya S, Gost A, Busquets E y grupo NEDES. Sintomatología y género en la esquizofrenia. Actas Esp Psiquiatr 2000; 28(4): 219-223.

51. McEvoy JP, Johnson J, Perkins D, Lieberman JA, Hamer RM, Keefe RS, et al. Insight in first-episode psychosis. Psychol Med 2006; 36: 1385-1393.

52. Cuesta, MJ., Peralta, V., Zarzuela, A. Psychopathological dimensions and lack of insight in schizophrenia. Psychol Rep 1998; 83: 895-898.

53. Goldstein JM, Seidman LJ, Santangelo S, Knapp PH, Tsuang MT. Are schizophrenic men at risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions. J Psychiatr Res 1994; 28(6): 483-498.

54. Seidman LJ, Goldstein JM, Goodman JM, Koren D, Turner WM, Faraone SV, et al. Sex differences in olfactory identification and Wisconsin Card Sorting performance in schizophrenia: relationship to attention and verbal ability. Biol Psychiatry 1997; 42: 104-115.

55. Goldberg TE, Gold JM, Torrey EF, Weinberger DR. Lack of sex differences in the neuropsychological performance in patients with schizophrenia. Am J Psychiatry 1995; 152: 883-888.

56. Andia AM, Zisook S, Heaton RK, Hesselink J, Jernigan T, Kuck J, et al. Gender differences in schizophrenia. J Nerv Ment Dis 1995; 183(8): 522-528.

57. Perlick D, Mattis S, Stastny P, Teresi J. Gender differences in cognition in schizophrenia. Schizophr Res 1992; 8: 69-73.

58. Lewine RRJ, Walker EF, Shurett R, Caudle J, Haden C. Sex difference in neuropsychological functioning among schizophrenic patients. Am J Psychiatry 1996; 153: 1178-1184.

59. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8: 470-484.

60. Lopez M, Rodriguez S, Apiquian R, Paez F, Nicolini H. Translation study and validation of the Premorbid Adjustment Scale for Schizophrenia. Salud Mental 1996; 19: 24-29.

61. Häfner H, Riecher-Rössier A, Hambrecht M, Maurer K, Meissner S, Schmidtke A, et al. IRAOS: an instrument for the assessment of onset and early coruse of schizophrenia. Schizophr Res 1992; 6(3): 536-548.

62. Kay SR, Fizbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13(2): 261-276.

63. Peralta V, Cuesta MJ. Validación de la Escala de los Síndromes Positivo y Negativo (PANSS) en una muestra de esquizofrénicos españoles. Actas Luso-Esp Neurol Psiquiatr 1994; 22(4): 1-7.

64. Villalta-Gil V, Vilaplana M, Ochoa S, Dolz M, Usall J, Haro JM, et al. Four Symptom dimensions in outpatients with schizophrenia. Compr Psychiatry 2006; 47(5): 384-388.

65. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl 2003; 416: 16-23.

66. Endincott J. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976; 33: 766-771.

67. Amador XF, Strauss DH, Yale SA, Gorman JM. Awareness of illness in schizophrenia. Schizophr Bull 1991; 17: 113-132.

68. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatr 1978; 133: 429-435.

69. Hambrecht M, Häfner H. Substance abuse and the onset of schizophrenia. Biol Psychiatry 1996; 40: 1155-1163.

70. Mueser KT, Yarnold PR, Bellack AS. Diagnostic an demographic correlates of substance abuse in schizophrenia and major affective disorder. Acta Psychiatr Scand 1992; 85(1): 48-55.

71. Hall WD. Cannabis use and psychosis. Drug Alcohol Rev 1998; 17: 433-444.

72. Rodríguez-Jiménez R, Bagney A, Jiménez-Arriero MA, Aragüés M, Koenecke A, Cubillo AI, et al. Esquizofrenia y trastornos adictivos: Comorbilidad en pacientes psiquiátricos agudos ingresados. Psiq Biol 2006; 13 (S3): 46-47.

Address for correspondence:
Susana Ochoa
Parc Sanitari Sant Joan de Déu
C/ Antoni Pujades 42. CP 08830
Sant Boi de Llobregat (Spain)
Tel. +34 93 640 63 50
Fax. +34 93 630 53 19
E-mail: sochoa@pssjd.org

Author Note

GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Corominа M, De Miquel L, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

STUDY 6: Edad de inicio del primer episodio psicótico: ¿hay diferencias clínicas entre varones y mujeres?

A. Barajas[a,b], I. Baños[a], S. Ochoa[a], J. Usall[a], V. Villalta-Gil[a], M.Dolz[b], B. Sánchez[b], J.M. Haro[a], Grupo GENIPE[1]

[a] Serveis de Salut Mental, Sant Joan de Déu, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, España
[b] Hospital Sant Joan de Déu de Barcelona, Esplugues de Llobregat, Barcelona,España

[1] Grupo GENIPE es un grupo de investigadores multidisciplinar: Araya S, Arteaga M, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Borrás M, Busquets E, De Miquel L, Dolz M, Elias M, Espezel I, Fargas A, Foix A, Fusté M, Godrid M, González O, Granell Ll, Haro JM, Martínez R, Miñambres A, Muñoz D, Nogueroles R, Ochoa S, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Sammut S, Sánchez M, Sánchez B, Tabuenca P, Urbano D, Usall J y Villalta V.

Psiquiatría Biológica 2007; 14(4): 136 –141 (see annex)

PART III:
GENERAL CONCLUSIONS

6. General discussion:

6.1. Main findings

The present thesis focuses on the study of the **incipient phases** of psychotic spectrum disorders in patients with a **recent-onset of psychosis**. It implies investigating these patients from a **retrospective approach**. This is a research project about **predictor factors** occurring in the premorbid and prodromal phases of psychosis and their association with the onset of psychosis.
As noted in the introduction, in the last two decades a climate of optimism has emerged highlighting preventive opportunities if the intervention directed toward psychotic spectrum disorders is carried out as soon as possible. For this, it is necessary to take into account the specific characteristics of incipient phases of psychosis to carry out an appropriate case identification and after to adapt the intervention to these features.
However, despite the fact that new **integrative theoretical models** developed on the bases of the phenotype of psychotic disorders produced by the influence of multiple factors have increased scientific evidence in recent years, this is not enough to determine objective quantifiable individual risk factors in early phases of psychosis. So, a further step would be to broaden our knowledge about the profile of early phases of psychotic spectrum disorders regarding clinical and functional issues. This may shed light on the **factors predisposing** to the development of psychosis and **factors precipitating** its onset. This thesis has been developed on the basis of the **continuum hypothesis of psychosis**, without ignoring the diagnostic categories of psychotic disorders that appear in international diagnostic classification. It is an appropriate mechanism to study the **phenomenological heterogeneity** and development of psychotic experiences. In conclusion, seeing psychotic phenomena as a point on a continuum with 'normal' experience is a useful heuristic device with many positive benefits, among them achieving an intervention model based on continuity risk.

To date, we do not have a clear consensus about the criteria for defining the threshold of onset of psychotic episode (Yung et al., 2010b). However, the clinical staging model represents an approximation to this question with clinical and etiological implications. The application of the **clinical staging model** is based on the idea that the disease progresses through different stages that are characterized by phase-specific clinical manifestations. One of the aims of this model is to prevent disease progression and broaden our knowledge of each of the early stages of illness regarding the social, biological, and personal risk and protective factors that influence progression from one stage to the next. It would be helpful to implement a more appropriate and preventive phase-specific assessment and intervention model.

According to the clinical staging model, psychosis can be defined along a continuum characterized by the sequential emergence of the following stages: premorbid, prodromal and psychotic phases. So, taking into account this sequence, the **key findings of this thesis** are summarized as follows:

Regarding the premorbid phase:

- One of the widely used scales to assess PA in patients with recent-onset of psychosis is the PAS. **PAS-S shows appropriate psychometric properties** in patients experiencing a psychotic disorder.

- **PA is more similar between consecutive developmental stages** (e.g. childhood and early adolescence) than non-consecutive stages (e.g. childhood and late adolescence), indicating the

usefulness of analyzing this construct in an evolutionary way. In this way, it is possible to detect at what specific stage a poorer PA appears.

- In relation to **construct validity**, taking into account the two-factors model (social and academic domain):

  - ✓ Regarding **convergent validity** of the PAS-S:
    - **Social PA is associated with negative psychotic symptoms and most of the disability measures.** It is indicative that an FEP with negative symptoms and functional impairment at the onset of episode may already be observed in the premorbid phase as a non-specific and more subtle premorbid impairment in social functioning.
    - **Academic PA is associated with general symptoms** of the (Positive and Negative Syndrome Scale) PANSS subscale.

  - ✓ Regarding **discriminant validity** of the PAS-S:
    - **Academic PA is not associated with positive and negative psychotic symptoms.** This means that specific psychotic symptoms at the onset of an episode, in constrast to non-specific symptoms (general symptoms of PANSS subscale), are not informative of subtle premorbid impairments of academic performance. In addition, **academic PA is not associated with most of the variables of social functioning and disability.**
    - **Social PA is not associated with positive and general symptoms** of the PANSS subscale.

- Compared to total PAS-S, **higher scores in internal consistency** are found in the PAS-S factors (social and academic domains), indicating that the included items in each domain assess the same construct.

- There is a limited association between social and academic domains suggesting that they share a relatively small proportion of variance and, hence, **PA could be considered a multidimensional construct**. However, **PA is better explained by three factors**, splitting the classic social factor into two components, Social PA and Socio-sexual PA domains.

- **Each domain shows a differential pattern of deterioration and specific correlates:**
  - ✓ **Academic domain:** a) a pattern of deterioration across age periods is observed, more evident between childhood and early adolescence; b) it is related exclusively to cognitive correlates (learning and verbal memory and premorbid IQ). Academic PA could be considered as an indirect measure of cognitive competence before the onset of psychotic illness.
  - ✓ **Social domain:** a) compared with the Academic domain, a smoother, steady pattern of impairment across development periods is observed from childhood; b) clinical (severity of positive symptoms) and functioning (social disability) correlates with Social PA are observed.
  - ✓ **Socio-sexual domain:** a) the slightest impairment is observed in this domain; b) it is related to negative symptoms. Socio-sexual PA domain could be considered as a good predictor of transition to psychosis in subjects initiating the illness with negative symptoms.

- Regarding gender differences in premorbid functioning, **males who start the psychotic episode earlier show poorer PA than women**, especially in early adolescence, supporting the late neurodevelopment hypothesis.

Regarding the prodromal phase:

- There is an **extensive symptomatic heterogeneity in the proximal prodromal phase** of transition to psychosis, characterized not only by subthreshold positive psychotic symptoms.

- Among **the most frequent prodromal symptoms** observed in the FEP sample are **APS** (mainly disturbances of thinking), **affective/negative and cognitive symptoms**.

- The **prodromal dimensions have differing capacities for predicting psychopathological dimensions** at the onset of psychosis:
  - ✓ **Attenuated or subthresthold psychotic symptoms** are predictors of positive and disorganized symptoms in the psychosis active phase.
  - ✓ **Language disturbances** are related to disorganised active symptoms at the onset of illness.
  - ✓ **Prodromal behavioural abnormalities** are the main, and exclusive, predictor of excited psychotic symptoms at the onset of FEP.
  - ✓ **Emotional disturbances** in the prodromal phase are the only predictor of the negative dimension at the onset of FEP.
  - ✓ **Non-hallucinatory disturbances of perception** show predictive capacity for psychotic episodes characterized by affective symptoms.

- The presence of **familial loading** for the illness is a significant predictor of disorganised and positive domains at the onset of the FEP.

- From a **quantitative approach**, a greater load of prodromal symptoms is associated with an onset of FEP characterized by disorganised psychotic symptoms.

- The great majority of, although not all, **FEP patients show at least some prodromal symptom** prior to onset of the psychotic disorder.

- Regarding the number of prodromal symptoms accumulated until culmination of the FEP, approximately a third of those analysed appeared **in the year immediately before the onset of the episode.**

- In relation to **gender differences in the prodromal phase**, analyzed from a prospective approach and based on the review of studies of high risk for psychosis published in recent years:
  - ✓ **Men at-risk for psychosis have more severe negative symptoms than women** before full-blown psychosis; it is more difficult to detect them across current risk criteria for psychosis focused on positive attenuated symptoms.
  - ✓ **Female gender is one of the independent significant predictors of affective psychosis.**
  - ✓ **Significant gender differences have not been found in DUI**, although it is shorter in women than in men in most of the studies. It is likely that more women seek help for psychological or medical problems than men.
  - ✓ **Men show lower functioning and social support than women** before full-blown psychosis. Also, social functioning is a stronger predictor of psychosis onset in men than women.
  - ✓ The **limited scientific evidence about cognitive impairment** in prodromal phase according to gender has indicated the importance of considering sexually differentiated patterns of cognitive decline in individuals with high risk for psychosis.

- Regarding gender differences in prodromal symptoms experienced in the FEP sample analyzed in this thesis, **women with an earlier onset of psychotic episode show a higher frequency of senso-perceptive subclinical disturbance** (hallucinations) in the prodromic phase. In addition, **men with a later onset of psychotic episode show a higher frequency of dysfunctional language** than women of the same age group.

Regarding the initial psychotic phase:

In a comprehensive review of gender differences in patients with a sub-clinical psychotic syndrome and psychotic spectrum disorder carried out for this thesis:

- **The results found to date regarding transition to psychosis are inconsistent**: some studies do not show gender differences and others indicate a greater risk for conversion to psychosis in men, suggesting that differential precipitating factors exist according to gender.
- **Better social functioning appears to be a particular strength of women** with psychosis spectrum disorders compared to men. However, not all studies confirm this finding.
- Gender differences in neuropsychological functioning have been reported in patients with psychotic spectrum disorders, indicating **higher levels of cognitive functioning in women**. However, a consensus has not been established as these differences have not been tested in some studies. In the FEP sample analyzed in several studies for this thesis no gender differences were found in executive functioning, attention or working memory. Instead, the performance in verbal memory was higher in men.
- The most replicated findings in relation to clinical expression of psychotic disorders suggest that **affective symptoms are more common in women while negative symptoms tend to be more predominant in men**. In the FEP sample analyzed in several studies for this thesis, clinical expression of psychotic symptoms was conditioned by age of onset of the psychotic episode:
    - ✓ In the under 18 group, men showed more severe negative psychotic symptoms and poorer awareness of the symptoms of disorder.
    - ✓ In the over 17 group, men showed more excitative and manic symptoms than women.

Other gender differences found **in the FEP sample analyzed for this thesis** were the following:

- Until the onset of FEP, women have a higher **educational competence** and men have a better **work status**.
- The **time average until contact with mental health services** is greater in men.
- No gender differences are observed with respect to **age at onset** of FEP.
- A greater frequency of **cannabis** consumers is observed in the male group, with daily consumption the most frequent pattern. In women, cannabis consumption is more common in a sporadic pattern.

Age at onset of FEP is an important variable to be considered in future studies about gender differences in psychotic disorders. In the FEP sample analyzed for this thesis, the following results are obtained:

- **Men with earlier onset of psychotic episode have a greater prevalence of negative symptoms** (mainly in emotional withdrawal, poor rapport and blunted affect) than men with later onset of FEP. However, differences in negative symptoms according to age at onset of the episode are not relevant in the group of women.
- **Women with earlier onset of psychotic episode have a greater prevalence of excited symptoms** than women with later onset of FEP. This predominance of excited symptoms is observed in men, but only in a subgroup with a later onset of FEP.

6.2. Overall discussion and clinical implications

This research represents a breakthrough regarding the identification of factors involved in the development of the early stages of psychosis, shedding light on the heterogeneity of these phases. In this way, clinicians can become aware of the different key factors up to the threshold of psychosis and thus tailor interventions and care to the needs of patients as early as possible. In this sense, the main findings of this thesis have important clinical implications regarding detection, assessment and intervention targeted at patients with an FEP.

Regarding the premorbid phase, studies like that of Strous et al. (2004) suggested that prior to the start of acute psychosis, there are specific precursors reflected in the premorbid functioning which could explain later manifestation of the disease. Thus, the premorbid functioning measures could be indicative of increased risk for the development of psychotic illness, which would manifest itself in a subtle form before the appearance of the first psychotic symptoms. For this reason, it seems truly important to assess functioning across different age groups to prevent or detect these symptoms. This thesis provides **a validated tool to assess premorbid functioning** with extensive international use. Mental health professionals have at their disposal an instrument **adapted to the cultural environment and with adequate psychometric properties** that can be used in both clinical practice and research. Furthermore, one of the advantages of the scale lies in its simplicity and its adaptability to a variety of information sources. It can be rated on the basis of personal interviews, family information, or chart histories, and is therefore of value for a variety of research purposes.

In addition, this research provides **a new factorial structure of the PA comprising three domains (Social PA, Socio-sexual PA and Academic PA)**, which can improve the search regarding their correlates at the onset of the episode that had not previously been identified due to lack of dimensionality of this construct. Each premorbid domain maintains specific associations with the initial phase of psychosis, suggesting the following clinical implications:

a) **the Academic PA domain** is related exclusively to cognitive correlates at the onset of psychosis, so that it may be considered as **an indirect measure of cognitive competence** before the onset of psychotic illness. Supporting the concept of the continuum of neurocognitive function in psychosis, it is possible to observe the results of cognitive difficulties before the transition to psychosis across the academic PA domain of PAS-S, a measure of fast and easy use in clinical practice. In addition, this performance can be explored at different stages of the life cycle of the person, including the period of adolescence marked by great changes both biological and psychosocial.
b) **the Social PA domain** is related to clinical symptoms (specifically, positive psychotic symptoms) and social functioning. In the line of the studies suggesting that deficits in social functioning before the onset of the FEP are often prognostic of later social functioning (Addington & Addington, 2005; Davidson et al., 1999; Häfner, Loffler, Maurer, Hambrecht, & an der Heiden, 1999), the results of this thesis support the **continuity between premorbid and morbid social impairment**. Future preventive efforts may be critical in the premorbid periods, as early as childhood, to minimise or prevent further social disability that will already have begun to develop by the time of symptom onset.
c) **the Socio-sexual PA domain** is the **new factor**, formerly considered within the Social PA domain, which assesses **social competence in intimate relationships and interest in maintaining close ties**, which may involve sexual activity, during adolescence. The main interest of this finding lies in the recognition of specific clinical correlates to Socio-sexual PA domain. In previous studies (Addington, van Mastrigt & Addington, 2003; Jeppesen et al., 2008; Monte et al., 2008; Strous et al., 2004),

negative symptoms were related to the classic premorbid social functioning domain, which included social and socio-sexual areas. In this research, **negative symptoms are associated exclusively with the Socio-sexual PA domain**. From a dimensional approach, these results suggest that the Socio-sexual PA domain may be considered a good predictor of transition to psychosis in subjects initiating the illness with negative symptoms. Thus, a poorer Socio-sexual PA domain could alert us to the need for intervention in order to avoid progression of the deterioration in this kind of social competence and accordingly, the emergence of negative symptoms, assuming progression to psychosis.

These deficiencies in different PA domains could reflect vulnerability to a specific clinical expression of the psychotic disorder as well as to cognitive and social impairment. So, interventions designed to prevent the development of psychotic symptoms (in particular, positive and negative psychotic symptoms), as well as social and cognitive impairment at the onset of psychosis, can be initiated at the earliest periods of life to achieve a better prognosis for the disorder. This requires a tool that is able to detect risk factors modulating the expression of the initial phase of psychosis, such as PAS-S. In this way, **PA could be understood as a risk factor modulating expression of psychosis onset**, whereby impairments in each PA domain might predispose individuals to develop different expressions of psychotic dimensions in relation to the particular impaired domain.

The importance of distinguishing among these three domains resides, on the one hand, in the decrease of the error associated with making multiple comparisons using the five domains included in the original scale, and on the other hand, in the possibility afforded by the scale of examining them at each age level and observing a differential pattern of deterioration in each domain.
The results of this study could contribute to improving our knowledge of the **Research Domain Criteria (R-DoC)**, a new way of classifying mental disorders based on dimensions (Insel et al., 2010), specifically in two domains: cognitive and social process systems. The Academic PA domain may be considered an indirect measure, among other behavioural analysis units, to study the cognitive domain, in particular attention, perception and declarative memory constructs; and the Social and the Socio-sexual PA domains may be considered units of analysis to study the social process domain, in particular social communication and perception and understanding of self/other constructs. Studies based on R-DoC criteria, by using PA domains as analysis units in cognitive and social process domains, would allow progress towards knowledge of new strategies for early detection and psychosocial interventions adapted to the needs of patients and focusing on disturbed constructs, not on diagnosis.

Regarding the prodromal phase, this thesis supports the existence of an extremely variable symptom profile in this phase, and one not based only on subthreshold positive psychotic symptoms. In this sense, this research adopts a broader approach considering **a variety of subclinical symptoms as potential predictors of different initial symptoms of psychosis onset**. The results indicate that attenuated positive psychotic symptoms are good predictors of positive symptoms in the psychosis active phase, but they are not the only ones. So, the definitions of risk criteria for psychosis should include a wider range of subclinical symptoms with good predictive capability for the onset of psychosis, such as **language problems, disorganized behavior, affective impairments, and non-hallucinatory disturbances of perception**. In addition, another factor that should be maintained in the definitions of risk for psychosis is the presence of psychotic familial loading in order to enhance the predictive power.
According to the findings and based on a dimensional approach, patients who experience language problems in the prodromal phase may develop psychosis with disorganised symptoms at the onset; patients who experience disorganised behavior may develop psychosis with excited symptoms at the onset; patients who experience affective impairments may develop psychosis with negative symptoms at

the onset; or patients who experience non-hallucinatory disturbances of perception may develop psychosis with depression and anxiety symptoms at the onset. In this sense, for the clinician, the identification of these prodromal symptoms should be considered as warning signs for possible development of psychosis. However, the nonspecificity of these symptoms should be noted as well as the fact that none of them are pathognomonic of psychosis.
Another indicator of imminent risk of psychosis for clinicians is the accumulation of prodromal symptoms or increased load of subclinical psychotic experiences. Kaymaz & van Os (2010) concluded that **the greater the load of subclinical psychotic experiences, the greater the probability of clinical outcome**.

Furthermore, the continuity from the prodromal phase to the psychotic phase has not only been studied from a symptomatic approach, but also in terms of sociodemographic characteristics, such as gender. The elucidation of a **differential pattern by gender during the prodrome to psychosis** is critical to understanding illness etiology and generating more powerful predictive models that would be maximally sensitive and specific. This may aid in development of individually tailored treatments, with consideration of the effects of gender, which could target different neurobiological systems and/or use alternative cognitive/behavioral approaches with optimal effect. In this sense, the findings found have the following clinical implications regarding,

a) **transition to psychosis:** the current UHR criteria definition are more effective in detecting 'true' prodromal cases among women than men (Amminger et al., 2006b) as they focus on positive attenuated symptoms (more prevalent in women), with minimal attention to negative symptoms (more prevalent in men) (Maric, Krabbendam, Volleberg, De Graaf, & van Os, 2003). By this way, **the current definitions of UHR for psychosis do not allow determination of real incidence rates of risk for psychosis** and they should include other subclinical symptoms to avoid identification biases.
b) **clinical expression:** symptom presentation likely plays an important role in determining treatment regimens and understanding gender differences in treatment response. **The differences between men and women in clinical presentation extend across the continuum of psychosis**: men having more 'typical' symptoms of non-affective psychosis and women having more 'typical' symptoms of affective psychosis (Willhite et al., 2008). For this reason, differential treatment according to gender should be implemented from the prodromal phases of psychosis. It should also be noted that women tend to express their emotions more readily and may be more likely to be misdiagnosed as having mood disorders (Folnegović & Folnegović -Smalc et al., 1994).
c) **social functioning:** it is important to consider the importance of preventive psychosocial interventions, specifically for men at risk for psychosis, as social functioning has been considered a better predictor of psychosis onset in men than women (Tarbox et al., 2013; Willhite et al., 2008). Also, the scientific evidence suggests that **women have better access to social networks and social support than men** (Gayer-Anderson & Morgan, 2013), although these gender differences in social functioning are more subtle and non-significant in previous phases at onset of psychosis (Willhite et al., 2008). Therefore, prevention strategies could be improved with a more comprehensive approach that involves developmentally earlier functional deficits.
d) **cognitive functioning:** the limited findings found to date have confirmed that **cognitive deficits are already present before the FEP** (Brewer et al., 2006; Hawkins et al., 2008; Seidman et al., 2010) and mental health professionals should be able to detect cognitive impairment in the prodromal phase. Gender may be an important factor in the expression of these deficits, which the clinicians should take into account in their assessments.

A reformulation of the definition of risk criteria for psychosis is needed, based on differences between women and men as regards clinical, social, and cognitive variables in the prodromal phase. Men and women may be vulnerable to different 'types' of psychotic disorders, or psychosis may develop differently according to gender.

Gender-sensitive services are a first step toward individual-specific personalized care, as men and women may differentially benefit from certain approaches to intervention.

In summary, the findings about the symptoms experienced in the prodromal phase may have clinical implications in relation to several issues:

a) prodromal characteristics could be regarded as **a new class of risk factors**, especially useful in prevention studies;
b) the psychosis risk algorithms used to date should be modified, taking into account **a broader approach with negative and less-specific prodromal symptoms** (such as behavioural, language and emotional disturbances). This might guide future research regarding the phenomenology of the 'attenuated psychosis symptoms syndrome', currently considered to be a category in the appendix of DSM-5;
c) **new specific and stage-appropriate treatments should be developed**, taking into account the heterogeneity of symptoms prior to the first manifestations of illness and aimed at ameliorating the distress caused by these symptoms (Carpenter, 2009).
d) **sexually differentiated predictors** need to be considered in order to understand the early development of psychosis. It may be helpful to improve risk identification using algorithms that take into account the gender variable.

Finally, **regarding the initial psychotic phase**, as well as the early phases at the onset of psychosis, gender differences are an important factor in the understanding of the manifestation and development of the spectrum psychotic disorders. Clinicians should take into account the gender factor from the premorbid phase through the active phase of psychosis, due to its influence in differential expression along the continuum of the disease, with specific characteristics for each gender.
One part of the findings of this thesis indicates that **there are gender differences in the early phases up to the threshold of psychosis, with better prognosis in women than in men**. For this reason, mental health professionals should be alert to male patients younger than 18, with greater severity in negative psychotic symptoms and poor awareness of the disease. This is the group with the worst prognosis and the one that is most resistant to therapeutic interventions. In the general population age-related gender differences in maturational processes have been observed, in particular, a significantly greater loss of cerebral grey matter in boys compared to girls (De Bellis et al., 2001), which may represent the underlying mechanism of men showing an earlier age of onset of psychosis than women in subclinical samples. An alternative explanation may be found in the differential exposure to estrogens, which may play a protective role by decreasing the risk for and the severity of psychotic disorders in women (Riecher-Rössler & Häfner, 2000).

Another important demographic factor to consider in the characterization of the development of the early phases of psychosis is age (or age period). It is important to know when the risk factors that have some relation to the development and onset of psychosis are experienced, throughout the life cycle of each person. In turn, **the age at onset of a psychotic episode represents an important variable in relation to prognosis and to establishing criteria for identifying people at risk for psychosis**. So one of the strengths of this thesis is related to the target population, which includes patients with psychosis onset that runs from adolescence to adulthood. It has allowed us to examine the differential expression of psychosis according to age at onset of FEP. In addition, this issue has important clinical implications, because this variable provides key information for establishing an appropriate therapeutic project, which should be adapted to the needs and characteristics of each patient in each period of the life cycle.
In summary, these sociodemographic characteristics should be taken into account to learn more about the different types of onset of the disease, its prevention and possible improvements in therapeutic approach.

7. Limitations:

⇒ General limitations:

The general aim of this thesis is related to the characterization of early phases of psychosis through a **retrospective approach**. This design entails a great limitation in the accuracy of assessment of predictors for psychosis when the illness has already appeared, which may lead to inaccurate reporting. However, the clinical information analyzed in this research has been collected and contrasted with a variety of information sources (personal interviews with patients, family information, professional information or/and chart histories) in an attempt to overcome this limitation. Further, retrospective designs provide an advantage compared to prospective studies with high-risk populations because they do not include false positives. Likewise, the study of predictors of onset of psychosis through patients with an FEP reduces interference due to treatment, which is more evident in chronic population.

This research implies tackling a highly heterogeneous reality, which is reflected in the difficulty of establishing the **specific boundaries between each of the early phases** up to the debut of psychosis. It was taken into account that there is a very narrow line between the premorbid phase and the onset of prodromal symptoms as well as between the prodromal phase and full-psychotic symptoms, making it difficult to establish differences between them. The specific limitations and future directions corresponding to each phase and the studies that comprise this thesis are the following:

⇒ Specific limitations regarding the studies of this thesis

Premobid phase (study 1 and study 2):

The specific limitations of the PAS-S scale are the following (**study 1**):

a) **Definition of premorbid period:** according to Cannon-Spoor et al. (1982), it ends 6 months before the first admission to hospital or the onset of florid psychotic symptoms. However, van Mastrigt and Addington (2002) recommended that the end of the premorbid period should be taken as 1 year before that date; this was the definition used in this thesis. However, nowadays there is much debate about determining the end of the premorbid period or, alternatively, establishing the onset of prodromal symptoms. There is research which shows that the duration of the prodromal period is greater than 1 year, considering the presence of negative and nonspecific symptoms (Häfner & Maurer, 2001).
b) **Adult and general subscales:** these must be reviewed, because the most common modifications to the PAS reported in the literature are exclusion of the general scale, the adult scale or both (van Mastrigt & Addington, 2002); the researchers who have excluded the general section suggested it is not strictly a measure of premorbid function (Gureje, Aberibigde, Olley, & Bamidele, 1994).
c) **Socio-sexual section:** another common modification in the literature is related to this section (Andreasen, Flaum, & Arndt, 1992; van Mastrigt & Addington, 2002). These items need to be updated and adapted to each cultural context.
d) **Assessment design:** premorbid functioning must be assessed retrospectively, which may lead to inaccurate reporting, especially in chronic patients. It is also possible that relatives give a description of the premorbid period influenced by the present experience with psychosis.

Note: the adapted version of PAS-S has been included in the annex of this thesis, in an attempt to overcome such limitations.

The specific limitations related to study of the factorial structure of PAS-S are the following (**study 2**):

a) **Diagnosis of spectrum psychotic disorders:** the subsample of chronic schizophrenia did not include patients with affective psychosis, in contrast to the FEP subsample. This could have influenced the results in both Social PA and Socio-sexual PA in the FEP subsample, with less detereoration than the Academic PA domain in psychotic mood disorders (Tarbox et al., 2012). However, we must take into account that, like patients included in the subsample of chronic schizophrenia, all patients included in the FEP subsample had experienced two or more psychotic symptoms.
b) **Assessment of academic domain:** academic functioning was not assessed through a systematic study of school records or interviews with teachers.
c) **Sample size:** the small sample sizes in analyses using subsamples of patients with FEP and chronic schizophrenia may have reduced statistical power, thus potentially increasing the occurrence of type II errors.
d) **Consensus in cognitive measures:** the lack of consensus in the scientific literature on the tests used to measure different cognitive domains makes it difficult to compare findings.
e) **Interference of treatment:** it is impossible to eliminate the effect of pharmacological treatment and this could introduce some variability in performance in some of the tests, inhibiting cognitive decline or even improving cognition over time (Lieberman et al., 2001).
f) **Assessment design:** the retrospective design of the PAS raises the possibility of recall bias; however, a previous study supported the results of the predictive and concurrent validity of the PAS based on self-report data (Brill, Reichenberg, Weiser, & Rabinowitz, 2008).

Prodromal phase (study 3 and study 4):

The specific limitations related to study of the predictive capacity of prodromal symptoms are the following (**study 3**):

a) **Assessment design:** the prodrome can only be assessed retrospectively with the limitations that this implies. However, this study investigates a broad spectrum of **proximal prodromal symptoms** (the year before the debut of FEP) reducing memory biases. Furthermore, an advantage of this study is the fact that only patients who had recently entered the psychotic stage were investigated for their prodromal symptoms and they therefore had better recollection of events in the pre-psychotic period.
b) **Limit between prodromal and psychotic symptoms:** the complexity of the phenomena under study resides in that there is a very narrow line between prodromal symptoms and full-psychotic symptoms, making it difficult to establish a distinction between them. In this research, the following criterion was determined to define a symptom as attenuated or prodromal and not fully psychotic: a lack of conviction about the 'real' nature of symptoms.

In order to adequately interpret the results of the review about gender differences in individuals at high risk of psychosis (**study 4**), the main limitations of the studies included in this review should be taken into account, among which are the following: the **limited sample size** with unequal distribution of participants by gender making it difficult to generalize the results (lack of sample-gender representativeness); a **strict age range**, which for example does not allow inclusion of a group of women at risk who could develop psychosis with later onset (or overrepresentation of men); the **lack of standardized instruments** to measure some variables (e.g., DUI); the **use of diagnostic criteria for the UHR** which could be identifying people with a psychotic active phase and not a subclinical syndrome or which include exclusively attenuated positive psychotic symptoms; many of the studies have a **high dropout rate**, making it difficult

to generalize the results found; the **lack of consensus in defining a patient at high risk** for psychosis among the studies examined, making it difficult to compare the results found about transition rates; the lack of consensus about the **measures used to assess social and cognitive functioning** impedes the generalization of results; in some studies the **longidtudinal framework** is limited and it does not allow drawing conclusions on progress towards psychosis.

Accordingly, the interpretation of the conclusions reached in this review should not ignore several issues regarding the limitations mentioned above:

a) **Representativeness of the samples:** the samples of these studies are not representative of the population of all UHR cases and may obscure or reduce the extent of gender-related differences found.
b) **Method used:** the methodological variability of these studies limits the generalizability of their findings.
c) **False-positive rates:** the gender differences might be less evident in UHR samples than in samples of people diagnosed with psychotic disorders because only a minority of UHR people develop full-blown psychosis (De Koning et al., 2009).

Initial psychotic phase: (study 5 and study 6):

The specific limitations related to study of the gender differences and age at onset in FEP are the following (**study 5** and **study 6**):

a) **Measuring instruments:** the lack of consensus with findings of previous studies regading gender differences in cognitive functioning could be due to the variability of measuring instruments utilised to evaluate the different cognitive domains; further, PAS scale and IRAOS interview are instruments for retrospective assessment, in which some information could be inaccurate as it relies on the patients' or family members' memory.
b) **Sample size:** the limited sample size of these studies does not permit generalizing the findings. It also makes it difficult to stratify the sample to study and compare different groups (it is necessary to use non-parametric tests).
c) **Control group:** The absence of a control group precludes a comparison between the two populations of healthy people and patients with a psychotic episode in relation to the premorbid and prodromic variables.
d) **Representativeness of the sample:** patients with an insidious onset of psychosis may delay contact, or avoid it entirely, with the mental health services. For this reason, not all the FEP could be represented in the sample analyzed in these studies.
e) **Pharmacological treatment:** the absence of control for pharmacological treatment could influence the analysis of certain variables, such as severity of symptoms 8 weeks after the onset of FEP or cognitive functioning.

8. Future directions:

Research on the prediction of psychosis onset, based on a retrospective approach, has provided evidence to generate prospective studies identifying individuals at increased imminent risk for psychosis relative to the general population. This thesis represents a broadening of such evidence regarding the identification of

early predictors of psychosis, which can be helpful in generating new methods and/or tools for early detection of psychosis. The next phase of research in this area should be focused on the following issues:

Future research should be directed at **increasing our knowledge about the relationship between premorbid impairments and prodromal symptoms** in longitudinal studies with UHR samples. This would be helpful to more accurately identify specific premorbid risk factors because the emergence of premorbid impairments is more proximal to the prodromal phase than to the onset of psychosis syndrome. Likewise, it could lead to better understanding of predictive power in relation to the transition to psychosis. In fact, some researchers have demonstrated that environmental characteristics and social adjustment are predictive of transition to psychosis in subjects at UHR (Dragt et al., 2011). These characteristics could be implemented in a model for prediction of psychosis, although more studies are needed to confirm this aspect. It is possible that the factors that precipitate the transition from premorbid to prodromal stage are not necessarily distinct from those involved in the transition to psychosis.

In relation to PA, another issue of interest to analyze in the future is the limited scope of PAS-S, as it assesses psychosocial functioning while neglecting cognitive ability. In this sense, it would be necessary **to complete the assessment of academic PA domain with other measures** in addition to scholastic performance and adaptation to school, such as exploring subjective cognitive complaints already detected at onset of FEP.

Furthermore, a further chance to improve the efficacy of predictive criteria of FEP may come from the analysis of prodromal symptomatic patterns. The findings of this thesis about the predictive capacity of prodromal symptoms indicate that the development of each subtype of full-blown psychosis is already differentially programmed from the prodromal phase. Future research should be directed at **studying whether or not identified specific groups of FEP** (Ochoa et al., 2013) **are characterised by different prodromal symptoms**. So, a new line of research might be to investigate the possibility of discriminating between UHR individuals that develop non-affective psychosis from those who are going to be affected by affective psychosis or other classifications of patients who will develop an FEP.

Other aspects of interest for future research include **creating new measurement instruments of prodromal symptoms with a comprehensive approach**, including APS, basic or non-specific symptoms as well as signs or symptoms indicating functional and cognitive impairment, to define ARMS criteria. Instruments combining a staged approach involving initial screening tests (with high sensitivity) followed by confirmatory tests (with high specificity) may reduce the overall risk of false-positive and false-negative predictions. The uncertain etiology of psychotic disorders has surely complicated the development of new instruments to predict or prevent such mental disturbance. It is essential to improve the effectiveness of predictive scales and criteria designed to assess the risk of FEP. A starting point for this line of future research should be the validation in the Spanish population of screening instruments and clinical interviews for the detection of high-risk patients. Currently, the author of this thesis is participating in serveral research projects to validate two clinical interviews for detecting subthreshold psychotic symptoms (CAARMS, ERIraos) in the Spanish population.

Multi-variate and multi-domain approaches to prediction of outcomes may therefore be more productive than individual predictors examined alone (Shah et al., 2013). Thus, future studies could **use the associated factors with onset of psychosis examined in this thesis, both in the premorbid phase as well as in the prodromal phase, to create new algorithms and risk-staging models in order to achieve greater predictive ability**. In this way, it would be possible to increase the capacity to detect different profiles of individuals with high risk for developing diverse subtypes of psychosis, thereby allowing intervention

before the onset of the FEP in an attempt to delay or ameliorate it. One of the main advantages of risk-staging models is the detection of the very early risk signs of mental disturbance. A very early detection of risk and appropriate symptomatic pattern classifications may provide a chance to better match prevention strategies with the development of psychosis. In fact, the possibility of applying a prevention programme is strongly connected with the ability to precisely identify only those individuals who later develop FEP.

In addition, this thesis has demonstrated that gender is a variable that must be taken into account. For this reason, future research should be focused on **improving detection algorithms for risk of psychosis using the gender variable**, due to differential expression of subclinical forms of psychosis according to it: e.g. based on the results found, there is a need to include negative symptoms in the risk criteria, which may help to identify more young men at risk for psychosis. Likewise, analyzing other variables or risk factors by gender such as substance use, family history, stress, and obstetric complications should be considered.
Similarly, it is important that future research about predictors of psychosis **take into account other specific variables in addition to gender, such as the age at onset**. This thesis has shown that it has differential influence on the expression of FEP.

Finally, one of the issues of interest in the study of FEP is related to **the detection of good prognostic factors or protector factors delaying conversion to psychosis**. In this regard, it would be useful to analyze factors occurring in the premorbid and prodromal phase that relate to clinical remission and functional recovery after the debut of FEP.

9. General conclusion:

The main conclusions of this thesis are:

- ✓ PAS-S shows appropriate psychometric properties regarding indicators of validity and reliability in patients experiencing a psychotic disorder.
- ✓ PA is best explained by three factors, splitting the classic social factor into two components, Social PA and Socio-sexual PA domains. Each domain shows a differential pattern of deterioration and specific correlates:
  - Academic domain is related exclusively to cognitive correlates
  - Social domain is related to clinical (severity of positive symptoms) and functioning (social disability) aspects
  - Socio-sexual domain is related to negative symptoms.
- ✓ There is an extensive symptomatic heterogeneity in the proximal prodromal phase of transition to psychosis, with prodromal dimensions having different capacities for predicting psychopathological dimensions at the onset of psychosis.
  - APS are predictors of positive and disorganized symptoms in the psychosis active phase.
  - Language disturbances are related to disorganised active symptoms at the onset of illness.
  - Prodromal behavioural abnormalities are the exclusive predictor of the excited psychotic symptoms at the onset of FEP.
  - Emotional disturbances in the prodromal phase are the only predictor of the negative dimension at the onset of FEP.
  - Non-hallucinatory disturbances of perception show predictive capacity for psychotic episodes characterized by affective symptoms.
- ✓ The differences between men and women in the expression of psychosis extend across a continuum, from the premorbid and subclinical forms of illness to the debut of psychosis, with better prognosis in women than in men.
- ✓ The age at onset of FEP is a relevant variable in the study of clinical expression of psychosis:
  - In men, those with earlier onset of psychotic episode have a higher prevalence of negative symptoms than those with later onset of FEP.
  - In women, those with earlier onset of psychotic episode have a higher prevalence of excited symtpoms than those with later onset of FEP.

This thesis shows that the appropriate level of analysis in the study of psychosis development is not found in the onset of psychotic episode but rather in earlier phases of psychosis (premorbid and prodromal periods). Throughout these phases several **risk factors** may occur, which can contribute to differential expression in the development of psychosis depending on which combination of these factors is given. There are **unmodifiable factors** (such as family history and gender) **and others that may be altered** if it is possible to intervene (such as impaired social functioning and sub-clinical symptoms). All of these should be considered in establishing new models of detection of patients at risk of psychosis.

Figure 9 depicts a conceptual model of **potential predictors of psychosis** derived from the integration of the results of this thesis and theoretical accounts.

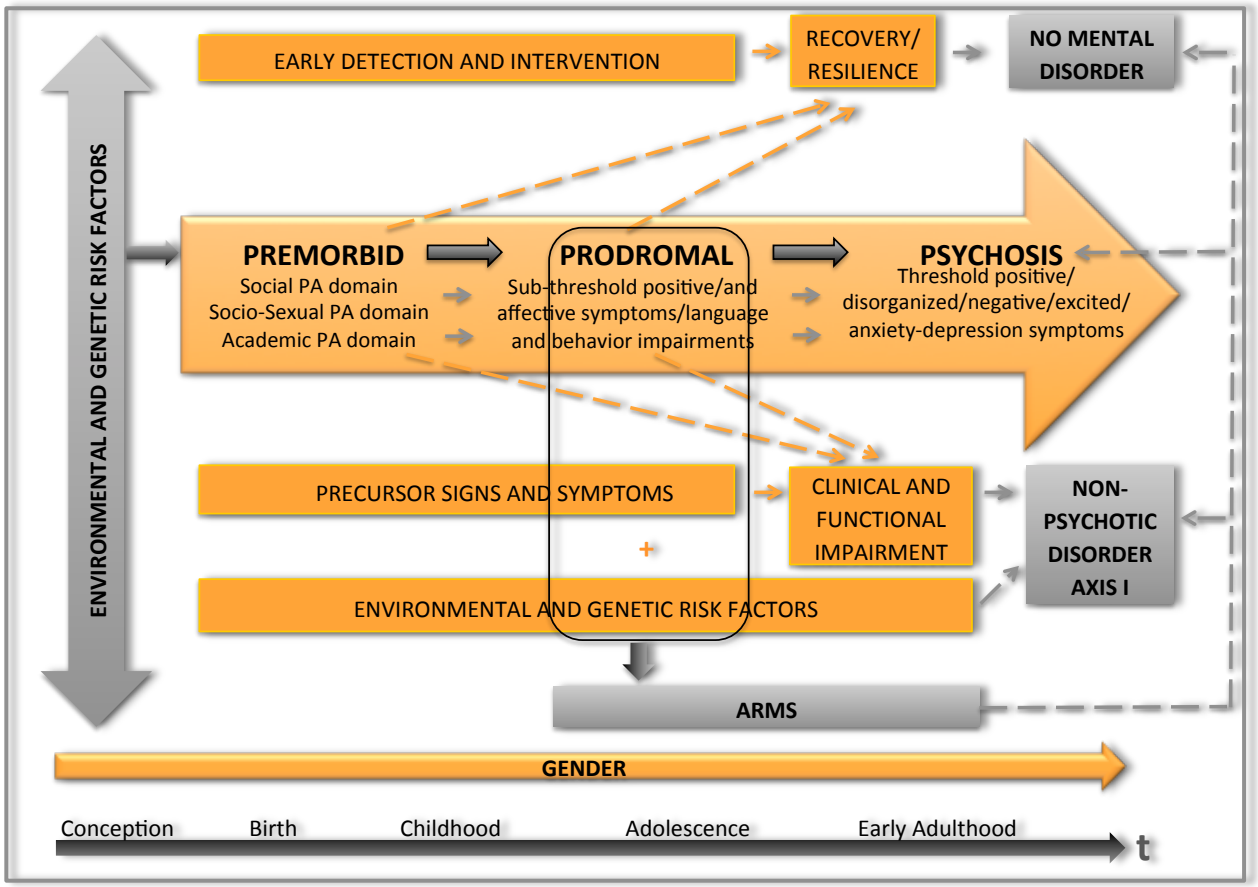


Fig. 9. Premorbid and prodromal variables as predictors at the onset of psychosis.

It illustrates features drawn from knowledge regarding the evolution and trajectory up to the onset of psychosis. Likewise, this schema shows other possible pathways according to the different factors involved throughout the life cycle stages of the person.

Perinatal, childhood, and adolescent and young adulthood periods are propitious for collection and measurement of early life risk variables; these could include **genetic and environmental factors**, such as family history or cannabis and other substance exposure, respectively. Other variables, such as **gender**, should also be taken into account in **all life periods** in order to study their influence on factors that appear at different stages of development of the individual. As time goes on, a minority of individuals will develop **premorbid disturbances** and persistent premorbid symptoms may or may not evolve into prodromal features with subclinical severity. In the prodromal phase, individuals experiencing the combination of **precursor signs and symptoms** with environmental and/or genetic risk factors could develop an ARMS, which could culminate in diverse outcomes. In some cases, if an evident clinical and functional impairment goes on, an **Axis I psychotic disorde**r could emerge or, in other cases, patients might remain symptomatic and functionally impaired and could develop an **Axis I non-psychotic disorder**. Finally, it may be possible that they **recover symptomatically and functionally**, some of them because of the benefits of early detection and intervention, and others because of their own resilience (protective factors).

Furthermore, **the heterogeneity of the psychotic spectrum begins early**, long before the onset of psychosis. From a dimensional approach to psychosis, precursor signs and symptoms of early phases could be understood as factors modulating expression of psychotic symptoms, whereby **specific premorbid and**

prodromal events might predispose individuals to develop different expressions of psychotic dimensions. In addition to PA in socio-sexual, academic and social areas, symptomatic heterogeneity in the proximal prodromal phase of transition to psychosis, not only including sub-threshold positive psychotic symptoms, has differing capacities for predicting psychopathological dimensions at the onset of psychosis.
Similarly, **gender differences in the expression of psychosis extend across a continuum**, from the premorbid phase and subclinical forms of illness to the debut of psychosis, mainly in aspects of clinical expression (such as more negative symptoms in men) and social functioning (such as premorbid and psychosocial functioning, worse in men). In addition, **these differences are related to age at onset of psychosis**. In this sense, men and women suffering a psychotic episode show features, characteristics and pecularities typical of their gender and their age at onset of psychosis.

Appropriate methods (algorithms and risk staging models) **and tools** are necessary to detect possible predictors in patients who could develop psychotic symptoms, taking into account all the factors mentioned above. These characteristics should be taken into account in exploring the different types of onset of the disease, its prevention and possible therapeutic improvements. This could encourage progress towards knowledge of **new strategies for early detection and psychosocial interventions adapted to the needs of patients** and focused on disturbed constructs, not on diagnosis.

REFERENCES

References

Abel, K.M., Drake, R., and Goldstein, J.M. (2010). Sex differences in schizophrenia. *International Review of Psychiatry*, 22(5), 417-428. doi: 10.3109/09540261.2010.515205

Addington, D., Addington, J., & Patten, S. (1996). Gender and affect in schizophrenia. *Canadian Journal of Psychiatry*, 41(5), 265-268.

Addington, J., & Addington, D. (2005). Patterns of premorbid functioning in first episode psychosis: relationship to 2-year outcome. *Acta Psychiatrica Scandinavica*, 112(1), 40-46. doi: 10.1111/j.1600-0447.2005.00511.x

Addington, J., Cornblatt, B.A., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., … Heinssen, R. (2011). At clinical high risk for psychosis: Outcome for nonconverters. *The American Journal of Psychiatry*, 168(8), 800-805. doi: 10.1176/appi.ajp.2011.10081191

Addington, J., Penn, D., Woods, S.W., Addington, D., & Perkins, D.O. (2008). Social functioning in individuals at clinical high risk for psychosis. *Schizophrenia Research*, 99(1-3), 119-124. doi: 10.1016/j.schres.2007.10.001

Addington, J., Stowkowy, J., & Weiser, M. (2015). Screening tools for clinical high risk for psychosis. *Early Intervention in Psychiatry*, 9(5), 345-356. doi: 10.1111/eip.12193

Addington, J., van Mastrigt, S., & Addington, D. (2003). Patterns of premorbid functioning in first-episode psychosis: initial presentation. *Schizophrenia Research*, 62(1-2), 23-30. doi: 10.1016/S0920-9964(02)00408-5

Alda, M., Ahrens, B., Lit, W., Dvorakova, M., Labelle, A., Zvolsky, P., & Jones, B. (1996). Age of onset in familial and sporadic schizophrenia. *Acta Psychiatrica Scandinavica*, 93(6), 447-450. doi: 10.1111/j.1600-0447.1996.tb10676.x

Aleman, A., Kahn, R.S., & Selten, J.P. (2003). Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Archives of General Psychiatry*, 60(6), 565-571. doi: 10.1001/archpsyc.60.6.565

Allen, D.N., Frantom, L.V., Strauss, G.P., & Kammen, D.P. (2005). Differential patterns of premorbid academic and social deterioration in patients with schizophrenia. *Schizophrenia Research*, 75(2-3), 389-397. doi: 10.1016/j.schres.2004.11.011

Allen, D.N., Kelley, M.E., Miyatake, R.K., Gurklis, J.A., & van Kammen, D.P. (2001). Confirmation of a two-factor model of premorbid adjustment in males with schizophrenia. *Schizophrenia Bulletin*, 27(1), 39-46. doi: 10/1093/oxfordjournals.schbul.a006858

Alvarez-Jimenez, M., Priede, A., Hetrick, S.E., Bendall, S., Killackey, E., Parker, A.G., … Gleeson, J.F. (2012). Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. *Schizophrenia Research*, 139(1-3), 116-128. doi: 10.1016/j.schres.2012.05.007

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders, 3rd ed*. Washington, DC: American Psychiatric Publishing.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*. Washington, DC: American Psychiatric Publishing.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision*. Washington, DC: American Psychiatric Publishing.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th ed*. Washington, DC: American Psychiatric Publishing.

Amminger, G.P., Harris, M.G., Conus, P., Lambert, M., Elkins, K.S., Yuen, H.P., & McGorry, P.D. (2006a). Treated incidence of first-episode psychosis in the catchment area of EPPIC between 1997 and 2000. *Acta Psychiatrica Scandinavica*, 114(5), 337-345.

Amminger, G.P., Henry, L.P., Harrigan, S.M., Harris, M.G., Alvarez-Jimenez, M., Herrman, H., … McGorry,P.D. (2011). Outcome in early-onset schizophrenia revisited: findings from the Early Psychosis Prevention and Intervention Centre long-term follow-up study. *Schizophrenia Research*, 131(1-3), 112-119. doi: 10.1016/j.schres.2011.06.009

Amminger, G.P., Leicester, S., Yung, A.R., Phillips, L.J., Berger, G.E., Francey, S.M., … McGorry, P.D. (2006b). Early-onset of symptoms predicts conversion to non-affective psychosis in ultra-high risk individuals. *Schizophrenia Research*, 84(1), 67-76. doi: 10.1016/j.schres.2006.02.018

Andia, A.M., Zisook, S., Heaton, R.K., Hesselink, J., Jernigan, T., Kuck, J., ... Braff, D.L. (1995). Gender differences in schizophrenia. *The Journal of Nervous and Mental Disease*, 183(8), 522-528. doi: 10.1097/00005053-199508000-00005

Andreasen, N.C., Flaum, M., & Arndt, S. (1992). The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Archives of General Psychiatry*, 49(8), 615-623. doi: 10.1001/archpsyc.1992.01820080023004

Angermeyer, M.C., & Kühn, L. (1988). Gender differences in age at onset of schizophrenia. An overview. *European Archives of Psychiatry and Neurological Sciences*, 237(6), 351-364.

Arranz, B., San, L., Ramírez, N., Dueñas, R.M., Perez, V., Salavert, J., … Alvarez, E. (2009). Clinical and serotonergic predictors of non-affective acute remitting psychosis in patients with a first-episode psychosis. *Acta Psychiatrica Scandinavica*, 119(1), 71-77. doi: 10.1111/j.1600-0447.2008.01253.x

Astrup, C., & Noreik, K. (1966). *Functional Psychoses, Diagnostic and Prognostic Models*. Springfield, Ill: Charles C Thomas, Publisher.

Ayesa-Arriola, R., Moríñigo, J.D., David, A.S., Pérez-Iglesias, R., Rodríguez-Sánchez, J.M., & Crespo-Facorro, B. (2014). Lack of insight 3 years after first-episode psychosis: an unchangeable illness trait determined from first presentation? *Schizophrenia Research*, 157(1-3), 271-277. doi: 10.1016/j.schres.2014.05.011

Ayesa-Arriola, R., Rodríguez-Sánchez, J.M., Pérez-Iglesias, R., González-Blanch, C., Pardo-García, G., Tabares-Seisdedos, R., … Crespo-Facorro, B. (2013). The relevance of cognitive, clinical and premorbid variables in predicting functional outcome for individuals with first-episode psychosis: a 3 year longitudinal study. *Psychiatry Research*, 209(3), 302-328. doi: 10.1016/j.psychres.2013.01.024

Bakst, S., Rabinowitz, J., & Bromet, E.J. (2010). Is poor premorbid functioning a risk factor for suicide attempts in first-admission psychosis? *Schizophrenia Research*, 116(2-3), 210-216. doi: 10.1016/j.schres.2009.11.005

Ballageer, T., Malla, A., Manchanda, R., Takhar, J., & Haricharan, R. (2005). Is adolescent-onset first-episode psychosis different from adult onset? *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(8), 782-789. doi: 10.1097/01.chi.0000164591.55942.ea

Barajas, A., Baños, I., Ochoa, S., Usall, J., Villalta-Gil, V., Dolz, M., … Grupo GENIPE. (2007). ¿Existen diferencias clínicas en el inicio del primer episodio psicótico entre hombres y mujeres? *Psiquiatría Biológica*, 14(4), 136-141. Retrieved from http://www.elsevier.es/es-revista-psiquiatria-biologica-46

Barajas, A., Baños, I., Ochoa, S., Usall, J., Huerta, E., Dolz, M., ... Grupo GENIPE. (2010). Gender differences in incipient psychosis. *The European Journal of Psychiatry*, 24(3), 176-194. doi: 10.4321/S0213-61632010000300006

Barajas, A., Ochoa, S., Baños, I., Dolz, M., Autonell, J., Sánchez, B., … Usall, J. (2013). Spanish validation of the Premorbid Adjustment Scale (PAS-S). *Comprehensive Psychiatry*, 54(2), 187-194. doi: 10.1016/j.comppsych.2012.07.007

Bayer, T.A., Falkai, P., & Maier, W. (1999). Genetic and non-genetic vulnerability factors in schizophrenia: the basis of the “two hit hypothesis”. *Journal of Psychiatric Research*, 33(6), 543-548.doi:10.1016/S0022-3956(99)00039-4

Bearden, C.E., Wu, K.N., Caplan, R., & Cannon, T.D. (2011). Thought disorder and communication deviance as predictors of outcome in youth at clinical high risk for psychosis. *Journal of the American Academy of Child and Adolescent Psychiatry*, 50(7), 669-680. doi: 10.1016/j.jaac.2011.03.021

Becker, H.E., Nieman, D.H., Dingemans, P.M., van de Fliert, J.R., De Haan, L., & Linszen, D.H. (2010). Verbal fluency as a possible predictor for psychosis. *European Psychiatry*, 25(2), 105-110. doi: 10.1016/j.eurpsy.2009.08.003

Bell, R.Q. (1992). Multiple-risk cohorts and segmenting risk as solutions to the problem of false positives in risk for the major psychoses. *Psychiatry*, 55(4), 370-381.

Bentall, R.P. (2003). *Madness Explained: Psychosis and Human Nature*. London, UK: Penguin Books Ltd.

Beratis, S., Gabriel, J., & Hoidas, S. (1994). Age at onset in subtypes of schizophrenic disorders. *Schizophrenia Bulletin*, 20(2), 287-296. doi: 10.1093/schbul/20.2.287

Birchwood, M., Fowler, D., & Jackson, C. (1998). Early intervention in psychosis. The critical period hypothesis. *British Journal of Psychiatry*, 172(33), 53-59.

Birchwood, M., McGorry, P., & Jackson, H. (1997). Early intervention in schizophrenia. *The British Journal of Psychiatry*, 170(1), 2-5. doi: 10.1192/bjp.170.1.2

Biswas, P., Malhotra, S., Malhotra, A., & Gupta, N. (2007). Comparative study of neurological soft signs in schizophrenia with onset in childhood, adolescence and adulthood. *Acta Psychiatrica Scandinavica*, 115(4), 295-303. doi: 10.1111/j.1600-0447.2006.00901.x

Bleuler, E. (1908). The prognosis of dementia praecox: the group of schizophrenias. In J. Cutting, & M. Shepherd (Eds.), *The clinical roots of the schizophrenia concept* (pp. 59-74). Cambridge, UK: University Press.

Bleuler, E. (1911). Dementia praecox oder Gruppe der Schizophrenien. In G. Aschaffenburg (Eds.). *Handbuch der Psychiatrie*, (pp. 1-420). Leipzig, Germany: Deuticke.

Bodatsch, M., Klosterkötter, J., Müller, R., & Ruhrmann, S. (2013). Basic disturbances of information processing in psychosis prediction. *Frontiers in Psychiatry*, 4, 93. doi: 10.3389/fpsyt.2013.00093

Bottlender, R., Strauß, A., & Möller, H.J. (2010). Social disability in schizophrenic, schizoaffective and affective disorders 15 years after first admission. *Schizophrenia Research*, 116(1), 9-15. doi: 10.1016/j.schres.2009.10.008.

Bozikas, V.P., Kosmidis, M.H., Peltekis, A., Giannakou, M., Nimatoudis, I., Karavatos, A.,… Garyfallos, G. (2010). Sex differences in neuropsychological functioning among schizophrenia patients. *Australian and New Zealand Journal of Psychiatry*, 44(4), 333-341. doi: 10.3109/00048670903489833

Bratlien, U., Øie, M., Lien, L., Agartz, I., Lie Romm, K., Vaskinn, A., … Melle, I. (2013). Social dysfunction in first-episode psychosis and relations to neurocognition, duration of untreated psychosis and clinical symptoms. *Psychiatry Research*, 207(1-2), 33-39. doi: 10.1016/j.psychres.2012.10.010

Breitborde, N.J.K., Srihari, V.H., & Woods, S.W. (2009). Review of the operational definition for first-episode psychosis. *Early Intervention in Psychiatry*, 3(4), 259-265. doi: 10.1111/j.1751-7893.2009.00148.x

Brewer, W.J., Wood, S.J., Phillips, L.J., Francey, S.M., Pantelis, Ch., Yung, A.R., …, McGorry, P.D. (2006). Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. *Schizophrenia Bulletin*, 32(3), 538-555. doi: 10.1093/schbul/sbj077

Brill, N., Reichenberg, A., Weiser, M., & Rabinowitz, J., (2008). Validity of the premorbid adjustment scale. Schizophrenia Bulletin, 34(5), 981-983. doi: 10.1093/schbul/sbm128

Cameron, D.E. (1938). Early schizophrenia. *American Journal of Psychiatry*, 95(3), 567-578. doi: 10.1176/ajp.95.3.567

Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., … Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of General Psychiatry*, 65(1), 28-37. doi: 10.1001/archgenpsychiatry.2007.3

Cannon-Spoor, H.E., Potkin, S.G., & Wyatt, R.J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin*, 8(3), 470-484. doi: 10.1093/schbul/8.3.470

Cardno, A.G., Marshall, E.J., Coid, B. Macdonald, A.M., Ribchester, T.R., Davies, N.J., … Murray, R.M. (1999). Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Archives General of Psychiatry*, 56(2), 162-168. doi:10.1001/archpsyc.56.2.162

Carpenter, W.T. (2009). Anticipating DSM-V: should psychosis risk become a diagnostic class?. Schizophrenia Bulletin, 35(5), 841-843. doi: 10.1093/schbul/sbp071

Carpenter, W.T., & van Os, J. (2011). Should attenuated psychosis syndrome be a DSM-5 diagnosis? *American J ournal of Psychiatry*, 168(5), 460-463. doi: 10.1176/appi.ajp.2011.10121816

Carr, V., Halpin, S., Lau, N., O'Brien, S., Beckmann, J., & Lewin,T. (2000). A risk factor screening and assessment protocol for schizophrenia and related psychosis. *Australian and New Zealand Journal of Psychiatry*, 34(s2), S170-S180.

Carrión, R.E., McLaughlin, D., Goldberg, T.E., Auther, A.M., Olsen, R.H., Olvet, D.M., ... Cornblatt, B.A. (2013). Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry*, 70(11), 1133-1142. doi: 10.1001/jamapsychiatry.2013.1909

Castagnini, A., & Berrios, G.E. (2009). Acute and transient psychotic disorders (ICD-10 F23): a review froma European perspective. *European Archives of Psychiatry and Clinical Neuroscience*, 259(8), 433-443. doi: 10.1007/s00406-009-0008-2

Castle, D.J., & Murray, R.M. (1993). The epidemiology of late-onset schizophrenia. *Schizophrenia Bulletin*, 19(4), 691-700. doi: 10.1093/schbul/19.4.691

Castle, D.J,. Sham, P., Murray, R.M. (1998). Differences in distribution of ages of onset in males and females with schizophrenia. *Schizophrenia Research*, 33(3), 179-183. doi: 10.1016/S0920-9964(98)00070-X

Castle, D.J., Wessely, S., & Murray, R.M. (1993). Sex and schizophrenia: effects of diagnostic stringency, and associations with premorbid variables. *The British Journal of Psychiatry*, 162(5), 658-664. doi: 10.1192/bjp.162.5.658

Cetingök, M., Chu, C.C., & Park, D.B. (1990). The effect of culture on the sex differences in schizophrenia. *The International Journal of Social Psychiatry*, 36(4), 272-279. doi: 10.1177/002076409003600405

Chang, W.C., Hui, C.L., Tang, J.Y., Wong, G.H., Lam, M.M., Chan, S.K., & Chen, E.Y. (2011). Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. *Schizophrenia Research*, 133(1-3), 22-28. doi: 10.1016/j.schres.2011.09.006.

Chang, W.C., Tang, J.Y., Hui, C.L., Wong, G.H., Chan, S.K., Lee, E.H., & Chen, E.Y. (2013). The relationship of early premorbid adjustment with negative symptoms and cognitive functions in first-episode schizophrenia: a prospective three-year follow-up study. *Psychiatry Research*, 209(3), 353-360. doi: 10.1016/j.psychres.2013.02.014

Chapman, J.P. (1966). The early symptoms of schizophrenia. *The Bristish Journal of Psychiatry*, 112(484), 225-251. doi: 10.1192/bjp.112.484.225

Chapman, L.J., Day, D., & Burstein, A. (1961). The process-reactive distinction and prognosis in schizophrenia. *The Journal of Nervous and Mental Disease*, 133, 383–391.

Chapman, L.J., & Chapman, J.P. (1987). The search for symptoms predictive of schizophrenia. *Schizophrenia Bulletin*, 13(3), 497-503. doi: 10.1093/schbul/13.3.497

Cocchi, A., Lora, A., Meneghelli, A., La Greca, E., Pisano, A., Cascio, M.T., … Desio Early Intervention Service Team. (2014). Sex differences in first episode psychosis and in people at ultra-high risk. *Psychiatry Research*, 215(2), 314-322. doi: 10.1016/j.psychres.2013.11.023

Collip, D., Myin-Germeys, I., & van Os, J. (2008). Does the concept of "Sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophrenia Bulletin*, 34(2), 220–225. doi: 10.1093/schbul/sbm163

Compton, M.T., Broussard, B., Ramsay, C.E., & Stewart, T. (2011). Pre-illness cannabis use and the early course of nonaffective psychotic disorders: associations with premorbid functioning, the prodrome, and mode of onset of psychosis. *Schizophrenia Research*, 126(1-3), 71-76. doi: 10.1016/j.schres.2010.10.005

Conrad, K. (1958). *Die beginnende Schizophrenie. Versuch einer Gestaltanalyse des Wahns*. Stuttgart, Germany: Thieme-Verlag.

Corcoran, C.M., Kimhy, D., Parrilla-Escobar, M.A., Cressman, V.L., Stanford, A.D., Thompson, J., … Malaspina, D. (2011). The relationship of social function to depressive and negative symptoms in individuals at clinical high risk for psychosis. *Psychological Medicine*, 41(2), 251-261. doi: 10.1017/S0033291710000802

Cornblatt, B.A., Carrión, R.E., Addington, J., Seidman, L., Walker, E.F., Cannon, T.D., … Lencz, T. (2012). Risk factors for psychosis: impaired social and role functioning. *Schizophrenia Bulletin*, 38(6), 1247-1257. doi: 10.1093/schbul/sbr136

Cornblatt, B.A., Lencz, T., & Kane, J.M. (2001). Treatment of the schizophrenia prodrome: is it presently ethical? *Schizophrenia Bulletin*, 51(1), 31-38. doi: 10.1016/S0920-9964(01)00236-5

Cornblatt, B.A., Lencz, T., Smith, C.W., Correll, C.U., Auther, A.M., & Nakayama, E. (2003). The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophrenia Bulletin*, 29(4), 633-651. doi: 10.1093/oxfordjournals.schbul.a007036

Corroon E.B. (2005). A Review of the Neurodevelopmental Hypothesis of Schizophrenia. *Trinity Student Medical Journal*, 6, 39(43). Retrieved from http://www.tcd.ie/tsmj/2005/3943.Schizo.pdf

Cotton, S.M., Lambert, M., Schimmelmann, B.G., Foley, D.L., Morley, K.I., McGorry, P.D., & Conus, P. (2009). Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. *Schizophrenia Research*, 114(1-3), 17-24. doi: 10.1016/j.schres.2009.07.002

Crespo-Facorro, B., de la Foz, V.O., Ayesa-Arriola, R., Pérez-Iglesias, R., Mata, I., Suarez-Pinilla, P., … Vázquez-Barquero, J.L. (2013). Prediction of acute clinical response following a first episode of non affective psychosis: results of a cohort of 375 patients from the Spanish PAFIP study. *Progress in Neuro-psychopharmacology and Biological Psychiatry*, 44(), 162-167. doi: 10.1016/j.pnpbp.2013.02.009

Cuesta, M.J., Peralta, V., Campos, M.S., & Garcia-Jalon, E. (2011). Can insight be predicted in first-episode psychosis patients? A longitudinal and hierarchical analysis of predictors in a drug-naïve sample. *Schizophrenia Research*, 130(1-3), 148-156. doi: 10.1016/j.schres.2011.04.032

Cuijpers, P. (2003). Examining the effects of prevention programs on the incidence of new cases of mental disorders: the lack of statistical power. *The American Journal of Psychiatry*, 160(8), 1385-1391. Retrieved from http://ajp.psychiatryonline.org/

Cullberg, J., Levander, S., Holmqvist, R., Mattsson, M., & Wieselgren, I.M. (2002). One-year outcome in first episode psychosis patients in the Swedish Parachute project. *Acta Psychiatrica Scandinavica*, 106(4), 276-285. doi: 10.1034/j.1600-0447.2002.02376.x

Daneault, J.G., Stip, E. & Refer-O-Scope Group. (2013). Genealogy of instruments for prodrome evaluation of psychosis. *Frontiers in Psychiatry*, 4, 25. doi: 10.3389/fpsyt.2013.00025

David, A.S. (2010). Why we need more debate on whether psychotic symptoms lie on a continuum with normality. *Psychological* Medicine, 40(12), 1935-1942. doi: 10.1017/S0033291710000188

Davidson, M., Reichenberg, A., Rabinowitz, J., Weiser, M., Kaplan, Z., Mark, M. (1999). Behavioural and intellectual markers for schizophrenia in apparently healthy male adolescents. *The American Journal of Psychiatry*, 156(9), 1328-1355. Retrieved from http://ajp.psychiatryonline.org/toc/ajp/156/9

De Bellis, M.D., Keshavan, M.S., Beers, S.R., Hall, J., Frustaci, K., Masalehdan, A., … Boring, A.M. (2001). Sex differences in brain maturation during childhood and adolescence. *Cerebral Cortex*, 11(6), 552-557. doi: 10.1093/cercor/11.6.552

De Herdt, A., Wampers, M., Vancampfort, D., De Hert, M., Vanhees, L., Demunter, H., ... Probst, M. (2013). Neurocognition in clinical high risk young adults who did or did not convert to a first schizophrenic psychosis: a meta-analysis. *Schizophrenia Research*, 149(1-3), 48-55. doi: 10.1016/j.schres.2013.06.017

De Koning, M.B, Bloemen, O.J., van Amelsvoort, T.A., Becker, H.E., Nieman, D.H., van der Gaag, M., & Linszen, D.H. (2009). Early intervention in patients at ultra high risk of psychosis: benefits and risks. *Acta Psychiatrica Scandinavica*, 119(6), 426-442. doi: 10.1111/j.1600-0447.2009.01372.x

DeLisi, L.E. (1992). The significance of age of onset for schizophrenia. Schizophrenia Bulletin, 18(2), 209-215. doi: 10.1093/schbul/18.2.209

Demjaha, A., Valmaggia, L., Stahl, D., Byrne, M., & McGuiere, P. (2012). Disorganization/cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. *Schizophrenia Bulletin*, 38(2), 351-359. doi: 10.1093/schbul/sbq088

Dragt, S., Nieman, D.H., Veltman, D., Becker, H.E., van de Fliert, R., de Haan, L., & Linszen, .H. (2011). Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk. *Schizophrenia Research*, 125(1), 69-76. doi: 10.1016/j.schres.2010.09.007

Eaton, W.W., Badawi, M., & Melton, B. (1995). Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. *The American Journal of Psychiatry*, 152(7), 967-972.

Eaton, W.W., Thara, R., Federman, B., Melton, B., & Liang, K.Y. (1995). Structure and course of positive and negative symptoms in schizophrenia. *Archives of General Psychiatry*, 52(2), 127-134. doi: 10.1001/archpsyc.1995.03950140045005

Edwards, J., & McGorry, P.D. (2002). *Implementing early intervention in psychosis: A guide to establishing early psychosis services*. London: Martin Dunitz.

Eggers, C. (2011). *Schizophrenie des Kindes- und Jugendalters*. Stuttgart, Germany: MWV Medizinisch Wissenschaftliche Verlagsgesellschaft.

Esterberg, M.L., Trotman, H.D., Holtzman, C., Compton, M.T., & Walker, E.F. (2010). The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: a meta-analysis. *Schizophrenia Research*, 120(1-3), 121-130. doi: 10.1016/j.schres.2010.01.011

Fatemi, S.H. (2005). Prenatal viral infection, brain development and schizophrenia. In S.H. Fatemi (Eds.), *Neuropsychiatric Disorders and Infection*. London, UK: Taylor and Francis.

Fava, G.A., & Kellner, R. (1991). Prodromal symptoms in affective disorders. *American Journal of Psychiatry*, 148(7), 823-830.

Fava, G.A., & Kellner, R. (1993). Staging: a neglected dimension in psychiatric classification. *Acta Psychiatrica Scandinavica*, 87(4), 225-230. doi: 10.1111/j.1600-0447.1993.tb03362.x

Feinberg, I. (1983). Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, 17(4), 319-334. doi: 10.1016/0022-3956(82)90038-3

Foerster, A., Lewis, S., Owen, M., & Murray, R. (1991). Premorbid adjustment and personality in psychosis. Effects of sex and diagnosis. *The British Journal of Psychiatry*, 158(2), 171-176. doi: 10.1192/bjp.158.2.171

Folnegović, Z., & Folnegović-Smalc, V. (1994). Schizophrenia in Croatia: age of onset differences between males and females. *Schizophrenia Research*, 14(1), 83-91. doi: 10.1016/0920-9964(94)90012-4

Fresan, A., Apiquián, R., Ulloa, R.E., & Nicolini, H. (2007). Reliability study of the translation into Spanish of the PRIME Screen Questionnaire for Prodromic Symtoms. *Actas Españolas de Psiquiatría,* 5(6), 368-371.

Fusar-Poli, P., Bechdolf, A., Taylor, M.J., Bonoldi, I., Carpenter, W.T., Yung, A.R., & McGuire, P. (2013a). At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophrenia Bulletin*, 39(4), 923–932. doi: 10.1093/schbul/sbs060

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, D., Kempton, M.J., Valmaggia, L., … McGuire, P. (2012a). Predicting psychosis: a meta-analysis of transition outcomes in individuals at high clinical risk. *Archives General of Psychiatry*, 69(3), 220-229. doi: 10.1001/archgenpsychiatry.2011.1472

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., … Yung, A. (2013b). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*, 70(1), 107-120. doi: 10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., Carpenter, W.T., Woods, S.W., & McGlashan, T.H. (2014a). Attenuated Psychosis Syndrome: Ready for DSM-5.1? *Annual Review Clinical Psychology*, 10(1), 155-192. doi: 10.1146/annurev-clinpsy-032813-153645

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A.R., Howes, O., ... Borgwardt, S. (2012b). Cognitive functioning in prodromal psychosis: a meta-analysis. *Archives of General Psychiatry*, 69(6), 562-571. doi: 10.1001/archgenpsychiatry.2011.1592

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., & McGuire, P.K. (2014b). Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophrenia Bulletin*, 40(1), 120-131. doi: 10.1093/schbul/sbs136

Fusar-Poli, P., & van Os, J. (2013). Lost in transition: setting psychosis threshold in prodromal research. *Acta Psychiatrica Scandinavica*, 127(3), 248-252. doi: 10.1111/acps.12028

Galderisi, S., Bucci, P., Üçok, A., & Peuskens, J. (2012). No gender differences in social outcome in patients suffering from schizophrenia. *European Psychiatry*, 27(6), 406-408.

Gangadhar, B.N., Panner Selvan, C., Subbakrishna, D.K., & Janakiramaiah, N. (2002). Age-at-onset and schizophrenia: reversed gender effect. *Acta Psychiatrica Scandinavica*, 105(4), 317-319. doi: 10.1034/j.1600-0447.2002.1153.x

Gayer-Anderson,C., & Morgan, C. (2013). Social networks, support and early psychosis: a systematic review. *Epidemiology and Psychiatric Sciences*, 22(2), 131-146. doi: 10.1017/S2045796012000406

Gee, D.G., & Cannon, T.D. (2011). Prediction of conversion to psychosis: review and future directions. *Revista brasileira de psiquiatria*, 33(Suppl. 2), S129-S142.

Gittelman-Klein, R., & Klein, D.F. (1969). Premorbid asocial adjustment and prognosis in schizophrenia. *Journal of Psychiatric Research*, 7(1), 35-53. doi: 10.1016/0022-3956(69)90010-7

Goldberg, T.E., Gold, J.M., Torrey, E.F. & Weinberger, D.R. (1995). Lack of sex differences in the neuropsychological performance of patients with schizophrenia. *The American Journal of Psychiatry*, 152(6), 883-888. doi: 10.1176/ajp.152.6.883

González-Blanch, C., Álvarez-Jiménez, M., Ayesa-Arriola, R., Martínez-García, O., Pardo-García, G., Balanzá-Martínez, V., … Crespo-Facorro, B. (2014). Differential associations of cognitive insight components with pretreatment characteristics in first-episode psychosis. *Psychiatry Research*, 215(2), 308-313. doi: 10.1016/j.psychres.2013.12.003

Gordon, R. (1987). An operational classification of disease prevention. In J.A. Steinberg, & M.M. Silverman (Eds.), *Prevention of Mental Disorders* (pp. 20-26). Rockville, MD: Department of Health and Human Services.

Griesinger, W. (1969). Prodrome und Vorpostensyndrome schizophrener Erkrankungen. In G. Huber (Eds.), *Schizophrenie und Zyklothymie* (pp. 177-187). Stuttgart, Germany: Thieme.

Gross, G. (1989). The 'basic' symptoms of schizophrenia. *The British Journal of Psychiatry*, 155 (Suppl 7), S21-S25.

Gross, G., Huber, G., Klosterkötter, J., & Linz, M. (1987). *Boon Scale for the Assessment of Basic Symptoms – BSABS*. Berlin: Springer.

Grossman, L.S., Harrow, M., Rosen, C., Faull, R., & Strauss, G.P. (2008). Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery. *Comprehensive Psychiatry*, 49(6), 523-529. doi: 10.1016/j.comppsych.2008.03.004

Gupta, S., Rajaprabhakaran, R., Arndt, S., Flaum, M., & Andreasen, N.C. (1995). Premorbid adjustment as a predictor of phenomenological and neurobiological indices in schizophrenia. *Schizophrenia Research*, 16(3), 189-197. doi: 10.1016/0920-9964(94)00073-H

Gur, R.E., Petty, R.G., Turetsky, B.I. & Gur, R.C. (1996). Schizophrenia throughout life: sex differences in severity and profile of symptoms. *Schizophrenia Research*, 21(1), 1-12. doi: 10.1016/0920-9964(96)00023-0

Gureje, O., Aberibigde, Y.A., Olley, O., & Bamidele, R.W. (1994). Premorbid functioning in schizophrenia: a controlled study of Nigerian patients. *Comprehensive Psychiatry*, 35(6), 437-440. doi: 10.1016/0010-440X(94)90226-7

Häfner, H., an der Heiden, W., Behrens, S., Gattaz, W.F., Hambrecht, M., Löffler, W., … Stein, A. (1998a). Causes and consequences of the gender difference in age at onset of schizophrenia. *Schizophrenia Bulletin*, 24(1), 99-113. doi: 10.1093/oxfordjournals.schbul.a033317

Häfner, H., Hambrecht, M., Loffler, W., Munk-Jorgensen, P., & Riecher-Rossler, A. (1998b). Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. *Psychological Medicine*, 28(2), 351-365. doi: 10.1017/S0033291797006399

Häfner, H., Loffler, W., Maurer, K., Hambrecht, M., an der Heiden, W. (1999). Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatrica Scandinavica*, 100(2), 105-118. doi: 10.1111/j.1600-0447.1999.tb10831.x

Häfner, H., & Maurer, K. The prodromal phase of psychosis. (2001). In T. Miller, S.A. Mednick, Th.H. McGlashan, J. Libiger, & J.O. Johannessen (Eds.), *Early Intervention in Psychotic Disorders* (pp. 71-100). Dordrecht, Netherlands: Kluwer Academic.

Häfner, H., Maurer, K., & an der Heiden, W. (2013). ABC Schizophrenia study: an overview of results since 1996. *Social Psychiatry and Psychiatric Epidemiology*, 48(7), 1021-1031. doi: 10.1007/s00127-013-0700-4

Häfner, H., Maurer, K., Löffler, W., an der Heiden, W., Munk-Jorgensen, P., Hambrecht, M, & Riecher-Rössler, A. (1998c). The ABC schizophrenia study: a preliminary overview of the results. *Social Psychiatry and Psychiatric Epidemiology*, 33(8), 380-386. doi: 10.1007/s001270050069

Häfner, H., Maurer, K., Löffler, W., Bustamante, S., an der Heiden, W., Riecher-Rössler, A., & Nowotny, B. (1995). Onset and early course of schizophrenia. In H. Häfner, & H. Gattaz (Eds.), *Search for the Causes of Schizophrenia*, vol III (pp. 43-66). Berlin, Germany: Springer-Verlag.

Häfner, H., Maurer, K., Trendler, G., van der Heiden, W. & Schmidt, M. (2005). The early course of schizophrenia and depression. *European Archives of Psychiatry and Clinical Neuroscience*, 255(3), 167-173. doi: 10.1007/s00406-005-0584-8

Häfner, H., Riecher-Rössler, A., an der Heiden, W., Maurer, K., Fätkenheuer, B., & Löffler, W. (1993). Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. *Psychological Medicine,* 23(4), 925-940. doi: 10.1017/S0033291700026398

Häfner, H., Riecher-Rössler, A., Hambrecht, M., Maurer, K., Meissner, S., Schmidtke, A., … van der Heiden, W. (1992). IRAOS: an instrument for the retrospective assessment of the onset of schizophrenia. *Schizophrenia Research*, 6(3), 209-223. doi: 10.1016/0920-9964(92)90004-O

Häfner, H., Riecher, A., Maurer, K., Löffler, W., Munk-Jørgensen, P., & Strömgren, E. (1989). How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. *Psychological Medicine*, 19(4), 903-918. doi: 10.1017/S0033291700005626

Hambrecht, M., & Häfner, H, (1993), 'Trema, Apophänie, Apokalypse' – Ist Conrads Phasenmodell empirisch begründbar? *Fortschritte der Neurologie Psychiatrie*, 61(12), 418-423. doi: 10.1055/s-2007-999113

Hanssen, M., Bak, M., Bijl, R., Vollebergh, W., & van Os, J. (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *Brisith Journal of Clinical Psychology*, 44(2), 181-191. doi: 10.1348/014466505X29611

Harrigan, S.M., McGorry, P.D., & Krstev, H. (2003). Does treatment delay in first-episode psychosis really matter? *Psychological Medicine*, 33(1), 97-110. doi: 10.1017/S003329170200675X

Harris, J.G. (1975). An abbreviated form of the Phillips Rating Scale of Premorbid Adjustment in schizophrenia. *Journal of Abnormal Psychology*, 84(2), 129-137. doi: 10.1037/h0076983

Haas, G.L., & Sweeney, J.A. (1992). Premorbid and onset features of first-episode schizophrenia. *Schizophrenia Bulletin*, 18(3), 373-386. doi: 10.1093/schbul/18.3.373

Hawkins, K.A., Keefe, R.S.E., Christensen, B.K., Addington, J., Woods, S.W., Callahan, J., … McGlashan, T.H. (2008). Neuropsychological course in the prodrome and first episode of psychosis: findings from the PRIME North America Double Blind Treatment Study. *Schizophrenia Research*, 105(1-3), 1-9. doi: 10.1016/j.schres.2008.07.008

Hayashi, N., Igarashi, Y., Yamashina, M., & Suda, K. (2002). Is there a gender difference in a factorial structure of the positive and negative syndrome scale? A test by structural equation modeling. *Psychopathology*, 35(1), 28-35. doi: 10.1159/000056213

Heinimaa, M., Salokangas, R.K., Ristkari, T., Plathin, M., Huttunen, J., Ilonen, T., … McGlashan, T.H. (2003). PROD-screen--a screen for prodromal symptoms of psychosis. *International journal of methods in psychiatric research*, 12(2), 92-104. doi: 10.1002/mpr.146

Howes, O.D., McDonald, C., Cannon, M., Arseneault, L., Boydell, J., & Murray, R.M. (2004). Pathways to schizophrenia: the impact of environmental factors. *International Journal of Neuropsychopharmacology*, 7(1), S7-S13. doi: 10.1017/S1461145704004122

Huber, G. (1966). Reine Defektsyndrome und Basisstadien endogener Psychosen. *Fortschritte der Neurologie-Psychiatrie*, 34, 409-426.

Insel, T.R. (2007). The arrival of preemptive psychiatry. *Early Intervention in Psychiatry*, 1(1), 5-6. doi: 10.1111/j.1751-7893.2007.00017.x

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., … Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry*, 167(7), 748-751. doi: 10.1176/appi.ajp.2010.09091379

Ising, H.K., Veling, W., Loewy, R.L., Rietveld, M.W., Rietdijk, J., Dragt, S., … van der Gaag, M. (2012). The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophrenia Bulletin*, 38(6), 1288-1296. doi: 10.1093/schbul/sbs068

Jablensky, A. (1995). Schizophrenia: the epidemiological horizon. In S.R. Hirsch & D.R. Weinberger (Eds.), *Schizophrenia* (pp. 206-252). Oxford, UK: Blackwell Science.

Jablensky, A., & Cole, S. (1997). Is the earlier age at onset of schizophrenia in males a confounded finding? Results from a cross-cultural investigation. *The British Journal of Psychiatry*, 170(3), 234-240. doi: 10.1192/bjp.170.3.234

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J.E., …, Bertelsen A. (1992). Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Medicine. Monograph Supplement*, 20, 1-97. doi 10.1017/S0264180100000904

Jacobs, E., Kline, E., & Schiffman, J. (2012). Defining treatment as usual for attenuated psychosis syndrome: a survey of community practitioners. Psychiatric Services, 63(12), 1252-1256. doi: 10.1176/appi.ps.201200045

Jané-Llopis, E., & Anderson, P. (2006). *Mental health promotion and mental disorder prevention across European Member States: a collection of country stories*. Luxembourg: European Communities.

Jeppesen, P., Petersen, L., Thorup, A., Abel, M.B., Øhlenschlaeger, J., Christensen, T.Ø., … Nordentoft. M. (2008). The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. *Psychological Medicine*, 38(8), 1157-1166. doi: 10.1017/S0033291708003449.

Joa, I., Johannessen, J.O., Langeveld, J., Friis, S., Melle, I., Opjordsmoen, S., … Larsen, T.K. (2009). Baseline profiles of adolescent vs. adult-onset first-episode psychosis in an early detection program. *Acta Psychiatrica Scandinavica*, 119(6), 494-500. doi: 10.1111/j.1600-0447.2008.01338.x

Jørgensen, P., Nordentoft, M., Abel, M.B., Gouliaev, G., Jeppesen, P., & Kassow, P. (2000). Early detection and assertive community treatment of young psychotics: the Opus Study Rationale and design of the trial. *Social Psychiatry & Psychiatry Epidemiology*, 35(7), 283-287.

Kalus, P., Buri, C., Slotboom, J., Gralla, J., Remonda, L., Dierks, T., … Kiefer, C. (2004). Volumetry and diffusion tensor imaging of hippocampal suregions in schizophrenia. Neuroreport, 15(5), 867-871. doi: 10.1097/00001756-200404090-00027

Kantor, R.E., & Herron, W.G. (1965). Perceptual learning in the process-reactive schizophrenic. *Journal of Projective Techniques & Personality Assessment*, 29(1), 58-70. doi: 10.1080/0091651X.1965.10120177

Kantor, R., Wallner, J., & Winder, C. (1953). Process and reactive schizophrenia. *Journal of Consulting Psychology*, 17(3), 157-162. doi: 10.1037/h0059210

Kaymaz, N., & van Os, J. (2010). Extended psychosis phenotype—yes: single continuum—unlikely. *Psychological Medicine*, 40(12), 1963-1966. doi: 10.1017/S0033291710000358

Kendall, P.C., & Kessler, R.C. (2002). The impact of childhood psychopathology interventions on subsequent substance abuse: policy implications, comments, and recommendations. *Journal of Consulting and Clinical Psychology*, 70(6), 1303-1306. doi: 10.1037/0022-006X.70.6.1303

Keshavan, M.S. (1999). Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. *Journal of Psychiatric Research*, 33(6), 513–521. doi:10.1016/S0022-3956(99)00033-3

Keshavan, M.S., & Amirsadri, A. (2007). Early intervention in schizophrenia: current and future perspectives. *Current Psychiatry Reports*, 9(4), 325-328.

Keshavan, M.S., & Schooler, N.R. (1992). First-episode studies in schizophrenia: criteria and characterization. *Schizophrenia Bulletin*, 18(3), 491-513. doi: 10.1093/schbul/18.3.491

Kessler, R.C., Amminger, G.P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustün, T.B. (2007). Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry*, 20(4), 359-364. doi: 10.1097/YCO.0b013e32816ebc8c

Kirch, D.G., Keith, S.J., & Matthews, S.M. (1992). Research on first-episode psychosis: report on a National Institute of Mental Health Workshop. *Schizophrenia Bulletin*, 18(2), 179-184. doi: 10.1093/schbul/18.2.179

Kline, E., & Schiffman, J. (2014). Psychosis risk screening: a systematic review. *Schizophrenia Research*, 158(1-3) 11-18. doi: 10.1016/j.schres.2014.06.036

Kline, E., Wilson, C., Ereshefsky, S., Denenny, D., Thompson, E., Pitts, S.C., … Schiffman, J. (2012). Psychosis risk screening in youth: a validation study of three self-report measures of attenuated psychosis symptoms. *Schizophrenia Research*, 141(1), 72-77. doi: 10.1016/j.schres.2012.07.022

Klosterkötter, J., Ebel, H., Schultze-Lutter, F., & Steinmeyer, E.M. (1996). Diagnostic validity of basic symptoms. *European Archives of Psychiatry and Clinical Neuroscience*, 246(3), 147-154. doi: 10.1007/BF02189116

Klosterkötter, J., Hellmich, M., Steinmeyer, E.M., & Schultze-Lutter, F. (2001). Diagnosing schizophrenia in the initial prodromal phase. Archives of General Psychiatry, 58(2), 158-164. doi: 10.1001/archpsyc.58.2.158

Klosterkötter, J., Ruhrmann, S., Schultze-Lutter, F., Salokangas, R.K., Linszen, D., Birchwood, M., … von Reventlow, H. (2005). The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. *World Psychiatry*, 4(3), 161-167.

Klosterkötter, J., Schultze-Lutter, F., Bechdolf, A., & Ruhrmann, S. (2011). Prediction and prevention of schizophrenia: what has been achieved and where to go next? *World Psychiatry*, 10(3), 165-174. doi: 10.1002/j.2051-5545.2011.tb00044.x

Kobayashi, H., Nemoto, T., Koshikawa, H., Osono, Y., Yamazawa, R., Murakami, M., … Mizuno, M. (2008). A self-reported instrument for prodromal symptoms of psychosis: testing the clinical validity of the PRIME Screen-Revised (PS-R) in a Japanese population. *Schizophrenia Research*, 106(2-3), 356-362. doi: 10.1016/j.schres.2008.08.018

Köhn, D., Pukrop, R., Niedersteberg, A., Schultze-Lutter, F., Ruhrmann, S., Bechdolf, A., ... Klosterkötter, J. (2004). Pathways to care: help-seeking behavior in first-episode psychosis. Fortschritte der Neurologie-Psychiatrie, 72(11), 635-642. doi: 10.1055/s-2004-818418

Kokes, R.F., Strauss, J.S., & Klorman, R. (1977). Premorbid adjustment in schizophrenia. Part II. Measuring premorbid adjustment: the instruments and their development. *Schizophrenia Bulletin*, 3(2), 186-213. doi: 10.1093/schbul/3.2.186

Køster, A., & Lajer, M., Lindhardt, A., & Rosenbaum, B. (2008). Gender differences in first episode psychosis. *Social Psychiatry and Psychiatric Epidemiology*, 43(12), 940-946. doi: 10.1007/s00127-008-0384-3

Koutsouleris, N., Davatzikos, C., Bottlender, R., Patschurek-Kliche, K., Scheuerecker, J., Decker, P., ... Meisenzahl, E.M. (2012). Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. *Schizophrenia Bulletin*, 38(6), 1200-1215. doi: 10.1093/schbul/sbr037

Kraepelin, E. (1983). *Psychiatrie*. Ein kurzes Lehrbuch. Leipzig, Germany: Ambrosius Abel.

Krauss, H., Marwinski, K., Held, T., Rietschel, M., & Freyberger, H.J. (1998). Reliability and validity of the premorbid adjustment scale (PAS) in a German sample of schizophreniac and schizoaffective patients. *European Archives of Psychiatry and Clinical Neuroscience*, 248(6), 277-281. doi: 10.1007/s004060050050

Kretschmer, E. (1925). *Psysique and Character: An Investigation of the Nature of Constitution and of the Theory of Temperament*. London, UK: Kegan Paul, Trench, Trubner.

Kulkarni, J., de Castella, A., Fitzgerald, P.B., Gurvich, C.T., Bailey, M., Bartholomeusz, C., & Burger, H. (2008). Estrogen in severe mental illness: a potential new treatment approach. *Archives of General Psychiatry*, 65(8), 955-960. doi: 10.1001/archpsyc.65.8.955

Large, M., Sharma, S., Compton, M.T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of General Psychiatry*, 68(6), 555-561. doi: 10.1001/archgenpsychiatry.2011.5

Larsen, T.K., Friis, S., Haahr, U., Johannessen, J.O., Melle, I., Opjordsmoen, S., … McGlashan, T.H. (2004). Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. *The Bristish Journal of Psychiatry*, 185(2), 108-115. doi: 10.1192/bjp.185.2.108

Larsen, T.K., McGlashan, T.H., & Moe, L.C. (1996). First-episode schizophrenia: I. Early course parameters. *Schizophrenia Bulletin*, 22(2), 241-256. doi: 10.1093/schbul/22.2.241

Lee, T.Y., Shin, Y.S., Shin, N.Y., Kim, S.N., Jang, J.H., Kang, D.H., & Kwon, J.S. (2014). Neurocognitive function as a possible marker for remission from clinical high risk for psychosis. *Schizophrenia Research*, 153(1-3), 48-53. doi: 10.1016/j.schres.2014.01.018

Leeson, V.C., Harrison, I., Ron, M.A., Barnes, T.R., & Joyce, E.M. (2012). The effect of cannabis use and cognitive reserve on age at onset and psychosis outcomes in first-episode schizophrenia. *Schizophrenia Bulletin*, 38(4), 873-880. doi: 10.1093/schbul/sbq153

Lemos, S., Vallina, O., Fernández, P., Ortega, J.A., García, P., Gutiérrez, A., … Miller T. (2006). Predictive validity of the Scale of Prodromal Symptoms (SOPS). *Actas Españolas de Psiquiatria*, 34(4), 216-223.

Lemos-Giráldez, S., Vallina-Fernández, O., Fernández-Iglesias, P., Vallejo-Seco, G., Fonseca-Pedrero, E., Paíno-Piñeiro, M., ... Ortega-Ferrández, J.A. (2009). Symptomatic and functional outcome in youth at ultrahigh risk for psychosis: a longitudinal study. *Schizophrenia Research*, 115(2-3), 121-129. doi: 10.1016/j.schres.2009.09.011

Leung, A. & Chue, P. (2000). Sex differences in schizophrenia, a review of the literature. *Acta Psychiatrica Scandinavica*, *Supplement*, 101(401), 3-38.

Levy, E., Pawliuk, N., Joober, R., Abadi, S., & Malla, A. (2012). Medication-adherent first-episode psychosis patients also relapse: why? *Canadian Journal of Psychiatry*, 57(2), 78-84.

Lewine, R.R.J., Walker, E.F., Shurett, R., Caudle, J., & Haden, C. (1996). Sex differences in neuropsychological functioning among schizophrenic patients. *The American Journal of Psychiatry*, 153(9), 1178-1184. doi: 10.1176/ajp.153.9.1178

Lieberman, J.A., Perkins, D., Belger, A., Chakos, M., Jarskog, F., Boteva, K., & Gilmore, J. (2001). The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biological Psychiatry*, 50 (11), 884-897. doi: 10.1016/S0006-3223(01)01303-8

Lindström, E. & Von Knorring, L. (1994). Symptoms in schizophrenic syndromes in relation to age, sex, duration of illness and number of previous hospitalizations. *Acta Psychiatrica Scandinavica*, 89(4), 274-278. doi: 10.1111/j.1600-0447.1994.tb01513.x

Linszen, D., Dingemans, P., & Lenior, M. (2001). Early intervention and a five-year follow-up in young adults with a short duration of untreated psychosis: ethical implications. *Schizophrenia Research*, 51(1), 55-61. doi:10.1016/S0920-9964(01)00239-0

Loewy, R.L., Bearden, C.E., Johnson, J.K., Raine, A., & Cannon, T,D. (2005). The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. *Schizophrenia Research*, 79(1), 117-125. doi: 10.1016/j.schres.2005.03.007

Loewy, R.L., Pearson, R., Vinogradov, S., Bearden, C.E., & Cannon, T.D. (2011). Psychosis risk screening with the Prodromal Questionnaire--brief version (PQ-B). *Schizophrenia Research*, 129(1), 42-46. doi: 10.1016/j.schres.2011.03.029

Lucas, S., Redoblado-Hodge, M.A., Shores, A., Brennan, J., & Harris, A. (2008). Predictors of outcome three years after diagnosis of first episode psychosis. *Psychiatry Research*, 161(1), 11-18. doi: 10.1016/j.psychres.2007.10.004

MacBeth, A., & Gumley, A. (2008). Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. *Acta Psychiatrica Scandinavica*, 117(2), 85-99. doi: 10.1111/j.1600-0447.2007.01134.x

MacBeth, A., Gumley, A., Schwannauer, M., Carcione, A., Fisher, R., McLeod, H.J., & Dimaggio, G. (2014). Metacognition, symptoms and premorbid functioning in a first episode psychosis sample. *Comprenhensive Psychiatry*, 55(2), 268-273. doi: 10.1016/j.comppsych.2013.08.027

MacBeth, A., Gumley, A., Schwannauer, M., & Fisher, R. (2013). Service engagement in first episode psychosis: clinical and premorbid correlates. *The Journal Nervous of Mental Disease*, 201(5), 359-364. doi: 10.1097/NMD.0b013e31828e0e19

MacBeth, A., Gumley, A., Schwannauer, M., & Fisher, R. (2015). Self-reported quality of life in a Scottish first-episode psychosis cohort: associations with symptomatology and premorbid adjustment. *Early Intervention in Psychiatry*, 9(1), 53-60. doi: 10.1111/eip.12087

Mahmoodi-Gharaei, J., Basirnia, A., Abedi, N., Shadloo, B., Jafari, S., Salesian, N., … Sharifi, V. (2010). Association of premorbid adjustment with symptom profile and quality of life in first episode psychosis in a tertiary hospital in tehran, iran. *Iranian Journal of Psychiatry*, 5(1), 23-27.

Mäki, P., Veijola, J., Jones, P.B., Murray, G.K., Koponen, H., Tienari, P., … Isohanni, M. (2005). Predictors of schizophrenia – a review. *British Medical Bulletin*, 73-74(1), 1-15. doi: 10.1093/bmb/ldh046

Malla, A., Norman, R., McLean, T., Scholten, D., & Townsend, L. (2003). A Canadian programme for early intervention in non-affective psychotic disorders. *Australian & New Zealand Journal of Psychiatry*, 37(4), 407-413. doi: 10.1046/j.1440-1614.2003.01194.x

Maric, N., Krabbendam, L., Vollebergh, W., De Graaf, R., & van Os, J. (2003). Sex differences in symptoms of psychosis in a nonselected, general population sample. *Schizophrenia Research*, 63(1-2), 89-95. doi: 10.1016/S0920-9964(02)00380-8

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association betwwen duration of untreated psychosis and outcome in cohorts of first-episode patients: A systematic review. *Archives of General Psychiatry*, 62(9), 975-983. doi:10.1001/archpsyc.62.9.975.

Mason, O., Startup, M., Halpin, S., Schall, U., Conrad, & A., Carr, V. (2004). Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. *Schizophrenia Research*, 71(2-3), 227-237. doi: 10.1016/j.schres.2004.04.006

Mass R. (2000). Characteristic subjective experiences of schizophrenia. *Schizophrenia Bulletin*, 26(4), 921-931. doi: 10.1093/oxfordjournals.schbul.a033506

Mass, R., Haasen, C., & Borgart, E.J. (2005). Abnormal subjective experiences of schizophrenia: evaluation of the Eppendorf Schizophrenia Inventory. *Psychiatry Research*, 135(2), 91-101. doi: 10.1016/j.psychres.2004.08.011

Maurer, K., Hörrmann, F., Trendler, G., Schmidt, M., & Häfner H. (2006). Früherkennung des Psychoserisikos mit dem Early Recognition Inventory (ERIraos) – Beschreibung des Verfahrens und erste Ergebnisse zur Reliabilität und Validität der Checkliste. *Nervenheilkunde*, 25(1), 11-16.

Mayer-Gross, W. (1932). Die Klinik. In O. Bumke (Eds.). *Handbuch der Geisterkrankheiten*, *Vol.9:Die Schizophrenie*, (pp. 293-578). Berlin, Germany: Springer.

McClellan, J., Breiger, D., McCurry, C., & Hlastala, S.A. (2003). Premorbid functioning in early-onset psychotic disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(6), 666-672. doi: 10.1097/01.CHI.0000046844.56865.6B

McGlashan, T.H. (1998). Early detection and intervention of schizophrenia: rationale and research. *The British Journal of Psychiatry*, 172(33), 3-6.

McGlashan, T.H. (2008). Premorbid Adjustment, Onset Types, and Prognostic Scaling: Still Informative? *Schizophrenia Bulletin*, 34(5), 801-805. doi: 10.1093/schbul/sbn073

McGlashan, T.H., & Hoffman, R.E. (2000). Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Archives of General Psychiatry*, 57(7), 637-648. doi: 10.1001/archpsyc.57.7.637

McGrath, J.J. (2006). Variations in the incidence of schizophrenia: data versus dogma. *Schizophrenia Bulletin*, 32(1), 195-197. doi: 10.1093/schbul/sbi052

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, 30(1), 67-76. doi: 10.1093/epirev/mxn001

McGorry, P.D., Hickie, I.B., Yung, A.R., Pantelis, C., & Jackson H.J. (2006). Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Australian and New Zealand Journal of Psychiatry*, 40(8), 616-622. doi: 10.1080/j.1440-1614.2006.01860.x

McGorry, P.D., Nelson, B., Goldstone, S., & Yung, A.R. (2010). Clinical staging: a heuristic and practical strategy for new research and better health and social outcomes for psychotic and related mood disorders. *Canadian Journal of Psychiatry*, 55(8), 486-497.

McGorry, P.D., Purcell, R., & Hickie, I.B. (2007). Clinical staging: a heuristic model for psychiatry and youth mental health. *Medical Journal of Australia*, 187(7), S40-S42.

McGorry, R.D., & Singh, B.S. (1995). Schizophrenia: risk and possibility of prevention. In B. Raphael, & G.D. Burrows (Eds.), *Handbook of Preventive Psychiatry* (pp. 492-514). Amsterdam, Netherlands: Elsevier.

Meehl, P.E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist*, 17(12), 827-838. doi: 10.1037/h0041029

Menezes, N.M., & Milovan, E. (2000). First-episode psychosis: a comparative review of diagnostic evolution and predictive variables in adolescents versus adults. *Canadian Journal of Psychiatry*, 45(8), 710-716.

Michel, C., Ruhrmann, S., Schimmelmann, B.G., Klosterkötter, J., & Schultze-Lutter, F. (2014). A stratified model for psychosis prediction in clinical practice. *Schizophrenia Bulletin*, 40(6), 1533-1542. doi: 10.1093/schbul/sbu025

Miller, T.J., Chicchetti, D., Markovich, P.J., McGlashan, T.H., & Woods, S.W. (2004). The SIPS Screen: a brief self-report screen to detect the schizophrenia prodrome. *Schizophrenia Research*, 70 (Suppl 1), 78. doi: 10.1016/j.schres.2004.06.006

Miller, T.J., McGlashan, T.H., Rosen, J.L., Cadenhead, K., Cannon, T., Ventura, J., … Woods, S.W. (2003). Prodromal assessment with the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin*, 29(4), 703-715. doi: 10.1093/oxfordjournals.schbul.a007040

Miller, T.J., McGlashan, T.H., Rosen, J.L., Somjee, L., Markovich, P.J., Stein, K., & Woods, S.W. (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry*, 159(5), 863-865. doi. 10.1176/appi.ajp.159.5.863

Miller, T.J., McGlashan, T.H., Woods, S.W., Stein, K., Driesen, N., Corcoran, C.M., … Davidson, L. (1999). Symptom assessment in schizophrenic prodromal states. *Psychiatric Quarterly*. 70(4), 273-287. doi: 10.1023/A:1022034115078

Monte, R.C., Goulding, S.M., & Compton, M.T. (2008). Premorbid functioning of patients with first-episode nonaffective psychosis: a comparison of deterioration in academic and social performance, and clinical correlates of Premorbid Adjustment Scale scores. *Schizophrenia Research*, 104(1-3), 206-213. doi: 10.1016/j.schres.2008.06.009

Morgan, V.A., Castle, D.J., & Jablensky, A.V. (2008). Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Australian and New Zealand Journal of Psychiatry*, 42(1), 74-82. doi: 10.1080/00048670701732699

Moriarty, P.J., Lieber, D., Bennett, A., White, L., Parrella, M., Harvey, P.D., & David, K.L. (2001). Gender differences in poor outcome patients with lifelong schizophrenia. *Schizophrenia Bulletin*, 27(1), 103-113. doi: 10.1093/oxfordjournals.schbul.a006850

Mrazek, P.J. (1998). Selective and indicated preventive interventions. In R. Jenkins, & R.B. Üstun (Eds.), *Preventing mental illness: mental health promotion in primary care* (pp. 35-44). Sussex, UK: John Wiley & Sons.

Mrazek, P.J., & Haggerty, R.J. (1994). *Reducing Risk for Mental Disorders: Frontiers for Preventive Intervention Research.* Washington, DC: National Academy Press.

Mukherjee, S., Reddy, R., & Schnur, D.B. (1991). A developmental model of negative syndromes in schizophrenia. In J. Greden & R. Tandon (Eds.), *Negative schizophrenic symptoms: pathophysiology and clinical implications* (pp. 173-178). Washington DC: American Psychiatric Press.

Murray, R.M., & Lewis, S.W. (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal*, 295(6600), 6-12. doi: 10.1136/bmj.295.6600.681

Murray, R.M., O'Callaghan, E., Castle, D.J., & Lewis, S.W. (1992). A neurodevelopmental approach to the classification of schizophrenia. *Schizophrenia Bulletin*, 18(2), 319-322. doi: 10.1093/schbul/18.2.319

Myin-Germeys, I., Delespaul, P., & van Os, J. (2005). Behavioural sensitization to daily life stress in psychosis. *Psychological Medicine*, 35(5), 733-741. doi: 10.1017/S0033291704004179

Myles-Worsley, M., Blailes, F., Ord, L.M., Weaver, S., Dever, G., & Faraone, S.V. (2007). The Palau Early Psychosis Study: distribution of cases by level of genetic risk. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 144B(1), 5-9. doi; 10.1002/ajmg.b.30362

Naqvi, H., Khan, M.M., & Faizi, A. (2005). Gender differences in age at onset of schizophrenia. *Journal of the College of Physicians and Surgeons--Pakistan*, 15(6), 345-348.

Nieman, D.H., Ruhrmann, S., Dragt, S., Soen, F., van Tricht, M.J., Koelman, J.H., … de Haan, L. (2014). Psychosis prediction: stratification of risk estimation with information-processing and premorbid functioning variables. *Schizophrenia Bulletin*, 40(6), 1482-1490. doi: 10.1093/schbul/sbt145

Niessen, M.A., Dingemans, P.M., van de Fliert, R., Becker, H.E., Nieman, D.H., & Linszen, D. (2010). Diagnostic validity of the Eppendorf Schizophrenia Inventory (ESI): a self-report screen for ultrahigh risk and acute psychosis. *Psychological Assessement*, 22(4), 935-944. doi: 10.1037/a0020974

Nordentoft, M., Thorup, A., Petersen, L., Ohlenschlaeger, J., Melau, M., Christensen, T.Ø.… Jeppesen, P. (2006). Transition rates fromschizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment. *Schizophrenia Research*, 83(1), 29-40.

Norman, R.M.G., Malla, A.K., Manchanda, R., & Townsend, L. (2005). Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains. *Acta Psychiatrica Scandinavica*, 112(1), 30-39. doi: 10.1111/j.1600-0447.2005.00555.x

O'Callaghan, E., Turner, N., Renwick, L., Jackson, D., Sutton, M., Foley, S.D., … Kinsella, A. (2010). First episode psychosis and the trail to secondary care: help-seeking and health-system delays. *Social Psychiatry and Psychiatric Epidemiology*, 45(3), 381-391. doi: 10.1007/s00127-009-0081-x

Ochoa, S., Haro, J.M., Torres, J.V., Pinto-Meza, A., Palacín, C., Bernal, M., ... Autonell, J. (2008). What is the relative importance of self reported psychotic symptoms in epidemiological studies? Results from the ESEMED–Catalonia Study. *Schizophrenia Research*, 102(1-3), 261-269. doi: 10.1016/j.schres.2008.04.010

Ochoa, S., Huerta-Ramos, E., Barajas, A., Iniesta, R., Dolz, M., Baños, I., … Usall, J. (2013). Cognitive profiles of three clusters of patients with a first-episode psychosis. *Schizophrenia Research*, 150(1), 151-156. doi: 10.1016/j.schres.2013.07.054

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. *Schizophrenia Research and Treatment*, Article ID 916198, 1-9. doi: 10.1155/2012/916198

Olsen, K.A., & Rosenbaum, B. (2006a). Prospective investigations of the prodromal state of schizophrenia: assessment instruments. *Acta Psychiatrica Scandinavica*, 113(4), 273-282. doi: 10.1111/j.1600-0447.2005.00698.x

Olsen, K.A., & Rosenbaum, B. (2006b). Prospective investigations of the prodromal state of schizophrenia: review of studies. *Acta Psychiatrica Scandinavica*, 113(4), 247-72. doi: 10.1111/j.1600-0447.2005.00697.x

Ord, L.M., Myles-Worsley, M., Blailes, F., & Ngiralmau, H. (2004). Screening for prodromal adolescents in an isolated high-risk population. *Schizophrenia Research*,;71(2-3), 507-508. doi: 10.1016/j.schres.2004.03.014

Owoeye, O., Kingston, T., Scully, P.J., Baldwin, P., Browne, D., Kinsella, A., … Waddington, J.L. (2013). Epidemiological and clinical characterization following a first psychotic episode in major depressive disorder: comparisons with schizophrenia and bipolar I disorder in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Schizophrenia Bulletin*, 39(4), 756-765. doi: 10.1093/schbul/sbt075

Parellada, M., Boada, L., Fraguas, D., Reig, S., Castro-Fornieles, J., Moreno, D., … Arango, C. (2011). Trait and state attributes of insight in first episodes of early-onset schizophrenia and other psychoses: a 2-year longitudinal study. *Schizophrenia Bulletin*, 37(1), 38-51. doi: 10.1093/schbul/sbq109

Parnas, J., Raballo, A., Handest, P., Jansson, L., Vollmer-Larsen, A., & Saebye, D. (2011). Self-experience in the early phases of schizophrenia: 5-year follow-up of the Copenhagen Prodromal Study. *World Psychiatry*, 10(3), 200-204. doi: 10.1002/j.2051-5545.2011.tb00057.x

Paus, T., Keshavan, M., & Giedd, J.N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews. Neuroscience*, 9, 947-957. doi: 10.1038/nrn2513

Payá, B., Rodríguez-Sánchez, J.M., Otero, S., Muñoz, P., Castro-Fornieles, J., Parellada, M., … Arango, C. (2013). Premorbid impairments in early-onset psychosis: differences between patients with schizophrenia and bipolar disorder. *Schizophrenia Research*, 146(1-3), 103-110. doi: 10.1016/j.schres.2013.01.029

Perälä, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., … Lönnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry*, 64(1), 19-28. doi:10.1001/archpsyc.64.1.19

Peralta, V., & Cuesta, M.J. (2007). A dimensional and categorical architecture for the classification of psychotic disorders. *World Psychiatry*, 6(2), 36–37.

Perkins, D.O., Gu, H., Boteva, K., & Lieberman, J.A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: A critical review and meta-analysis. *The American Journal of Psychiatry*, 162(10), 1785-1804. Retrieved from http://ajp.psychiatryonline.org/

Petersen, L., Thorup, A., Øqhlenschlaeger, J., Christensen, T.Ø., Jeppesen, P., Krarup, G., … Nordentoft, M. (2008). Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. *Canadian Journal of Psychiatry*, 53(10), 660-670.

Phillips, L. (1953). Case history data and prognosis in schizophrenia. *Journal of Nervous and Mental Disease*, 117(6), 515-525. doi: 10.1097/00005053-195306000-00004

Piras, S., Casu, G., Casu, M.A., Orrù, A., Ruiu, S., Pilleri, A., … Marchese, G. (2014). Prediction and prevention of the first psychotic episode: new directions and opportunities. *Therapeutics and clinical risk management*, 10, 241-253. doi: 10.2147/TCRM.S55770

Pogue-Geile, M.F. (1997). Developmental aspects of schizophrenia, In M.S. Keshavan & R.M. Murray (Eds.), *Neurodevelpment and adult psychopathology* (pp. 137-154). Cambridge, UK: Cambridge University Press.

Poulton, R., Caspi, A., Moffitt, T.E., Cannon, M., Murray, R., & Harrington, H.L. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Archives of General Psychiatry*, 57(11), 1053-1058. doi: 10.1001/archpsyc.57.11.1053

Purcell, D.W., Lewine, R.R.J., Caudle, J., & Price, L.R. (1998). Sex differences in verbal IQ-performance IQ discrepancies among patients with schizophrenia and normal volunteers. *Journal of Abnormal Psychology*, 107(1), 161-165. doi: 10.1037/0021-843X.107.1.161

Rabinowitz, J., Levine, S.Z., & Häfner, H. (2006). A population based elaboration of the role of age of onset on the course of schizophrenia. *Schizophrenia Research*, 88(1-3), 96-101. doi: 10.1016/j.schres.2006.07.007

Rabinowitz, J., Napryeyenko, O., Burba, B., Martinez, G., Neznanov, N.G., Fischel, T., … Schreiner, A. (2011). Premorbid functioning and treatment response in recent-onset schizophrenia: prospective study with risperidone long-acting injectable. *Journal of Clinical* Psychopharmacology, 31(1), 75-81.

Raine A. (1991). The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin*, 17(4), 555-564. doi: 10.1093/schbul/17.4.555

Rajji, T.K., Ismail, Z., & Mulsant, B.H. (2009). Age at onset and cognition in schizophrenia: meta-analysis. *The British Journal of Psychiatry*, 195(4), 286-293. doi: 10.1192/bjp.bp.108.060723

Ramirez, N., Arranz, B., Salavert, J., Alvarez, E., Corripio, I., Dueñas, R.M., … San, L. (2010). Predictors of schizophrenia in patients with a first episode of psychosis. *Psychiatry Research*, 175(1-2), 11-14. doi: 10.1016/j.psychres.2009.03.013

Rapoport, J.L., Addington, A.M., Frangou, S., & Psych, M.R. (2005). The neurodevelopmental model of schizophrenia: update 2005. *Molecular Psychiatry*, 10(5), 434-449. doi:10.1038/sj.mp.4001642

Rausch, F., Eifler, S., Esser, A., Esslinger, C., Schirmbeck, F., Meyer-Lindenberg, A., & Zink, M. (2013). The Early Recognition Inventory ERIraos detects at risk mental states of psychosis with high sensitivity. *Comprehensive Psychiatry*, 54(7), 1068-1076. doi: 10.1016/j.comppsych.2013.04.016

Remschmidt, H. (2004). *Schizophrene Erkrankungen im Kindes- und Jugendalters. Klinik, Ätiologie, Therapie und Rehabilitation*. Stuttgart, Germany: Schattauer.

Riecher-Rössler, A., Aston, J., Borgwardt, S., Bugra, H., Fuhr, P., Gschwandtner, U., ... Zimmermann, R. (2013). Prediction of psychosis by stepwise multilevel assessment--the Basel FePsy (Early Recognition of Psychosis)-Project. *Fortschritte der Neurologie-Psychiatrie*. 81(5), 265-275. doi: 10.1055/s-0033-1335017

Riecher-Rössler, A., Aston, J., Ventura, J., Merlo, M., Borgwardt, S., Gschwandtner, U., & Stieglitz, R.D. (2008). The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity. *Fortschritte der Neurologie-Psychiatrie*, 76(4), 207-216. doi: 10.1055/s-2008-1038155

Riecher-Rössler, A., Gschwandtner, U., Aston, J., Borgwardt, S., Drewe, M., Fuhr, P., … Stieglitz RD. (2007). The Basel early-detection-of-psychosis (FEPSY)-study--design and preliminary results. *Acta Psychiatrica Scandinavica*, 115(2), 114-125. doi: 10.1111/j.1600-0447.2006.00854.x

Riecher-Rössler, A., & Häfner, H. (2000). Gender aspects in schizophrenia: bridging the border between social and biological psychiatry. *Acta Psychiatrica Scandinavica*. *Supplement,* 102(s407), 58-62. doi: 10.1034/j.1600-0447.2000.00011.x

Riecher-Rössler, A., Häfner, H., Stumbaum, M., Maurer, K., & Schmidt, R. (1994). Can estradiol modulate schizophrenic symptomatology? *Schizophrenia Bulletin*, 20(1), 203-214. doi: 10.1093/schbul/20.1.203

Riecher-Rössler, A., Pflüger, M.O., Aston, J., Borgwardt, S.J., Brewer, W.J., Gschwandtner, U., & Stieglitz, R. (2009). The efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. *Biological Psychiatry*, 66(11), 1023-1030. doi: 10.1016/j.biopsych.2009.07.020

Ritsner, M.S. (2011). Toward a Multidimensional Continuum Model of Functional Psychoses of Research Purposes. In M.S., Ritsner (Eds.), *Handbook of Schizophrenia Spectrum Disorders: Conceptual Issues and Neurobiological Advances* (pp. 85-113). London, UK: Springer Science+Business Media.

Ritsner, M., Kurs, R., Gibel, A., Hirschmann, S., Shinkarenko, E., & Ratner, Y. (2003). Predictors of quality of life in major psychoses: a naturalistic follow-up study. *J Clin Psychiatry*, 64(3), 308-315. doi: 10.4088/JCP.v64n0313

Rodnick, E.H., & Goldstein, M.J. (1974). Premorbid adjustment and the recovery of mothering function in acute schizophrenic women. *Journal of Abnormal Psychology*, 83(6), 623-628. doi: 10.1037/h0037468

Rodríguez-Sánchez, J.M., Ayesa-Arriola, R., Mata, I., Moreno-Calle, T., Perez-Iglesias, R., González-Blanch, C., … Crespo-Facorro, B. (2010). Cannabis use and cognitive functioning in first-episode schizophrenia patients. *Schizophrenia Research*, 124(1-3), 142-151. doi: 10.1016/j.schres.2010.08.017

Romm, K.L., Melle, I., Thoresen, C., Andreassen, O.A., & Rossberg, J.I. (2012). Severe social anxiety in early psychosis is associated with poor premorbid functioning, depression, and reduced quality of life. *Comprehensive Psychiatry*, 53(5), 434-440. doi: 10.1016/j.comppsych.2011.06.002

Romm, K.L., Rossberg, J.I., Berg, A.O., Barrett, E.A., Faerden, A., Agartz, I., … Melle, I. (2010). Depression and depressive symptoms in first episode psychosis. *The Journal of Nervous Mental Disease*, 198(1), 67-71. doi: 10.1097/NMD.0b013e3181c81fc0

Romm, K.L., Rossberg, J.I., Hansen, C.F., Haug, E., Andreassen, O.A., & Melle, I. (2011). Self-esteem is associated with premorbid adjustment and positive psychotic symptoms in early psychosis. *BioMed Central Psychiatry*, 11(1), 136-143. doi: 10.1186/1471-244X-11-136.

Rubio-Abadal, E., Ochoa, S., Barajas, A., Baños, I., Dolz, M., Sanchez, B., … Usall, J. (2015). Birth weight and obstetric complications determine age at onset in first episode of psychosis. *Journal of Psychiatric Research*, 65, 108-114. doi: 10.1016/j.jpsychires.2015.03.018

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R.K., Heinimaa, M., Linszen, D., Dingemans, P., … Klosterkötter, J. (2010). Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Archives of General Psychiatry*, 67(3), 241-251. doi: 10.1001/archgenpsychiatry.2009.206.

Ruhrmann, S., Schultze-Lutter, F., Schmidt, S.J., Kaiser, N., & Klosterkötter, J. (2014). Prediction and prevention of psychosis: current progress and future tasks. *European Archives of Psychiatry and Clinical Neuroscience*, 264 (Suppl. 1), S9-S16. doi: 10.1007/s00406-014-0541-5

Ruiz-Veguilla, M., Cervilla, J.A., Barrigón, M.L., Ferrín, M., Gutiérrez, B., Gordo, E., … Gurpegui, M. (2008). Neurodevelopmental markers in different psychopathological dimensions of first episode psychosis: the ESPIGAS study. *European Psychiatry*, 23(8), 533-540. doi: 10.1016/j.eurpsy.2008.04.003

Rund, B.R. (1998). A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophrenia Bulletin*, 24(3), 425-435. doi: 10.1093/oxfordjournals.schbul.a033337

Rund, B.R. (2009). Is schizophrenia a neurodegenerative disorder? *Nordic Journal of Psychiatry*, 63(3), 196–201. doi: 10.1080/08039480902767286

Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLoS Medicine*, 2(5), article e141, 413-433. doi: 10.1371/journal.pmed.0020141

Salokangas, R.K., Dingemans, P., Heinimaa, M., Svirskis, T., Luutonen, S., Hietala, J., ... EPOS group. (2013a). Prediction of psychosis in clinical high-risk patients by the Schizotypal Personality Questionnaire. Results of the EPOS project. *European Psychiatry*, 28(8), 469-475. doi: 10.1016/j.eurpsy.2013.01.001

Salokangas, R.K., Heinimaa, M., From, T., Löyttyniemi, E., Ilonen, T., Luutonen, S., … EPOS group. (2014). Short-term functional outcome and premorbid adjustment in clinical high-risk patients. Results of the EPOS project. *European Psychiatry*, 29(6), 371-380. doi: 10.1016/j.eurpsy.2013.10.003

Salokangas, R.K., Heinimaa, M., Ilonen, T., Suomela, T., Korkeila, J., Plathin, M., … McGlashan, T.H. (2001). Epidemiology of prodrome in familial schizophrenia – description of the DEEP project. In T. Miller, S.A. Mednick T.H. McGlashan, J. Libiger, J. Johannesen (Eds.), *Early intervention in psychotic disorders* (pp. 47-69). Dordrecht, Netherlands: Kluwer Academic Publishers.

Salokangas, R.K., Nieman, D.H., Heinimaa, M., Svirskis, T., Luutonen, S., From, T., … EPOS group. (2013b). Psychosocial outcome in patients at clinical high risk of psychosis: a prospective follow-up. *Social Psychiatry and Psychiatric Epidemiology*, 48(2), 303-311. doi: 10.1007/s00127-012-0545-2.

Salokangas, R.K., Ruhrmann, S., von Reventlow, H.G., Heinimaa, M., Svirskis, T., From, T., ... EPOS group. (2012). Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. *Schizophrenia Research*, 138(2-3), 192-197. doi: 10.1016/j.schres.2012.03.008

Schmidt, M., Blanz, B., Dippe, A., Koppe, T., & Lay, B. (1995). Course of patients diagnosed as having schizophrenia during first episode occurring under age 18 years. *European Archives of Psychiatry and Clinical Neuroscience*, 245(2), 93-100. doi: 10.1007/BF02190735

Schimmelmann, B.G., Conus, P., Cotton, S., McGorry, P.D., & Lambert, M. (2007). Pre-treatment, baseline, and outcome differences between early-onset and adult-onset psychosis in an epidemiological cohort of 636 first-episode patients. *Schizophrenia Research*, 95(1-3), 1-8. doi: 10.1016/j.schres.2007.06.004

Schultze-Lutter, F., & Klosterkötter, J. (2004). *Schizophrenia prediction instrument, adult version – SPI-A*. Cologne, Germany: Department of Psychiatry and Psychotherapy, University of Cologne.

Schultze-Lutter, F., Klosterkötter, J., Picker, H., Steinmeyer, E.M., & Ruhrmann, S. (2007). Predicting first-episode psychosis by basic symptom criteria. *Clinical Neuropsychiatry*, 4(1), 11-22.

Schultze-Lutter, F., Klosterkötter, J., & Ruhrmann, S. (2014). Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. *Schizophrenia Research*, 154(1-3), 100-116. doi: 10.1016/j.schres.2014.02.010

Schultze-Lutter, F., Ruhrmann, S., Fusar-Poli, P., Bechdolf, A., Schimmelmann, BG., & Klosterkötter, J. (2012). Basic symptoms and the prediction of first-episode psychosis. *Current Pharmaceutical Design*, 18(4), 351-357. doi: 10.2174/138161212799316064

Schultze-Lutter, F., Wieneke, A., Picker, H., Rolff, Y., Steinmeyer, E.M., Ruhrmann, S., & Klosterkötter, J. (2004). The schizophrenia prediction instrument, adult version (SPI-A). *Schizophrenia Research*, 70 (suppl.1), 76-77. doi: 10.1016/j.schres.2004.06.006

Schwab, S.G., & Wildenauer, D.B. (2009). Update on key previously proposed candidate genes for schizophrenia. *Current Opinion in Psychiatry*, 22(2), 147–153. doi: 10.1097/YCO.0b013e328325a598

Seeman, M.V. (1985). Sex and schizophrenia. *Canadian Journal of Psychiatry*, 30(5), 313-315.

Seeman, M.V. (2012). Women and psychosis. *Women's Health*, 8(2), 215-224. doi: 10.2217/whe.11.97

Seidman, L.J., Giuliano, A.J., Meyer, E.C., Addington, J., Cadenhead, K.S., Cannon, T.D., ... North American Prodrome Longitudinal Study (NAPLS) Group. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Archives of General Psychiatry*, 67(6), 578-588. doi: 10.1001/archgenpsychiatry.2010.66.

Sevy, S., Robinson, D.G., Napolitano, B., Patel, R.C., Gunduz-Bruce, H., Miller, R., … Kane, J. (2010). Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia. *Schizophrenia Research*, 120(1-3), 101-117. doi: 10.1016/j.schres.2010.03.037

Shah, J.L., Tandon, N., & Keshavan, M.S. (2013). Psychosis prediction and clinical utility in familial high-risk studies: selective review, synthesis, and implications for early detection and intervention. *Early Intervention in Psychiatry*, 7(4), 345-360. doi: 10.1111/eip.12054

Sharpe, D. (1997). Of apples and oranges, file drawers and garbage: why validity issues in meta-analysis will not go away. *Clinical Psychology Review*, 17(8), 881-901. doi: 10.1016/S0272-7358(97)00056-1

Simon, A.E., Dvorsky, D.N., Boesch, J., Roth, B., Isler, E., Schueler, P., … Umbricht, D. (2006). Defining subjects at risk for psychosis: a comparison of two approaches. *Schizophrenia Research*, 81(1), 83-90. doi: 10.1016/j.schres.2005.10.006

Simon, A.E., & Umbricht, D. (2010). High remission rates from an initial ultra-high risk state for psychosis. *Schizophrenia Research*, 116(2-3), 168-172. doi: 10.1016/j.schres.2009.10.001

Simon, A.E., Velthorst, E., Nieman, D.H., Linszen, D., Umbricht, D., & de Haan, L. (2011). Ultra high-risk state for psychosis and non-transition: a systematic review. *Schizophrenia Research*, 132(1), 8-17. doi: 10.1016/j.schres.2011.07.002

Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R.D., Drewe, J., … Borgwardt, S.J. (2010). Neuroimaging predictors of transition to psychosis - a systematic review and meta-analysis. *Neuroscience Biobehavioral Reviews*, 34(8), 1207-1222. doi: 10.1016/j.neubiorev.2010.01.016

Smith, S. (2010). Gender differences in antipsychotic prescribing. *International Review of Psychiatry*, 22(5), 472-484. doi: 10.3109/09540261.2010.515965

Sommer, I.E. (2010). The continuum hypothesis of psychosis: David's criticisms are timely. *Psychological Medicine*, 40(12), 1959-1961. doi: 10.1017/S0033291710000218

Stephens, J.H. (1970). Long-term course and prognosis in schizophrenia. *Seminars in Psychiatry*, 2(4), 464-485.

Strauss, G.P., Allen, D.N., Miski, P., Buchanan, R.W., Kirkpatrick, B., & Carpenter, W.T. (2012). Differential patterns of premorbid social and academic deterioration in deficit and nondeficit schizophrenia. *Schizophrenia Research*, 135(1-3), 134-138. doi: 10.1016/j.schres.2011.11.007

Strauss, J.S., & Carpenter, W.T. (1977). Prediction of outcome in schizophrenia. III. Five-year outcome and its predictors. *Archives of General Psychiatry*, 34(2), 159-163. doi: 10.1001/archpsyc.1977.01770140049005

Strauss, J.S., Kokes, R.F., Klorman, R. & Sacksteder, J.L. (1977). Premorbid adjustment in schizophrenia: concepts, measures, and implications. Part I. The concept of premorbid adjustment. *Schizophrenia Bulletin*, 3(2), 182-185. doi: 10.1093/schbul/3.2.182

Strous, R.D., Alvir, J.M., Robinson, D., Gal, G., Sheitman, B., Chakos, M., & Lieberman, J.A. (2004). Premorbid functioning in schizophrenia: relation to baseline symptoms, treatment response, and medication side effects. Schizophrenia Bulletin, 30(2), 265-278. doi: 10.1093/oxfordjournals.schbul.a007077

Sullivan, H.S. (1927). The onset of schizophrenia. *American Journal of Psychiatry*, 84(1), 105-134. doi: 10.1176/ajp.84.1.105

Süllwold, L., & Huber, G. (1986). Basic schizophrenic disorders. *Monographien aus dem Gesamtgebiete der Psychiatrie*, 42(), 1-177.

Szymanski, S., Lieberman, J.A., Alvir, J.M., Mayerhoff, D., Loebel, A., Geisler, S., ... Cooper T. (1995). Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. *The American Journal of Psychiatry*, 152(5), 698-703. doi: 10.1176/ajp.152.5.698

Tandon, R., Keshavan, M.S., & Nasrallah, H.A. (2008). Schizophrenia, "Just the Facts": what we know in 2008 part 1: overview. *Schizophrenia Research*, 100(1-3), 4-19. doi: 10.1016/j.schres.2008.01.022

Tandon, N., Montrose, D., Shah, J., Rajarethinam, R.P., Diwadkar, V.A., & Keshavan, M.S. (2012a). Early prodromal symptoms can predict future psychosis in familial high-risk youth. *Journal of Psychiatric Research*, 46(1), 105-110. doi: 10.1016/j.jpsychires.2011.09.019

Tandon, N., Shah, J., Keshavan, M.S., & Tandon, R. (2012b). Attenuated psychosis and the schizophrenia prodrome: current status of risk identification and psychosis prevention. *Neuropsychiatry*, 2(4), 345-353. doi: doi: 10.2217/NPY.12.36

Tarbox, S.I., Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Perkins, D.O., …Woods, S.W. (2013). Premorbid functional development and conversion to psychosis in clinical high-risk youths. *Development and Psychopathology*, 25(4 Pt 1), 1171-1186. doi: 10.1017/S0954579413000448

Tarbox, S.I., Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Perkins, D.O., ... Woods, S.W. (2014). Functional development in clinical high risk youth: prediction of schizophrenia versus other psychotic disorders. *Psychiatry Research*, 215(1), 52-60. doi: 10.1016/j.psychres.2013.10.006

Tarbox, S.I., Brown, L.H., & Haas, G.L. (2012). Diagnostic specificity of poor premorbid adjustment: comparison of schizophrenia, schizoaffective disorder, and mood disorder with psychotic features. *Schizophrenia Research*, 141(1), 91-97. doi: 10.1016/j.schres.2012.07.008

Thompson, A., Nelson, B., & Yung, A. (2011). Predictive validity of clinical variables in the "at risk" for psychosis population: international comparison with results from the North American Prodrome Longitudinal Study. *Schizophrenia Research*, 126(1-3), 51-57. doi: 10.1016/j.schres.2010.09.024

Thorup, A., Waltoft, B.L., Pedersen, C.B., Mortensen, P.B., & Nordentoft, M. (2007). Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychological Medicine*, 37(4), 479-484. doi: 10.1017/S0033291707009944

Tienari, P., Wynne, L.C., Sorri, A., Lahti, I., Läksy, K., Moring, J., … Wahlberg, K.E. (2004). Genotype-environment interaction in schizophrenia-spectrum disorder. Long-term follow-up study of Finnish adoptees. *The British Journal of Psychiatry*, 184(3), 216-222. doi: 10.1192/bjp.184.3.216

Turner, N., Browne, S., Clarke, M., Gervin, M., Larkin, C., Waddington, J.L., & O'Callaghan, E. (2009). Employment status amongst those with psychosis at first presentation. *Social Psychiatry and Psychiatric Epidemiology*, 44(10), 863-869. doi: 10.1007/s00127-009-0008-6

Üçok A., & Ergül, C. (2014). Persistent negative symptoms after first episode schizophrenia: A 2-year follow-up study. *Schizophrenia Research*. 158(1-3), 241-246. doi: 10.1016/j.schres.2014.07.021

Ullmann, L., & Giovannoni, J. (1964). The development of a self-report measure of the process-reactive continuum. *Journal of Nervous and Mental Disease*, 138(1), 38-42. doi: 10.1097/00005053-196401000-00005

Usall, J., Haro, J.M., Ochoa, O., Márquez, M., & Araya, S. (2002). Influence of gender on social outcome in schizophrenia. *Acta Psychiatrica Scandinavica*, 106(5), 337-342. doi: 10.1034/j.1600-0447.2002.01351.x

Usall, J., Huerta-Ramos, E., Iniesta, R., Cobo, J., Araya, S., Roca, M., … Ochoa, S. (2011). Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. *The Journal of Clinical Psychiatry*, 72(11), 1552-1557. doi: 10.4088/JCP.10m06610

Vaillant, G.E. (1962). The prediction of recovery in schizophrenia. *Journal of Nervous and Mental Disease*, 135(6), 534-543. doi: 10.1097/00005053-196212000-00006

Valli, I., Tognin, S., Fusar-Poli, P., & Mechelli, A. (2012). Episodic memory dysfunction in individuals at high-risk of psychosis: a systematic review of neuropsychological and neurofunctional studies. *Current Pharmaceutical Design*, 18(4), 443-458. doi: 10.2174/138161212799316271

Valmaggia, L.R., Stahl, D., Yung, A.R., Nelson, B., Fusar-Poli, P., McGorry, P.D., & McGuire, P.K. (2013). Negative psychotic symptoms and impaired role functioning predict transition outcomes in the at-risk mental state: a latent class cluster analysis study. *Psychological Medicine*, 43(11), 2311-2325. doi: 10.1017/S0033291713000251

Van Mastrigt, S., & Addington, J. (2002). Assessment of premorbid function in first-episode schizophrenia: modifications to the Premorbid Adjustment Scale . *Journal of Psychiatry and Neuroscience*, 27(2), 92-101.

Van Os, J., Linscott, R.J., Myin-Germys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological Medicine*, 39(2), 179-195. doi: 10.1017/S0033291708003814

Vaskinn, A., Sundet, K., Simonsen, C., Hellvin, T., Melle, I., & Andreassen, O.A. (2011). Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder. *Neuropsychology*, 25(4), 499-510.

Vázquez-Bourgon, J., Salvador-Carulla, L., Crespo-Facorro, B., & Vázquez-Barquero, J.L. (2013). The feasibility of applying the clinical staging paradigm to the care of people with mental disorders. In G. Thornicroft, M. Ruggeri, & D. Goldberg (Eds.), *Improving Mental Health Care: The Global Challenge* (pp. 145-162). Oxford, UK: John Wiley & Sons.

Velthorst, E., & de Haan, L. (2014). Social dysfunction of young persons with an ultra high risk of developing first-episode psychosis. *Tijdschrift voor psychiatrie*, 56(1), 40-49.

Velthorst, E., Derks, E.M., Schothorst, P., Becker, H., Durston, S., Ziermans, T., … de Haan, L. (2013a). Quantitative and qualitative symptomatic differences in individuals at Ultra-High Risk for psychosis and healthy controls. *Psychiatry Research*, 210(2), 432-437. doi: 10.1016/j.psychres.2013.07.018

Velthorst, E., Nelson, B., Wiltink, S., de Haan, L., Wood, S.J., Lin, A., & Yung, A.R. (2013b). Transition to first episode psychosis in ultra high risk populations: does baseline functioning hold the key? *Schizophrenia Research*, 143(1), 132-137. doi: 10.1016/j.schres.2012.10.025

Velthorst, E., Nieman, D.H., Linszen, D., Becker, H., de Haan, L., Dingemans, P.M., ... Ruhrmann, S. (2010). Disability in people clinically at high risk of psychosis. *The British Journal of Psychiatry*, 197(4), 278-284. doi: 10.1192/bjp.bp.109.075036

Verdoux, H., Geddes, J.R., Takei, N. Lawrie, S.M., Bovet, P., Eagles, J.M., … Murray, R.M. (1997). Obstetric complications and age at onset in schizophrenia: An international collaborative meta-analysis of individual patient data. *The American Journal of Psychiatry*, 154(9), 1220–1227.

Vila-Rodriguez, F., Ochoa, S., Autonell, J., Usall, J., & Haro, J.M. (2011). Complex interaction between symptoms, social factors, and gender in social functioning in a community-dwelling sample of schizophrenia. *Psychiatric Quarterly*, 82(4), 261-274. doi: 10.1007/s11126-011-9168-0

Vyas, N.S., Patel, N.H., & Puri, B.K. (2011). Neurobiology and phenotypic expression in early onset schizophrenia. *Early Intervention in Psychiatry*, 5(1), 3-14. doi: 10.1111/j.1751-7893.2010.00253.x

Walder, D.J., Holtzman, C.W., Addington, J., Cadenhead, K., Tsuang, M., Cornblatt, B., … Walker, E.F. (2013). Sexual dimorphisms and prediction of conversion in the NAPLS psychosis prodrome. *Schizophrenia Research*, 144(1-3), 43-50. doi: 10.1016/j.schres.2012.11.039

Walder, D.J., Mittal, V., Trotman, H.D., McMillan, A.L., & Walker, E.F. (2008). Neurocognition and conversion to psychosis in adolescents at high-risk. *Schizophrenia Research*, 101(1-3), 161-168. doi: 10.1016/j.schres.2007.12.477

Walsh, T., McClellan, J.M., McCarthy, S.E., Addington, A.M., Pierce, S.B., Cooper, G.M., … Sebat, J. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science*, 320(5875), 539–543. doi: 10.1126/science.1155174

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, 44(7), 660-669. doi: 10.1001/archpsyc.1987.01800190080012.

Weinberger, D.R. & McClure, R.K. (2005). Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain?. *Archives of General Psychiatry*, 59(6), 553–558. doi: 10.1001/archpsyc.59.6.553

Wiffen, B.D., Rabinowitz, J., Lex, A., & David, A.S. (2010). Correlates, change and 'state or trait' properties of insight in schizophrenia. *Schizophrenia Research*, 122(1-3), 94-103. doi: 10.1016/j.schres.2010.03.005

Willhite, R.K., Niendam, T.A., Bearden, C.E., Zinberg, J., O'Brien, M.P., & Cannon, T.D. (2008). Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder. *Schizophrenia Research*, 104(1-3), 237-245. doi: 10.1016/j.schres.2008.05.019

Wittman, P. (1941). Scale for measuring prognosis in schizophrenic patients. *Elgin State Hospital Papers*, 4, 20-33.

Woodberry, K.A., Seidman, L.J., Giuliano, A.J., Verdi, M.B., Cook, W.L., & McFarlane, W.R. (2010). Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. *Schizophrenia Research*, 123(2-3), 188-198. doi: 10.1016/j.schres.2010.06.021

World Health Organization. (1992). *International Classification of Diseases and Related Health Problems*, *10th revision*. Geneva: World Health Organization.

Yung, A.R., Killackey, E., Hetrick, S.E., Parker, A.G., Schultze-Lutter, F., Klosterkoetter, J., … McGorry, P. (2007a). The prevention of schizophrenia. *International Review of Psychiatry*, 19(6), 633-646. doi: 10.1080/09540260701797803

Yung, A.R., Killackey, E.J., Nelson, B., & McGorry, P.D. (2010a). The Impact of Early Intervention in Schizophrenia. In W.F. Gattaz & G. Busatto (Eds.), *Advances in Schizophrenia Research 2009* (pp. 299-316). New York, NY: Springer Science+Business Media.

Yung, A.R., & McGorry, P.D. (1996). The prodromal phase of first-episode psychosis: past and current conceptualitzations. *Schizophrenia Bulletin*, 22(2), 353-370. doi: 10.1093/schbul/22.2.353

Yung, A.R., McGorry, P.D., McFarlane, C.A., Jackson, H.J., Patton, & G.C., Rakkar, A. (1996). Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin*, 22(2), 283–303. 10.1093/schbul/22.2.283

Yung, A.R., Nelson, B., Thompson, A., & Wood, S.J. (2010b). The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? *Schizophrenia Research*, 120, (1-3), 1-6. doi: 10.1016/j.schres.2010.03.014

Yung, A.R., Organ, B.A., & Harris, M.G. (2003a). Management of early psychosis in a generic adult mental health service. *Australian & New Zealand Journal of Psychiatry*, 37(4), 429-436. doi: 10.1046/j.1440-1614.2003.01196.x

Yung, A.R., Phillips, L.J. & McGorry, P.D. (2004). *Treating Schizophrenia in the Pre-Psychotic Phase*. London, UK: Dunitz.

Yung, A.R., Phillips, L.J., McGorry, P.D., McFarlane, C.A., Francey, S., Harrigan, S., … Jackson, H.J. (1998). Prediction of psychosis. A step towards indicated prevention of schizophrenia. *The British Journal of Psychiatry*. *Supplement*, 172(33), 14-20.

Yung, A.R., Phillips, L.J., McGorry, P.D., Ward, J.L., Donovan, K., & Thompson, K. (2002). *Comprehensive assessment of at risk mental states (CAARMS)*. Melbourne, Australia: PACE Clinic, Department of Psychiatry, University of Melbourne.

Yung, A.R., Phillips, L.J., McGorry, P.D., Ward, J.L., & Thompson, K. (2000). *The Comprehensive Assessment of At-Risk Mental States (CAARMS)*. Melbourne, Australia: University of Melbourne.

Yung, A.R., Phillips, L.J., Yuen, H.P., Francey, S.M., McFarlane, C.A., Hallgren, M., & McGorry, P.D. (2003b). Psychosis prediction: 12-month follow up of a high-risk ('prodromal') group. *Schizophrenia Research*, 60(1), 21-32. doi: 10.1016/S0920-9964(02)00167-6

Yung, A.R., Woods, S.W., Ruhrmann, S., Addington, J., Schultze-Lutter, F., Cornblatt, B.A., …, McGlashan, T.H. (2012). Whither the attenuated psychosis syndrome? *Schizophrenia Bulletin*, 38(6), 1130-1134.

Yung, A.R., Yuen, H.P., Berger, G., Francey, S., Hung, T.C., Nelson, B., … McGorry, P. (2007b). Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophrenia Bulletin*, 33(3), 673-681. doi: 10.1093/schbul/13.3.497

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio M., & Buckby, J. (2005). Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Australian and New Zealand Journal of Psychiatry*, 39(11-12), 964-971. doi 10.1080/j.1440-1614.2005.01714.x

Ziermans, T.B., Schothorst, P.F., Sprong, M., & van Engeland, H. (2011). Transition and remission in adolescents at ultrahigh risk for psychosis. *Schizophrenia Research*, 126(1-3), 58-64. doi: 10.1016/j.schres.2010.10.022

Zigler, E., & Phillips, L. (1961). Social competence and outcome in psychiatric disorder. *Journal of Abnormal and Social Psychology*, 63(2), 264-271. doi: 10.1037/h0046232

Zimmermann, R., Gschwandtner, U., Wilhelm, F.H., Pflueger, M.O., Riecher-Rössler, A., & Fuhr, P. (2010). EEG spectral power and negative symptoms in at-risk individuals predict transition to psychosis. *Schizophrenia Research*, 123(2-3), 208-216. doi: 10.1016/j.schres.2010.08.031

ANNEX

Additional studies:

STUDY 3: Predictive capacity of prodromal symptoms in first-episode psychosis of recent-onset

A. Barajas[a,b,c,d,e], T. Pelaez[b], O. González[b], J. Usall[b], R. Iniesta[d], M. Arteaga[b], C. Jackson[f], I. Baños[d], B. Sánchez[c], M. Dolz[c], J.E. Obiols[e], J.M. Haro[b], GENIPE group[g], S. Ochoa[b]

[a] Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain
[b] Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain
[c] Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[d] Fundació Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
[e] Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
[f] Birmingham Early Intervention Service, Birmingham and Solihull Mental Health Foundation Trust, Birmingham, UK

[1] GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, Dachs I, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Miquel L, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V.

Under review for publication in Comprehensive Psychiatry

TITLE: PREDICTIVE CAPACITY OF PRODROMAL SYMPTOMS IN FIRST-EPISODE PSYCHOSIS OF RECENT-ONSET

AUTHOR(S):

A. Barajas[1,2,3,4,5,*], T. Pelaez[2], O. González[2], J. Usall[2], R. Iniesta[4], M. Arteaga[2], C. Jackson[6], I. Baños[4], B. Sánchez[3], M. Dolz[3], J.E. Obiols[5], J.M. Haro[2], GENIPE group[7], S. Ochoa[2*]

AUTHOR (S) AFFILIATION(S):

1. Department of Research, Centre d'Higiene Mental Les Corts, Barcelona, Spain
2. Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de Llobregat, Barcelona, Spain
3. Hospital Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
4. Fundació Sant Joan de Déu de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Esplugues de Llobregat, Barcelona, Spain
5. Departament de Psicologia Clínica i de la Salut, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Vallès, Spain
6. Birmingham Early Intervention Service, Birmingham and Solihull Mental Health Foundation Trust, Birmingham, UK
7. GENIPE group is a multidisciplinary group of researchers: Araya S, Arranz B, Arteaga M, Asensio R, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Blanc M, Borrás M, Busquets E, Carlson J, Carral V, Castro M, Corbacho C, Coromina M, Dachs I, De Miquel L, Dolz M, Domenech MD, Elias M, Espezel I, Falo E, Fargas A, Foix A, Fusté M, Godrid M, Gómez D, González O, Granell L, Gumà L, Haro JM, Herrera S, Huerta E, Lacasa F, Mas N, Martí L, Martínez R, Matalí J, Miñambres A, Muñoz D, Muñoz V, Nogueroles R, Ochoa S, Ortiz J, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Rubio E, Sammut S, Sánchez M, Sánchez B, Serrano E, Solís C, Stephanotto C, Tabuenca P, Teba S, Torres A, Urbano D, Usall J, Vilaplana M, Villalta V

***CORRESPONDING AUTHORS:**

Susana Ochoa Güerre/Ana Barajas Vélez

Parc Sanitari Sant Joan de Déu. CIBERSAM

C/ Antoni Pujades, 42. CP 08830

Sant Boi de Llobregat (Spain)

Tel. +34 93 640 63 50

Fax. +34 93 630 53 19

E-mails: sochoa@pssjd.org; ana.barajas@chmcorts.com

ABSTRACT

BACKGROUND: Both the nature and number of a wide range of prodromal symptoms have been related to the severity and type of psychopathology in the psychotic phase. However, at present there is an incomplete picture focused mainly on the positive pre-psychotic dimension. **AIMS:** To characterize the prodromal phase retrospectively, examining the number and nature of prodromal symptoms as well as their relationship with psychopathology at the onset of first-episode psychosis. **METHODS:** Retrospective study of 79 patients experiencing a first-episode psychosis of less than one year from the onset of full-blown psychosis. All patients were evaluated with a comprehensive battery of instruments including socio-demographic and clinical questionnaire, IRAOS interview, PANSS, stressful life events scale (PERI), and WAIS/WISC (vocabulary subtest). Bivariate associations and multiple regression analysis were performed. **RESULTS:** Regression models revealed that several prodromal dimensions of IRAOS (Delusions; Affect; Language; Behavior; Non-hallucinatory disturbances of perception) predicted the onset of psychosis, with positive (22.4% of the variance) and disorganized (25.6% of the variance) dimensions being the most widely explained. **CONCLUSION:** In addition to attenuated positive symptoms, other symptoms as affective, behavioural, and language disturbances, should also be considered in the definitions criteria of at-high-risk people.

Keywords: prodrome; psychosis; first episode; phenomenology; recent-onset.

1. INTRODUCTION

The early course of psychosis has traditionally consisted of three phases: premorbid phase, prodromal phase, and initial psychotic phase [1]. The prodromal phase of psychosis refers to the period before the onset of frank psychotic symptoms in which the first manifestations of illness or prodromal symptoms appear. There is great variability between patients regarding how their prodromes manifest; however, certain signs and symptoms are commonly described, most of them being non-specific [2]: reduced concentration and attention; reduced drive and motivation; depressed mood; sleep disturbances; anxiety; social withdrawal; suspiciousness; deterioration of role functioning; and irritability.

Although not all patient report prodromal symptoms, approximately 80% to 90% of patients with psychotic spectrum disorder have described a variety of subacute symptoms in the months and years preceding psychosis. For this reason, in the last two decades, great research efforts have been made to develop and test operational criteria based mainly on subthreshold levels of psychotic symptoms [3-5]. In a recent meta-analysis [6], it was shown that there was a mean transition risk of 22% (17-28%) at 1-year follow-up, independent of the different high-risk definitions used. Nonetheless, a majority of participants, also known as false positives, consistently do not develop psychosis over time. However, as the annual incidence for all forms of psychosis in the general population is only about 0.034% [7], even the lowest conversion rates found still indicates a dramatic increase in the relative risk of illness. In this sense, having an effective mechanism to detect risk of psychosis could contribute to the development of more appropriate indicated prevention tasks. However, to date, there is a lack of consensus on the specific symptoms to include in the definition of the population at risk of psychosis, which focuses almost exclusively on positive symptoms. We still need to learn the predictive capacity of different kinds of prodromal dimensions involved in the course of the illness. Addington et al. [8] concluded that prodromal attenuated positive symptoms may predict a more severe condition in some, but by no means all, cases (approximately 35% developed a psychotic illness). Accordingly, positive symptoms *per se* do not make good predictors of psychosis.

Recent findings suggest that negative symptoms, cognitive impairment and a decline in functioning at baseline [9-11] are strongly associated with higher risk of transition to psychosis at follow-up. Moreover, Klosterkötter et al. [4], who followed up high-risk people for 9.6 years, demonstrated that the presence/absence of at least one basic symptom correctly predicted the presence/absence of a subsequent transition to schizophrenia in 78.1% of cases.

Then, whereas conversion to full-blown psychosis is one possible outcome of current definitions of high-risk for psychosis, this occurs in a minority of persons. In this sense, due to limited predictive capacity and lack of consensus on the definition of the algorithms used in scientific literature to detect high-risk patients for psychosis, it is necessary to deepen into the characterization of the prodromal symptoms nearest at the onset of the psychotic episode from a retrospective approach. Thus, it will be possible to refine the definition of the population at high-risk for psychosis to be used in prospective studies, to improve their predictive capacity and to reduce the rate of false positives.

Furthermore, a combination of potential psychopathological predictors with other risk factors could help to create a new algorithm to identify who is at risk with accuracy. Among these widely studied factors are the following: genetic markers (such as family history [12] and gender [13]), environmental factors (such as stressful life events [14] and cannabis exposure [15]), and clinical predictors (such as age at onset [16] and duration of untreated illness (DUI) [17]).

Follow-up studies of the general population with psychotic experiences consider psychosis to be a dimensional phenomenon lying on a continuum with normality. These studies have demonstrated that shifts from nonclinical to clinical outcomes of psychosis are associated with the number and severity of symptoms [18-19]. Similarly, in a study of patients with schizophrenia, Moukas et al. [20] concluded that both the nature and number of the prodromal symptoms were related to the severity as well as to the type of psychopathology in the psychotic phase. These observations appear to be of clinical importance because they may lead to the development of quantitative (accumulation of prodromal symptoms) and qualitative (type of prodromal symptoms) criteria to identify full-blown psychosis. However, to our knowledge,

there are no published studies linking prodromal dimensions with severity of psychopathological dimensions at onset of FEP, including non-affective and affective psychotic disorders.

1.1. Aims of the study

In order to characterise the prodromal phase in a sample of patients with recent-onset FEP, we set out the following aims: (a) to study the frequency of the experienced prodromal symptoms; (b) to analyse the relationship between the number and nature of prodromal symptoms and the severity of psychopathology at the onset of FEP; and (c) to assess the predictive capacity of the prodromal symptoms, taking into account certain risk factors, in the development of different psychopathological dimensions at the onset of psychosis: negative, positive, excited, disorganised and anxiety-depression dimensions (using Positive and Negative Syndrome Scale [PANSS]).

2. METHOD:

2.1. Sample

The sample was composed of 79 consecutive patients with recent-onset FEP. The patients were recruited from adult mental health services (AMHS) at Parc Sanitari Sant Joan de Déu and from the child and adolescent mental health services (CAMHS) at the Hospital San Joan de Déu, either at a hospital or at community psychiatric services belonging to the metropolitan area and outskirts of Barcelona (Spain).

Patients were entered into the study if they: (1) had two or more psychotic symptoms (delusions, hallucinations, disorganised speech, catatonic or disorganised behaviour, and negative symptoms); (2) were aged between 12 and 45; (3) had had an initial psychiatric visit at any centre participating in the study; (4) had had initial contact with the mental health services within the previous 6 months; and (5) had less than a year since onset of psychotic symptoms. These last two inclusion criteria allow achieve greater homogeneity in the sample of patients with a recent-onset of psychosis, thereby avoiding the inclusion of patients with long evolution

of the psychotic symptoms from the onset of the first episode. Patients were excluded if they: (1) had been diagnosed with intellectual disability, head injury, dementia or any organic psychoses; (2) had a low verbal IQ (IQ<85); or (3) had an inadequate command of Spanish or Catalan.

All participants were informed of the study aims by their psychiatrist or researcher and provided written informed consent, including parental consent for those under 18 years of age. This study was approved by the Research and Ethics Committee of Sant Joan de Déu (Barcelona, Spain) and was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. Instruments

a) Socio-demographic and clinical characteristics: The socio-demographic characteristics (date of birth, age, gender, level of education, occupational status, current marital status and current living situation) and clinical features of the sample (age at first adequate treatment, family history and cannabis use) were obtained with a questionnaire created specifically for this study.

b) Diagnosis: diagnosis was established through the following instruments depending on patient age: the Structured Clinical Interview for DSM-IV Axis I (SCID-I) [21] for adults and the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) [22-23] for adolescents. The K-SADS-PL was administered separately to parents and patients by trained researchers.

   Prodromal phase: *The Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS)* [24] is a semi-structured interview designed for the assessment of individual social development, premorbid adjustment, onset of prodromal signs and symptoms, functional impairment and social disability. We used the indicators of the psychiatric illness section to assess prodromal symptoms in the last year before onset of FEP, in particular, the following dimensions: Non-Hallucinatory Disturbances of Perception (IRAOS-NHDP); Hallucinations (IRAOS-H); Subjective Disturbances of

Thinking and Experiences (IRAOS-SDTE); Delusions (IRAOS-D); Cognitive Impairment and/or decline (IRAOS-CI); Behaviour (IRAOS-B); Affect (IRAOS-A); Language (IRAOS-L). The information registered about these dimensions was completed using all available data, including clinical history data and interviews with patients and relatives. The presence of each prodromal symptom, experimented during the last year before the onset of psychotic episode, was considered taking into account the degree of conviction of patients about these symptoms. When at least one persistent symptom (in both duration and frequency) was held with full conviction, the onset of the psychotic episode was then considered. However, if the patient was able to cast doubt on the symptom or was able to give plausible explanation for the experience, the presence of a prodromal symptom was then considered. Age at first prodromal features, age at onset of psychotic episode, duration of initial prodrome (DPR) and DUI were assessed using the IRAOS scale. DPR was defined as the period from onset of the late prodromal symptoms until the onset of psychotic episode; and DUI was defined as the period from onset of the late prodromal symptoms until the first appropriate treatment was received. In these definitions the late prodromal symptoms refer to the symptoms experienced just prior to the onset of psychotic episode.

c) Psychotic symptoms: PANSS [25-26] is a scale used for measuring symptom severity, which includes 30 items. The evaluation was carried out assessing the maximum severity of symptoms from the onset of psychotic episode. Prior to recruitment, inter-rater reliability for the PANSS was determined using the interclass correlation coefficient (ICC), which was always superior to 0.80. For the purpose of this study, the five-dimensional structure of PANSS determined by Emsley et al. [27] was used as dependent variable: negative factor; positive factor; excited factor; disorganised factor; and anxiety and depression factor.

d) Stressful life events: Psychiatric Epidemiology Research Interview – Life Events Scale (PERI) [28-29] collects information on the presence of 102 life events during the previous year. Higher scores indicate higher presence of stressful life events.

e) Estimated premorbid IQ: Wechsler Adult Intelligence Scale (WAIS-III) Spanish version [30] was used for people aged 16 or over and the Wechsler Intelligence Scale for Children (WISC-IV) Spanish version [31] was used for children and adolescents under 16. The estimated IQ was determined by vocabulary subtest, as several authors have previously suggested [32].

2.3. Statistical Analysis

Median, range, mean and standard deviation (SD) were used to describe continuous variables. Frequencies and percentages were used to describe categorical variables. A Kolmogorov-Smirnov test was used to test for the normality of variables. To discover the predictive power of the prodromal symptoms, multiple regression analyses were performed. First of all, we assessed the bivariate associations between the independent factors (dimensions and total score of IRAOS) and covariable factors (gender, family history, cannabis use, diagnosis, age, DPR, DUI, estimated premorbid IQ and stressful life events scale) with the 5 outcome variables (negative dimension; positive dimension; excited dimension; disorganised dimension; and anxiety and depression dimension) by t-test (or U-Mann-Whitney test for variables without normal distribution) for categorical predictor variables and by Pearson's correlation coefficient (or Spearman's correlation coefficient for variables deviating from normality) for continuous predictor variables. One-way ANOVA was carried out when the independent variable had three categories (such as IRAOS-CI). Significant variables found in bivariate analysis were then entered into the regression models using the stepwise method. Before performing the regression analyses, we analysed influential cases through Cook's distance (values greater than 1 may be cause for concern [33]) and studentised residuals (values greater than 3 may be cause for concern). We analysed the normality, independency and multicollinearity assumptions of each model through the Kolmogorov-Smirnov test, Durbin-Watson test (values around 2 indicate no autocorrelation ([34]) and the Variance Inflation Factor (VIF) (values greater than 10 may indicate a strong linear relationship with other predictors [35]). All analyses used two-tailed p-

values and a 0.05 significance level. All statistical analyses were performed with the SPSS statistical software package (version 18.0).

3. RESULTS:

A total of 79 people aged 12-45 were assessed. Approximately 73.4% of the sample (n=58) was composed of people experiencing a first non-affective psychotic episode. The median was a better indicator than the mean since DPR and DUI were heavily skewed, with 75% of the patients having the onset of a psychotic episode within 28.5 weeks after the onset of the late prodromal symptoms and having an appropriate treatment within 41.9 weeks from the onset of the late prodromal symptoms. Tables 1 and 2 describe socio-demographic and clinical characteristics of the sample.

INSERT TABLE 1 ABOUT HERE:

Table 1.Socio-demographic characteristics of the sample (n=79)

INSERT TABLE 2 ABOUT HERE:

Table 2.Clinical characteristics of the sample (n=79)

In our study, we analysed the frequency of 58 different prodromal symptoms (Table 3). All the patients in the sample except one had experienced at least some specific and proximal prodromal symptom before full-threshold psychosis; however, the quantity and nature were different in each individual case. The average number of symptoms experienced during the prodromal phase was 18 (range 0-37), with 6 being the lowest number of accumulated prodromal symptoms among individuals of the study sample which experiencing an active prodromal phase.

INSERT TABLE 3 ABOUT HERE:

Table 3.Prodromal symptoms in 79 patients with FEP

In terms of distribution, PANSS subscales had a normal distribution in all categorical variables except for PANSS positive and disorganised in relation to family history and PANSS negative

regarding diagnosis. In the continuous variables, all variables had a normal distribution except for age, DPR, DUI, and four IRAOS dimensions (IRAOS-NHDP, IRAOS-H, IRAOS-B, IRAOS-L). In these instances, non-parametric statistics were used.

Association analysis revealed that the accumulation of prodromal symptoms during the last year before full-threshold psychosis (total IRAOS) was correlated with the severity of incipient disorganised symptoms only. In relation to the nature of prodromal symptoms, most IRAOS dimensions, except for IRAOS-SDTE and IRAOS-CI dimensions, showed significant correlations with psychopathology dimensions assessed after the onset of episode using PANSS scale, (Table 4).

INSERT TABLE 4 ABOUT HERE:

Table 4.Associations between possible predictors and outcome variables

In addition, regarding risk factors considered in this study, a significant relationship between cannabis exposure and PANSS Negative subscale was found, indicating that patients who used cannabis showed more severity of negative psychotic symptoms at the onset of the episode than those who did not. Also, PANSS Positive and Disorganised scores were related to family history, indicating that patients having first- or second-degree relatives with a history of a non-affective or affective psychotic disorder showed more severity of positive and disorganised symptoms at the onset of the psychotic episode. No significant correlations were found between gender, diagnosis, age, DPR, DUI, estimated premorbid IQ and stressful life events scale with any PANSS subscales (Table 4).

A multiple regression model was created for each psychopathology dimensions of PANSS (negative, positive, excited, disorganised and anxiety/depression). All models were stable across the sample and no strong correlation between two or more predictors existed in the regression models (Cook's distance <1; VIF >10). The regression model constructed to explore the predictors of positive psychotic symptoms at onset of illness revealed that both family history and IRAOS-D were significant predictors. They explained 22.4% of the overall severity of positive symptom variance. Furthermore, in relation to the regression model used to study the

predictors of negative psychotic dimensions, IRAOS-A was the only significant predictor, explaining 8.5% of the overall severity of negative symptom variance. In relation to the severity of disorganised symptoms at the onset of illness, all predictors included in the model, family history, IRAOS-D, and IRAOS-L were significant predictors. This model explained 25.6% of the overall severity of disorganised symptom variance. In the regression model constructed to predict incipient excited psychotic symptoms, IRAOS-B was the only significant predictor, explaining 7.0% of the overall excited symptom variance. Lastly, we examined the predictors of anxiety/depression symptoms at the onset of illness. The regression model revealed that IRAOS-NHDP was the only significant predictor, explaining 7.9% of the overall severity of anxiety/depression symptom variance (Table 5).

INSERT TABLE 5 ABOUT HERE:

Table 5.Multiple regression analyses for each of the five PANSS dimensions

4. DISCUSSION

4.1. Main findings: qualitative approach

From a qualitative point of view, the results of this study revealed that the ten most frequent prodromal symptoms were the following: passivity experiences; increased distractibility/disturbance of attention; delusional mood; overvalued ideas; oversensitivity; delusions of persecution; delusions of reference; apathy; thought blocking; and weakness of focused thinking. Therefore, this is an extremely variable symptom profile, including attenuated psychotic symptoms (mainly disturbances of thinking), affective/negative and cognitive symptoms. In reference to the positive dimension, we found that prodromal symptoms, such as attenuated or subthreshold versions of psychotic symptoms (delusions or perceptual abnormalities), were good predictors of positive symptoms in the psychosis active phase. Similarly, Moukas et al. [20] concluded that 3 of the 5 prodromal symptoms that carried a significantly greater risk for severe PANSS positive psychopathology were positive pre-psychotic symptoms. Our results support the inclusion of attenuated psychotic symptoms in the

definitions of risk criteria for psychosis used in previous studies [36-38]. However, in this study, attenuated positive psychotic symptoms are not the only predictor of onset of psychosis. Other types of prodromal symptoms such as language disturbances were related to disorganised active symptoms at the onset of illness. Similarly, Gourzis et al. [39] showed that one of the prodromal symptoms with the greatest specificity for the disorganised subtype was poverty of content of speech. It seems that patients who experience delusions and language problems in the prodromal phase may develop more severe psychosis, similar to the disorganisation dimension defined by Murray et al. [40] which, among other symptoms, includes speech disturbances (i.e. difficult to understand or incoherent). Furthermore, we observed that the presence of familial loading for the illness was a significant predictor of disorganised and positive dimensions at the onset of the FEP. This finding provides more evidence regarding the criteria selected to define people with ultra-high risk for psychosis, adding a variable of genetic risk (family history) in order to enhance the predictive power.

In relation to the excited dimension, we found prodromal behavioural abnormalities to be the main and exclusive predictor. This finding supports the appropriateness of including "gross disorganised or catatonic behaviour" in the set of symptoms for the definition of the late initial prodromal stage (LIPS), which attempts to identify those at more immediate risk [41], or "odd behaviour" to define the attenuated psychotic symptoms (APS) group [36]. Disorganised behaviour is among the most replicated predictors of transition to psychosis and poor longitudinal functioning [6,9].

Regarding the negative dimension, our results showed that the emotional disturbances in the prodromal phase were the only predictor. These affect impairments could be considered as the expressivity dimension of attenuated negative symptoms. Our results show that a profile characterised by these prodromal symptoms could predict the first presentation of broader negative symptoms, not only related to expressivity symptoms (i.e. affective flattening) but also for an experiential dimension (i.e. social withdrawal or active social avoidance). Previous studies have also found that attenuated negative symptoms may be a risk factor for transition to psychosis in a clinical high-risk population [42-43], and have included emotional disturbances

such as subjectively abnormal emotional experiences [44] and blunted affect [44-45] among negative-type prodromal symptoms. A recent study [46] concluded that negative symptoms at prodrome onset predicted negative symptoms at first presentation with psychosis, specifically experiential symptoms.

In relation to the dimension of anxiety and depression analysed in this study, non-hallucinatory disturbances of perception showed predictive capacity for psychotic episodes characterized by affective symptoms. Moukas et al. [20] showed that patients experiencing hyperacusis during the prodromal phase scored significantly higher on the general PANSS at onset of frank psychosis. Both findings could be important for future retrospective studies geared to optimising risk criteria for affective psychosis.

4.2. Main findings: quantitative approach

From a quantitative approach, it should be noted that the great majority of, although not all, first-episode patients show at least some prodromal symptom prior to onset of the psychotic disorder [2,47]. In our sample, only one patient did not report the presence of prodromal symptoms. Regarding the number of prodromal symptoms accumulated until culmination of the FEP, this study shows that approximately a third of the prodromal symptoms analysed appeared in the last year before the onset of episode, and a greater presence of prodromal symptoms was associated with more disorganised psychosis. Similar results were found by Moukas et al. [20], but in relation to positive and general PANSS. Häfner et al. [48], in a follow-back study of first-episode schizophrenia, observed that in the year prior to onset, symptoms were accelerated in number and intensity up to the psychosis threshold. In addition, the study revealed that this accumulation in the early course of illness occurs in a mixture of three clinical symptom categories (nonspecific, negative and positive symptoms). From the psychosis continuum model, the accelerated accumulation of prodromal symptoms or greater load of subclinical psychotic experiences is considered to be a predictor of greater probability of clinical outcome [49].

Lastly, one limitation of our study is the retrospective evaluation of the prodromal phase. However, this study investigates a broad spectrum of proximal prodromal symptoms and identifies existing relationships with symptoms manifested after the onset of frank psychosis. Furthermore, an advantage of this study is the fact that only patients who had recently developed the psychotic stage were investigated for their prodromal symptoms and they therefore had better recollection of events in the pre-psychotic period. It was taken into account that there is a very narrow line between prodromal symptoms and full-psychotic symptoms, making it difficult to establish differences between them. The following criterion was determined to define a symptom as attenuated or prodromal and not fully psychotic: a lack of conviction about the "real" nature of symptoms.

In conclusion, this study provides evidence of symptomatic heterogeneity in the proximal prodromal phase of transition to psychosis, not only including sub-threshold positive psychotic symptoms. Secondly, the number of prodromal symptoms accumulated to full-threshold of psychosis is associated with the kind of psychopathology in the initial psychotic phase of the illness, specifically with disorganised dimension. Lastly, prodromal dimensions have differing capacities for predicting psychopathological dimensions at the onset of psychosis, with positive and disorganised dimensions being the most widely predicted.

These findings therefore indicate that the development of each dimension of full-blown psychosis is already differentially programmed from the prodromal phase. Future research should be directed at studying whether or not identified specific groups of FEP [50] are characterised by different prodromal symptoms.

Our findings may have clinical implications in relation to several issues: a) prodromal characteristics could be regarded as a new class of risk factors, especially useful in prevention studies; b) the psychosis risk algorithms used to date should be modified, taking into account a broader approach with negative and less-specific prodromal symptoms (such as behavioural, language and emotional disturbances) and this might guide future research regarding the phenomenology of the "attenuated psychosis syndrome", currently considered to be a category

in the Section III of DSM-5 under "conditions for further study". In addition, as indicated from the European Psychiatric Association (EPA) [51], other potential risk factors should be taken into account to increase the predictive capacity of these algorithms (e.g. a positive family history of psychosis or neurocognitive abnormalities, among others); c) new specific and stage-appropriate treatments should be developed, taking into account the heterogeneity of symptoms prior to the first manifestations of illness and aimed at ameliorating the distress caused by these symptoms [52]. The focus of interventions in high-risk patients needs to be broadened with regard to outcomes and intervention approaches, as recommended by the EPA [53].

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest concerning this article.

ACKNOWLEDGEMENTS

Acknowledgements are directed towards all patients and their relatives for their participation in the study and towards all the coordinating clinicians and staff from the psychiatric inpatient and outpatient units at Sant Joan de Déu who collaborated. This work was supported by Fondo de Investigaciones Sanitarias de España (FIS PI05/1115); Instituto de Salud Carlos III de España; Centro de Investigación en Red de Salud Mental (CIBERSAM) and Caja Navarra.

REFERENCES

[1] Tully E, McGlashan TH. The prodrome. In: Lieberman JA, Stroup TS, Perkins DO, editors. *The American Psychiatric Publishing textbook of schizophrenia*, Washington, DC: American Psychiatric Publishing; 2006, p. 341–52.

[2] Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull 1996;**22**(2):353–70.

[3] Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry 1998;**172**(33):14–20.

[4] Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. Arch Gen Psychiatry 2001;**58**(2):158–64.

[5] Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr Bull 2003;**29**(4):633–51.

[6] Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F et al. The psychosis high-risk state. A comprehensive state-of-the-art review. JAMA Psychiatry 2013;**70**(1):107–20.

[7] Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AESOP study. Arch Gen Psychiatry 2006;**63**(3):250–58.

[8] Addington J, Cornblatt BA, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO et al. At clinical high risk for psychosis: Outcome for nonconverters. Am J Psychiatry 2011;**168**(8): 800–05.

[9] Demjaha A, Valmaggia L, Stahl D, Byrne M, McGuiere P. Disorganization/cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. Schizophr Bull 2012;**38**(2):351–59.

[10] Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD et al. Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. Arch Gen Psychiatry 2010;**67**(6):578–88.

[11] Valmaggia LR, Stahl D, Yung AR, Nelson B, Fusar-Poli P, McGorry PD et al. Negative psychotic symptoms and impaired role functioning predict transition outcomes in the at-risk mental state: a latent class cluster analysis study. Psychol Med 2013;**43**(11):2311–25.

[12] Esterberg M, Compton M. Family history of psychosis negatively impacts age at onset, negative symptoms, and duration of untreated illness and psychosis in first-episode psychosis patients. Psychiatry Res 2012;**197**(1-2):23–8.

[13] Willhite RK, Niendam TA, Bearden CE, Zinberg J, O'Brien MP, Cannon TD. Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder. Schizophr Res 2008;**104**(1-3):237–45.

[14] Hotzman CW, Shapiro DI, Trotman HD, Walker EF. Stress and the prodromal phase of psychosis. Curr Pharm Des 2012;**18**(4):527–33.

[15] Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L et al. Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr Scand 2012;**125**(1):45–53.

[16] Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res 2004;**67**(2-3):131–42.

[17] Keshavan MS, Haas G, Miewald J, Montrose DM, Reddy R, Schooler NR et al. Prolonged untreated illness duration from prodromal onset predicts outcome in first episode psychoses. Schizophr Bull 2003;**29**(4):757–69.

[18] Hanssen M, Bak M, Bijl R, Vollebergh W, van Os J. The incidence and outcome of subclinical psychotic experiences in the general population. Br J Clin Psychol 2005;**44**(Pt.2):181–91.

[19] Welham J, Scott J, Williams G, Najman J, Bor W, O'Callaghan M et al. Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21-year birth cohort study. Psychol Med 2008;**39**(4):625–34.

[20] Moukas G, Stathopoulou A, Gourzis P, Beratis IN, Beratis S. Relationship of "prodromal" symptoms with severity and type of psychopathology in the active phase of schizophrenia. Compr Psychiatry 2010;**51**(1):1–7.

[21] First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM IV Axis I Disorders-Research Version (SCID-I, Version 2.0)*. New York: Biometrics Research Department, New York State Psychiatric Institute; 1996.

[22] Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;**36**(7):980–8.

[23] Ulloa RE, Ortiz S, Higuera F, Nogales I, Fresán A, Apiquian R et al. Interrater reliability of the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL). Actas Esp Psiquiatr 2006;**34**(1):36–40.

[24] Häfner H, Riecher-Rössler A, Hambrecht M, Maurer K, Meissner S, Schmidtke A et al. IRAOS: An instrument for the assessment of onset and early course of schizophrenia. Schizophr Res 1992;**6**(3):209–23.

[25] Kay SR, Fizbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;**13**(2):261–76.

[26] Peralta V, Cuesta MJ. Validation of positive and negative symptom scale (PANSS) in a sample of Spanish schizophrenia patients. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1994;**22**(4):171–7.

[27] Emsley R, Rabinowitz J, Torreman M, RIS-INT-35 Early Psychosis Global Working Group. The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. Schizophr Res 2003;**61**(1):47–57.

[28] Dohrenwend BS, Krasnoff L, Askenasy AR, Dohrenwend BP. Exemplification of a method for scaling life events: the Peri Life Events Scale. J Health Soc Behav 1978;**19**(2):205–29.

[29] Vizcarro R. *PERI modificada*. In: Fernández-Ballesteros R, editors. El ambiente: análisis psicológico, Madrid: Pirámide; 1987.

[30] Seisdedos N, Corral S, Cordero A, de la Cruz MV, Hernández MV, Pereña J. *WAIS III Escala de Inteligencia de Wechsler para Adultos III. Manual Técnico*. Madrid: TEA Ediciones; 1999.

[31] Corral S, Arribas D, Santamaría P, Sueiro MJ, Pereña J. *Escala de Inteligencia de Wechsler para niños-IV*. Madrid: TEA Ediciones; 2005.

[32] Miralbell J, Soriano JJ, López-Cancio E, Arenillas JF, Dorado L, Barrios M et al. Vascular risk factors and cognitive performance in patients 50 to 65 Years-Old. Neurología 2010;**25**(7):422–9.

[33] Cook RD, Weisberg S. *Residuals and Influence in Regression*. New York: Chapman and Hall; 1982.

[34] Doménech JM. *Tablas de estadística*. Barcelona: Signo; 2007.

[35] Chatterjee S, Price B. *Regression Analysis by Example*. 2 ed. New York: John Wiley and Sons; 1991.

[36] Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M et al. Psychosis prediction: 12-month follow up of a high risk ("prodromal") group. Schizophr Res 2003;**60**(1):21–32.

[37] Klosterkötter J, Ruhrman S, Schultze-Lutter F, Salokangas RK, Linszen D, Birchwood M et al. The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. World Psychiatry 2005;**4**(3):161–7.

[38] Addington J, Cadenhead KS, Cannon TD, Cornblatt B, McGlashan TH, Perkins DO et al. North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research. Schizophr Bull 2007;**33**(3):665–72.

[39] Gourzis P, Katrivanou A, Beratis A. Symptomatology of the initial prodromal phase in schizophrenia. Schizophr Bull 2002;**28**(3):415–29.

[40] Murray V, McKee I, Miller PM, Young D, Muir WJ, Pelosi AJ et al. Dimensions and classes of psychosis in a population cohort: a four-class, four-dimension model of schizophrenia and affective psychoses. Psychol Med 2005;**35**(4):499–510.

[41] Ruhrmann S, Schultze-Lutter F, Klosterkötter J. Early detection and intervention in the initial prodromal phase of schizophrenia. Pharmacopsychiatry 2003;**36**(Suppl. 3):162–7.

[42] Lencz T, Smith CW, Auther A, Correll CU, Cornblatt B. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. Schizophr Res 2004;**68**(1):37–48.

[43] Piskulic D, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R et al. Negative symptoms in individuals at clinical high risk of psychosis. Psychiatry Res 2012;**196**(2-3):220–4.

[44] Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005*;***39**(11-12):964–71.

[45] Mason O, Startup M, Halpin S, Schall U, Conrad A, Carr V. Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. Schizophr Res 2004;**71**(2-3):227–37.

[46] Lyne J, Renwick L, Madigan K, O'Donoghue B, Bonar M, Grant T et al. Do psychosis prodrome onset negative symptoms predict first presentation negative symptoms? Eur Psychiatry 2014;**29**(3):153–9.

[47] Häfner H, Maurer K, Löffler W, an der Heiden W, Hambrecht M, Schultze-Lutter F. Modeling the early course of schizophrenia. Schizophr Bull 2003;**29**(2):325–40.

[48] Häfner H, Maurer K, Löffler W, Bustamante S, an der Heiden W, Riecher-Rössler A. *Onset and early course of schizophrenia*. In: Gattaz WF, Häfner H, editors. Search for the Causes of Schizophrenia (vol.III), Berlin: Springer-Verlag; 1995, p. 43–66.

[49] Kaymaz N, van Os J. Extended psychosis phenotype—yes: single continuum—unlikely. Psychol Med 2010;**40**(12):1963–6.

[50] Ochoa S, Huerta-Ramos E, Barajas A, Iniesta R, Dolz M, Baños I et al. Cognitive profiles of three clusters of patients with a first-episode psychosis. Schizophr Res 2013;**150**(1):151–6.

[51] Schultze-Lutter F, Michel C, Schmidt SJ, Schimmelmann BG, Maric NP, Salokangas RKR et al. EPA guidance on the early detection of clinical high risk states of psychoses. Eur Psychiatry 2015;**30**(3):405–16.

[52] Carpenter WT. Anticipating DSM-V: should psychosis risk become a diagnostic class?. Schizophr Bull 2009;**35**(5):841–3.

[53] Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, Maric NP, Salokangas RKR, Riecher-Rössler A et al. EPA guidance on the early intervention in clinical high risk states of psychoses. Eur Psychiatry 2015;**30**(3):388–404.

Table 1.
Socio-demographic characteristics of the sample (n=79)

Sociodemographic characteristics:	
Age (mean, SD)	20.22 (6.71)
Gender (n, %)	
Female	35 (44.3%)
Male	44 (55.7%)
Level of education (n, %)	
Primary	46 (58.2%)
Secondary	21 (26.6%)
High school	7 (8.9%)
University	5 (6.3%)
Working currently (n, %)	
Yes	31 (39.2%)
No	46 (58.2)
Missing	2 (2.5%)
Current marital status (n, %)	
Single	72 (91.1%)
Married/cohabiting	5 (6.3%)
Separated/divorced	2 (2.5%)
Current living situation (n, %)	
Lives with others	76 (96.2%)
Lives alone	1 (1.3%)
Other	2 (2.5%)

Table 2.
Clinical characteristics of the sample (n=79)

Age at first prodromal feature (mean, SD)	19.41 (5.99)
Age at onset of psychotic episode (mean, SD)	19.90 (6.01)
Age at first appropriate treatment (mean, SD)	20.54 (6.68)
Duration of initial prodrome (DPR), in weeks	
Median (range)	15.66 (0-226.37)
Mean (SD)	25.46 (35.58)
Duration of untreated illness (DUI), in weeks	
Median (range)	15.52 (0-226.51)
Mean (SD)	26.79 (36.24)
Diagnosis (n, %)	
Schizophrenia	7 (8.9%)
Schizophreniform disorder	21 (26.6%)
Schizoaffective disorder	1 (1.3%)
Delusional disorder	2 (2.5%)
Brief psychotic disorder	3 (3.8%)
Substance-induced psychotic disorder	2 (2.5%)
Bipolar disorder with psychotic features	12 (15.2%)
Major depression with psychotic features	9 (11.4%)
Psychotic disorder NOS	22 (27.9%)

Table 3.
Prodromal symptoms in 79 patients with FEP

	Nº (%)
Non-hallucinatory disturbances of perception (IRAOS-NHDP)	
Derealisation	28 (35.4%)
Depersonalisation	31 (39.2%)
Unusual perception	30 (38.0%)
Unusual illusions	18 (22.8%)
Further perceptual disturbances (not hallucinations)	14 (17.7%)
Others	5 (6.3%)
Hallucinations (IRAOS-H)	
Auditory hallucinations	38 (48.1%)
Visual hallucinations	15 (19.0%)
Olfactory hallucinations	9 (11.4%)
Gustatory hallucinations	4 (5.1%)
Tactile hallucinations	12 (15.2%)
Kinesthetic hallucinations	6 (7.6%)
Cenesthetic hallucinations	18 (22.8%)
Other hallucinations	33 (41.8%)
Subjective disturbance of thinking and experiences (IRAOS-SDTE)	
Delusional mood	**61 (77.2%)**
Thoughts being read	31 (39.2%)
Thought insertion	7 (8.9%)
Thought broadcasting	26 (32.9%)
Thought echo or commentary	5 (6.3%)
Thought blocking	**46 (58.2%)**
Thought withdrawal	10 (12.7%)
Passivity experiences	**79 (100%)**
Weakness of focused thinking	**45 (57.0%)**
Delusions (IRAOS-D)	
Overvalued idea	**60 (75.9%)**
Delusions of control	25 (31.6%)
Delusions of reference	**55 (69.6%)**
Delusional perception, misperception	31 (39.2%)
Delusions of persecution	**56 (70.9%)**
Expansive delusions	27 (34.2%)
Delusions of love	15 (19.0%)
Delusions concerning appearance	9 (11.4%)
Delusions of guilt	22 (27.8%)
Nihilistic delusions	12 (15.2%)
Hypochondriacal delusions	14 (17.7%)
Bizarre delusions	21 (26.6%)
Delusional ideas	13 (16.5%)
Preoccupation with secret things/unusual thought contents	32 (40.5%)
Other delusions	8 (10.1%)

Table 3.(cont.)
Prodromal symptoms in 79 patients with FEP

	Nº (%)
Cognitive impairment and/or decline (IRAOS-CI)	
Impairment of memory	44 (55.7%)
Increased distractibility/disturbance of attention	**66 (83.5%)**
Behavior (IRAOS-B)	
Catatonic symptoms (hypokinesia or akinesia)	28 (35.4%)
Catatonic symptoms (hyperkinesia)	18 (22.8%)
Antisocial behavior	18 (22.8%)
Self-injury	22 (27.8%)
Odd behavior	4 (5.1%)
Other behavioral abnormalities	5 (6.3%)
Affect (IRAOS-A)	
Oversensitivity	**59 (74.7%)**
Affective flattening	41 (51.9%)
Loss of affective reactivity	36 (45.6%)
Lability of affect	40 (50.6%)
Incongruity of affect	15 (19.0%)
Other changes in affect	6 (7.6%)
Apathy	**50 (63.3%)**
Language (IRAOS-L)	
Poverty of content of speech	26 (32.9%)
Neologisms	9 (11.4%)
Incoherence	33 (41.8%)
Derailment	41 (51.9%)
Non-verbal communication	31 (39.2%)

The ten prodromal symptoms more frequent are showed in bold.

Table 4.
Associations between possible predictors and outcome variables

	PANSS POSITIVE		PANSS NEGATIVE		PANSS DISORGANIZED		PANSS EXCITED		PANSS ANXIETY & DEPRESSION	
	Stat.[1]	p	Stat.[1]	p	Stat.[1]	p	Stat.	p	Stat.[1]	p
Possible predictors										
Qualitative variables										
Gender	0.643[b]	0.522	-0.600[b]	0.550	0.100[b]	0.921	0.302[b]	0.763	0.076[b]	0.244
Family history*	383.500[a]	**0.002**	-0.584[b]	0.561	387.000[a]	**0.006**	0.614[b]	0.541	-0.092[b]	0.927
Cannabis exposure**	1.135[b]	0.261	478.000[a]	**0.008**	-0.759[b]	0.450	1.213[b]	0.229	-0.297[b]	0.767
Diagnosis***	-0.370[b]	0.712	-0.004[b]	0.997	-0.728[b]	0.469	-1.509[b]	0.136	-1.194[b]	0.237
Quantitative variables										
Age (yrs)	-0.209[d]	0.064	-0.263[d]	-0.187	-0.187[d]	0.106	-0.095[d]	0.407	-0.192[d]	0.089
DPR (wks)	-0.088[d]	0.480	0.123[d]	0.323	-0.196[d]	0.120	0.077[d]	0.538	0.039[d]	0.756
DUI (wks)	-0.132[d]	0.290	0.108[d]	0.387	-0.111[d]	0.387	-0.024[d]	0.847	-0.032[d]	0.800
IRAOS-NHDP	0.119[d]	0.296	0.123[d]	0.279	0.235[d]	**0.041**	0.027[d]	0.814	0.226[d]	**0.045**
IRAOS-H	0.272[d]	**0.015**	-0.127[d]	0.266	0.186[d]	0.108	0.224[d]	**0.047**	0.035[d]	0.762
IRAOS-SDTE	0.092[c]	0.422	0.030[c]	0.792	0.098[c]	0.402	-0.019[c]	0.870	0.092[c]	0.420
IRAOS-D	0.366[c]	**0.001**	0.033[c]	0.770	0.310[c]	**0.006**	0.146[c]	0.199	0.056[c]	0.622
IRAOS-CI	0.855[e]	0.429	0.230[e]	0.795	0.949[e]	0.392	0.090[e]	0.914	0.354[e]	0.703
IRAOS-B	0.134[d]	0.238	0.143[d]	0.208	0.202[d]	0.081	0.269[d]	**0.017**	0.301[d]	**0.007**
IRAOS-A	-0.183[c]	0.106	0.291[c]	**0.009**	0.181[c]	0.118	-0.075[c]	0.509	0.058[c]	0.610
IRAOS-L	-0.122[d]	0.285	-0.263[d]	**0.019**	0.276[d]	**0.016**	-0.085[d]	0.455	-0.016[d]	0.886
IRAOS total	0.191[c]	0.092	0.183[c]	0.107	0.358[c]	**0.002**	0.057[c]	0.615	0.150[c]	0.187
Estimated Premorbid IQ	0.187[c]	0.113	-0.025[c]	0.832	-0.027[c]	0.823	0.054[c]	0.652	-0.024[c]	0.841
Stressful life events scale	0.183[c]	0.142	-0.136[c]	0.278	-0.009[c]	0.946	0.140[c]	0.262	0.016[c]	0.896

Abbreviations: DPR, Duration of initial prodrome; DUI, Duration of untreated illness; IRAOS-NHDP, IRAOS-Non-hallucinatory disturbances of perception; IRAOS-H, IRAOS-Hallucinations; IRAOS-SDTE, IRAOS- Subjective disturbance of thinking and experiences; IRAOS-D, IRAOS-Delusions; IRAOS-CI, IRAOS- Cognitive impairment; IRAOS-B, IRAOS- Behavior; IRAOS-A, IRAOS- Affect; IRAOS-L, IRAOS- Language.

*Family history: Refers to first and second-degree relative with a history of a non-affective or affective psychotic disorder.

** Cannabis exposure: Refers to use vs. non-use of cannabis.

***Diagnosis: Refers to non-affective psychosis vs. affective psychosis.

[1] Stat. = statistic. Boldface indicates significant association.

- For qualitative variables the statistics are: [a] U Mann-Whitney test to non-parametric data; [b] t-test to parametric data (2-tailed);
- For quantitative variables the statistics are: [c] Pearson's correlation to parametric data; [d] Spearman correlation to non-parametric data; [e] One-Way ANOVA to independent variables with only 3 values.

Table 5.
Multiple regression analyses for each of the five PANSS dimensions

	Baseline predictors	R^2	*F*	*Beta*	*t-value*	Sig. of *t*
PANSS POSITIVE		0.224	10.999***			
	IRAOS-D			0.314	3.059	**0.003****
	Family history			0.305	2.979	**0.004****
PANSS NEGATIVE		0.085	7.133**			
	IRAOS-A			0.291	2.671	**0.009****
PANSS DISORGANIZED		0.256	8.257***			
	Family history			0.308	2.966	**0.004****
	IRAOS-L			0.296	2.891	**0.005****
	IRAOS-D			0.242	2.339	**0.022***
PANSS EXCITED		0.070	5.839*			
	IRAOS-B			0.265	2.416	**0.018***
PANSS ANXIETY & DEPRESSION		0.079	6.585*			
	IRAOS-NHDP			0.281	2.566	**0.012***

Abbreviations: IRAOS-NHDP, IRAOS-Non-hallucinatory disturbances of perception; IRAOS-H, IRAOS-Hallucinations; IRAOS-D, IRAOS-Delusions; IRAOS-B, IRAOS- Behavior; IRAOS-A, IRAOS- Affect; IRAOS-L, IRAOS- Language.
*p<0.05; **p<0.01; ***p<0.001.

STUDY 6: Edad de inicio del primer episodio psicótico: ¿hay diferencias clínicas entre varones y mujeres?

A. Barajas[a,b], I. Baños[a], S. Ochoa[a], J. Usall[a], V. Villalta-Gil[a], M.Dolz[b], B. Sánchez[b], J.M. Haro[a], Grupo GENIPE[1]

[a] Serveis de Salut Mental, Sant Joan de Déu, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, España
[b] Hospital Sant Joan de Déu de Barcelona, Esplugues de Llobregat, Barcelona,España

[1] Grupo GENIPE es un grupo de investigadores multidisciplinar: Araya S, Arteaga M, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Borrás M, Busquets E, De Miquel L, Dolz M, Elias M, Espezel I, Fargas A, Foix A, Fusté M, Godrid M, González O, Granell Ll, Haro JM, Martínez R, Miñambres A, Muñoz D, Nogueroles R, Ochoa S, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Sammut S, Sánchez M, Sánchez B, Tabuenca P, Urbano D, Usall J y Villalta V.

Psiquiatría Biológica 2007; 14(4): 136 –141

Localizador web
Artículo 212.825

Edad de inicio del primer episodio psicótico: ¿hay diferencias clínicas entre varones y mujeres?

Ana Barajas[a], Iris Baños[a], Susana Ochoa[a], Judith Usall[a], Vicky Villalta[a], Montse Dolz[b], Bernardo Sánchez[b], Josep María Haro[a], y Grupo GENIPE*

[a]Serveis de Salut Mental. Sant Joan de Déu. Fundació Sant Joan de Déu. Sant Boi de Llobregat. Barcelona. España.
[b]Hospital Sant Joan de Déu de Barcelona. Esplugues de Llobregat. Barcelona. España.

INTRODUCCIÓN: En la última década, los estudios sobre primeros episodios psicóticos han alcanzado relevancia. En nuestro estudio se analizan las diferencias por sexo en la edad de inicio, así como las diferencias en el tipo y la gravedad de los síntomas psicóticos en función de la edad de inicio, en varones y mujeres con un primer episodio psicótico.

MATERIAL Y MÉTODO: Estudio transversal de 24 casos consecutivos con un primer episodio psicótico. Criterios de inclusión: dos o más síntomas psicóticos; edad comprendida entre 7 y 65 años; primera consulta en el centro de estudio; menos de 6 meses desde el primer contacto con los servicios. Los instrumentos utilizados fueron un cuestionario clínico y sociodemográfico, la PANSS y la ICG-ESQ. Para el análisis de los datos se ha utilizado la prueba de U Mann-Whitney para datos no paramétricos, del SPSS.

RESULTADOS: En nuestra muestra, el 66,7% eran varones y el 41,7% tenía una edad < 18 años. No se observan diferencias por sexo significativas en la edad de inicio del episodio (p = 0,580). Se obtienen resultados significativos en la dimensión excitativa (p = 0,015) y tendencias en la dimensión positiva de la PANSS (p = 0,079) en los varones adultos respecto a los adolescentes. Además encontramos diferencias significativas en adultos frente a adolescentes en los ítems de la PANSS negativa: retraimiento emocional (p = 0,021) y contacto pobre (p = 0,036); sin embargo, sólo encontramos tendencia a la significación en la dimensión negativa de la PANSS (p = 0,080) en varones adolescentes respecto a adultos.

CONCLUSIONES: Se evidencia un patrón de inicio del episodio psicótico en varones adolescentes con predominio de sintomatología negativa. Este patrón de inicio con síntomas negativos se suma a las evidencias encontradas en otros estudios a lo largo de los años que apoyan la hipótesis del neurodesarrollo.

Palabras clave:
Sexo. Primer episodio psicótico. Edad. Psicopatología.

Age of onset of a first psychotic episode: are there any clinical differences between men and women?

INTRODUCTION: In the past decade, studies of first psychotic episodes have become increasingly important. In the present study, we analyzed gender differences in age of onset, as well as differences in the type and severity of psychotic symptoms according to age of onset, in men and women with a first psychotic episode.

MATERIAL AND METHOD: We performed a cross-sectional study of 24 consecutive patients with a first psychotic episode. Inclusion criteria consisted of two or more psychotic symptoms, age from 7 to 65 years, first visit to a center participating in the study, and a less than 6-month time lapse since the first contact with services. The instruments used were a clinical and sociodemographic questionnaire, the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression-Schizophrenia (CGI-SCH) scale. Data were analyzed using the Mann-Whitney U-test for non-parametric data with the SPSS statistical package.

Este proyecto ha recibido la ayuda financiera del Fondo de Investigaciones Sanitarias de España (FIS PI05/1115); del Instituto de Salud Carlos III de España, RETICS RD06/0011(REM-TAP Network) y de Caja Navarra.

*GENIPE es un grupo de investigadores multidisciplinario: Araya S, Arteaga M, Autonell J, Baños I, Bañuelos M, Barajas A, Barceló M, Borrás M, Busquets E, De Miquel L, Dolz M, Elias M, Espezel I, Fargas A, Foix A, Fusté M, Godrid M, González O, Granell Ll, Haro JM, Martínez R, Miñambres A, Muñoz D, Nogueroles R, Ochoa S, Pardo M, Planella M, Pelaez T, Peruzzi S, Rivero S, Rodriguez MJ, Sammut S, Sánchez M, Sánchez B, Tabuenca P, Urbano D, Usall J y Villalta V.

Correpondencia: Dra. A. Barajas.
Sant Joan de Déu-Serveis de Salut Mental.
Fundació Sant Joan de Déu. C/ Dr. Antoni Pujades 42.
08830 St. Boi de Llobregat. Barcelona. España.
Correo electrónico: abarajas@sjd-ssm.com

RESULTS: In our sample, 66.7% of the sample were male and 41.7% were < 18 years old. No significant gender differences in age at onset of a first psychotic episode were observed (p = 0.580). Significant differences were obtained in the excitative dimension (p = 0.015) and a tendency was found in the positive dimension of the PANSS (p = 0.079) between adult males and adolescents. Significant differences were also found between adult males and adolescents in the negative PANSS items: emotional withdrawal (p = 0.021) and poor rapport (p = 0.036); however only a tendency towards significance was found in the negative dimension of the PANSS (p = 0.080) between adolescent males and adults.

CONCLUSIONS: A pattern of onset of first psychotic episodes emerged in male adolescents with a predominance of negative symptoms. This pattern of onset with negative symptoms can be added to the evidence found in other studies over the years supporting the neurodevelopment hypothesis.

Key words:
Gender. First psychotic episode. Age. Psychopathology.

INTRODUCCIÓN

El actual interés por el estudio de las fases tempranas de los trastornos psicóticos se hace cada día más evidente. Este nuevo enfoque ha supuesto una serie de ventajas respecto a estudios anteriores, ya que en los estudios de primeros episodios psicóticos dejan de estar presentes los efectos confusionales de variables como el tratamiento farmacológico o factores relacionados con la cronicidad, entre otros. Este tipo de investigaciones permite realizar seguimiento y evaluación del pronóstico de las personas evaluadas y planificar una intervención precoz en fases tempranas de la psicosis.

No obstante, el término primer episodio psicótico engloba una realidad heterogénea respecto al modo de aparición de los síntomas (agudo o insidioso), a la edad de inicio y sintomatología, entre otras variables, por lo que resulta cada vez más necesario conocer en profundidad cómo se produce el inicio de la enfermedad psicótica. Ampliar este conocimiento va a permitir mejorar aspectos como la detección e intervención precoz, así como la comprensión de la etiología y la identificación de variables pronósticas en pacientes que presentan por primera vez síntomas psicóticos.

En la década de los ochenta del siglo pasado, Weinberger[1] y Murray et al[2] hicieron resurgir la teoría del neurodesarrollo de la esquizofrenia, que basa la etiopatogenia de la enfermedad en alteraciones durante el neurodesarrollo o en la interacción con factores de vulnerabilidad genética. Desde esta teoría se postula que ya antes de la aparición de los síntomas positivos hay dificultades en el funcionamiento general.

Estudios como el de Goldstein et al[3] y Castle et al[4] postulan la existencia de una entidad clínica que se ajusta a este modelo teórico. Goldstein et al[3] defienden la existencia de dos subgrupos de esquizofrenia en función del sexo: un primer grupo más frecuente en varones, caracterizado por mayor número de síntomas negativos y una deficiente adaptación premórbida, y un segundo grupo más frecuente en mujeres, con predominio de sintomatología positiva. Castle et al[4] postulan la existencia de un grupo de pacientes ligado a alteraciones del neurodesarrollo con predominio en varones.

Un resultado constante en los diferentes estudios acerca del inicio de la esquizofrenia es un inicio del primer episodio psicótico más temprano en varones que en mujeres, y así lo corroboran en sus trabajos Angermeyer et al[5], Goldstein et al[6] y Castle et al[7]. Éstos proponen 3 picos de inicio de la esquizofrenia de distinta distribución entre varones y mujeres: un pico de inicio temprano más prominente en varones, un pico de inicio medio más frecuente en mujeres y, por último, un pico de inicio tardío casi exclusivo de las mujeres, coincidiendo con Ochoa et al[8].

En estudios realizados con pacientes que presentan un primer episodio psicótico, Vázquez et al[9], Larsen et al[10] y Hafner et al[11] continúan corroborando esta idea.

Sin embargo, no en todos los estudios concuerdan estos resultados. Falnegovic et al[12], Addignton et al[13] y Naqvi et al[14] no hallaron diferencias respecto a la edad de inicio.

En la literatura científica encontramos estudios dedicados a investigar acerca de las diferencias sintomáticas en función del sexo en pacientes con esquizofrenia. Autores como Lewine[15], Walter et al[16] y Riecher-Rossler et al[17] encuentran un mayor número de síntomas afectivos en mujeres con esquizofrenia. En cambio, Shtasel et al[18], Cowell et al[19] y Riecher-Rossler et al[17] encuentran un menor número de síntomas negativos en mujeres con esquizofrenia. Sin embargo, hay estudios que no encuentran diferencias psicopatológicas entre varones y mujeres con esquizofrenia[13,20-22].

Estudios que han investigado acerca de las diferencias sintomáticas en el inicio de la enfermedad entre varones y mujeres muestran que las mujeres presentan menos pensamientos ilógicos, más ansiedad, afecto inapropiado y conductas extrañas[23]. Hafner et al[24], en el estudio ABC (Age, Beginning and Course) de la esquizofrenia, observan que la mayoría de los individuos con esquizofrenia empiezan con síntomas negativos varios años antes de que aparezcan los síntomas positivos, siguiendo en la línea de la hipótesis del neurodesarrollo.

Los objetivos que se plantean en este estudio son evaluar si hay diferencias en la edad de inicio del primer

episodio psicótico en función del sexo y analizar si hay diferencias en el tipo y la gravedad de los síntomas psicóticos, especialmente en síntomas negativos, en función de la edad de inicio en varones y mujeres que presentan un primer episodio psicótico.

MATERIAL Y MÉTODO

Se seleccionó de manera consecutiva a 24 sujetos que presentaron un primer episodio psicótico, a medida que consultaron a la red de servicios de adultos de Sant Joan de Déu o a la red de salud mental infanto-juvenil del Hospital Sant Joan de Déu, tanto en el ámbito hospitalario como en el comunitario. Estos servicios pertenecen a diversas poblaciones próximas al área metropolitana de Barcelona o al área de Barcelona capital.

Los criterios de inclusión fueron: dos o más síntomas psicóticos (ideas delirantes, alucinaciones, lenguaje desorganizado, comportamiento catatónico o desorganizado y síntomas negativos); edad comprendida entre 7 y 65 años; primera consulta psiquiátrica que es atendida en cualquiera de las unidades/centros que participan en el estudio; menos de 6 meses desde el primer contacto con los servicios. Se excluyó a los pacientes con un diagnóstico de retraso mental, traumatismo craneoencefálico o demencia.

Los individuos seleccionados fueron informados por su psiquiatra e investigador de los objetivos y la metodología del estudio, y todos ellos firmaron el consentimiento informado por escrito para participar en él. En el caso de los pacientes menores de edad, fueron los padres o tutores quienes firmaron el consentimiento informado.

Todos los pacientes fueron evaluados con los siguientes cuestionarios:

– Cuestionario clínico y sociodemográfico, que incluyó información sobre la edad de inicio de la enfermedad, sexo, estado civil, nivel de educación, primera consulta con servicios de psiquiatría, entre otras variables.

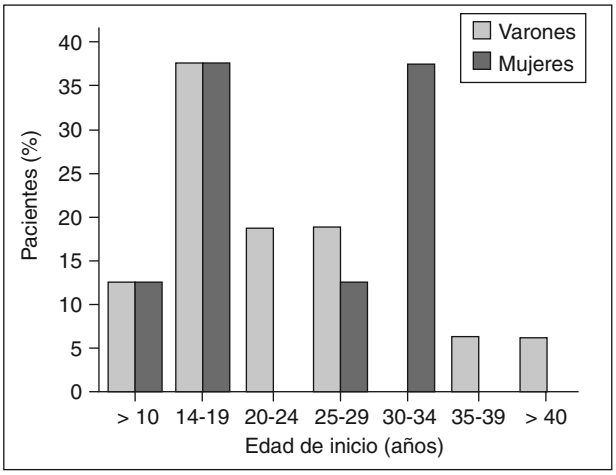


Figura 1. *Distribución de la edad de inicio del primer episodio psicótico en función del sexo.*

– Escala de los Síndromes Positivos y Negativos de la esquizofrenia (PANSS) de Kay[25], traducida y validada por Peralta et al[26]. Esta escala es la más ampliamente utilizada para valorar la síntomatología. Valora 30 síntomas en una escala de 1-7, en la que tienen más psicopatología quienes puntúan más alto. Está dividida en tres apartados: síntomas positivos, negativos y generales. Para el análisis de los datos también se han utilizado las dimensiones de la PANSS positiva, negativa, afectiva y excitativa que Villalta-Gil et al[27] encuentran realizando un análisis factorial de la escala.

– Impresión Clínica Global, versión esquizofrenia (ICG-ESQ). Evalúa la gravedad de la enfermedad (escala Likert de 1 a 7, de normal a mayor gravedad) y el grado de cambio (escala Likert de 1 a 7, de muchísimo mejor a muchísimo peor) en la esquizofrenia en los diferentes grupos de síntomas (positivos, negativos, cognitivos y depresivos) que están presentes y la gravedad general de la enfermedad. Su uso se ha validado en población española, con idéntica finalidad que en el presente estudio[28].

Análisis estadístico

En primer lugar, se realiza un análisis descriptivo de la muestra. Posteriormente, para el análisis de las diferencias por sexo en la edad de inicio y los síntomas psicóticos, se ha utilizado la prueba de U Mann-Whitney para datos no paramétricos. Por último, utilizando la misma técnica estadística, se realizan análisis de forma separada para el grupo de varones y el de mujeres. En cada uno de los grupos se compara la sintomatología presentada en función de la edad de inicio (inicio adolescente, edad < 18 años; inicio adulto, edad ≥ 18 años). Los análisis han sido realizados mediante el paquete estadístico SPSS (versión 14.0).

RESULTADOS

Se incluyó en el estudio a un total de 24 pacientes; 16 de ellos eran varones (66,7%) y, del total de la muestra, 10 (41,7%) pacientes tenían una edad < 18 años. La media de edad de inicio del primer episodio psicótico fue de 22,1 ± 8,1 años en los varones y 23,5 ± 7,8 años en las mujeres. Cuando analizamos la edad de inicio del primer episodio en función del sexo, no observamos diferencias significativas (p = 0,580). En la figura 1 se muestra la distribución de la edad de inicio del primer episodio psicótico en función del sexo.

En un primer análisis realizado acerca de las diferencias de sexo en la gravedad de la psicopatología de los pacientes con un primer episodio psicótico, no encontramos diferencias significativas entre varones y mujeres.

En un análisis posterior, en el que comparamos dos grupos (varones y mujeres) en función de la edad de inicio, observamos diferencias en sintomatología psicótica tanto en el subgrupo de varones como en el de mujeres.

Se obtienen resultados significativos en la dimensión excitativa (p = 0,015) y tendencias en la dimensión positiva (p = 0,079) de la PANSS en el grupo de los varones

TABLA 1. **Características clínicas en función de la edad de inicio del primer episodio psicótico en varones (n = 16)**

Variables	Edad de inicio del primer episodio psicótico (años)		
	< 18 años, media ± DE	> 18 años media ± DE	p
Escala de síndromes positivo y negativo			
PANSS-P	14,1 ± 7,6	21,7 ± 6,5	0,079
PANSS-N	18,1 ± 5,1	14 ± 4,8	0,080
PANSS-PG	35,1 ± 7,4	40 ± 9	0,185
Análisis factorial de la escala PANSS			
PANSS-positiva	16,6 ± 8,3	22,6 ± 8	0,101
PANSS-negativa	25,9 ± 8,5	21,8 ± 7,7	0,167
PANSS-afectiva	16,7 ± 4,6	17 ± 6,2	0,958
PANSS-excitativa	8,3 ± 3,3	14,3 ± 5	0,015*
Impresión Clínica Global (ICG-ESQ)			
ICG positivo	3,3 ± 2,3	4,7 ± 1,6	0,237
ICG negativo	3,1 ± 1,4	2,8 ± 1,1	0,616
ICG depresivo	3,1 ± 1,1	2,9 ± 1,2	0,696
ICG cognitivo	2,7 ± 1,1	3 ± 1,1	0,369
ICG global	3,9 ± 1,3	4,6 ± 1,3	0,278

DE: desviación estándar.
*p < 0,05.

TABLA 2. **Características clínicas en función de la edad de inicio del primer episodio psicótico en mujeres (n = 8)**

Variables	Edad de inicio del primer episodio psicótico (años)		
	< 18 años media ± DE	> 18 años media ± DE	p
Escala de síndromes positivo y negativo			
PANSS-P	18,7 ± 7,1	14,8 ± 4,4	0,549
PANSS-N	16,3 ± 3,1	15,6 ± 6	0,549
PANSS-PG	37,3 ± 4,2	36 ± 4,6	0,549
Análisis factorial de la escala PANSS			
PANSS-positiva	22,3 ± 6,7	19 ± 4,1	0,653
PANSS-negativa	23,7 ± 7	23 ± 7,9	0,881
PANSS-afectiva	15,3 ± 5,9	17,4 (3,7	0,549
PANSS-excitativa	11 ± 1,7	7 ± 2	0,050*
Impresión Clínica Global (ICG-ESQ)			
ICG positivo	4 ± 1	4,2 ± 1,8	0,879
ICG negativo	3 ± 1	3,4 ± 1,7	0,877
ICG depresivo	3 ± 1,7	3,8 ± 0,8	0,359
ICG cognitivo	2,7 ± 1,2	2,6 ± 0,9	1,000
ICG total	4 ± 1	4,2 ± 1,3	0,877

DE: desviación estándar.
*p < 0,05.

adultos respecto a varones adolescentes que presentan un primer episodio psicótico. Asimismo, se observan tendencias en la dimensión negativa de la PANSS (p = 0,080) en el grupo de los varones adolescentes respecto a varones adultos (tabla 1).

En el grupo de las mujeres únicamente encontramos diferencias significativas en la dimensión excitativa de la PANSS en función de la edad de inicio (p = 0,050), en sentido contrario al de los varones (tabla 2).

En ninguno de los dos grupos encontramos diferencias significativas en las dimensiones de la escala ICG-ESQ en función de la edad de inicio del primer episodio psicótico.

Por último, en un análisis realizado para conocer las diferencias significativas en sintomatología negativa en función de la edad de inicio, encontramos que los adolescentes inician el episodio con más síntomas negativos que los adultos, tanto varones como mujeres. En varones las diferencias significativas las encontramos en los siguientes ítems: PANSS N2, retraimiento emocional (p = 0,021) y PANSS N3, contacto pobre (p = 0,036); encontramos tendencias en PANSS N1, embotamiento afectivo (p = 0,068). En las mujeres no encontramos diferencias significativas en sintomatología negativa, únicamente una tendencia en PANSS N6, ausencia de espontaneidad y fluidez en la conversación (p = 0,051).

DISCUSIÓN

El hecho de que la muestra analizada esté formada por dos tercios de población masculina y un tercio de femenina concuerda con la composición por sexos que encontramos en la población de pacientes con esquizofrenia[29,30]. No obstante, sería necesario esperar la confirmación de tal diagnóstico transcurridos 6 meses de evolución de la enfermedad. La media de la edad de inicio de nuestra muestra es muy similar entre varones y mujeres, pero observamos un ligero inicio más tardío del episodio psicótico en las mujeres, tendencia que sigue la línea de otros estudios[31,32].

En la muestra incluida hasta el momento no encontramos diferencias en los síntomas psicóticos entre varones y mujeres con un primer episodio psicótico, coincidiendo con resultados encontrados en otros estudios con pacientes crónicos esquizofrénicos[21,22].

Si tenemos en cuenta la edad de inicio del episodio psicótico, encontramos patrones diferenciales de presentación sintomática de la enfermedad, tanto en el grupo de varones como en el de mujeres. Los varones adultos que inician la psicosis lo hacen con más síntomas excitativos y positivos; en cambio, en los varones adolescentes predomina la sintomatología negativa, en concreto, presentan mayor grado de embotamiento afectivo, retraimiento emocional y contacto pobre. Este patrón de inicio se suma a las evidencias encontradas en otros estudios a lo largo de los años que apoyan la hipótesis del neurodesarrollo[3,4,33]. En un estudio de Schürhoff et al[34], observaron que las formas de inicio precoz aparecen en varones, con subtipos no paranoides y alto riesgo familiar para los trastornos del espectro esquizofrénico y trastornos afectivos, y las formas de inicio tardío se daban de forma predominantemente en mujeres con subtipos paranoides y mayor probabilidad de estar casadas y con hijos.

En nuestra muestra, las mujeres presentan un predominio de sintomatología excitativa cuando el episodio psicótico se inicia en edad adolescente. No hay estudios que señalen este aspecto en pacientes adolescentes, pero es posible que estos síntomas estén relacionados con su aparición en la adolescencia, un período de riesgo de desarrollar esquizofrenia, debido a los cambios hormonales y neuroquímicos que se suceden.

Se ha intentado explicar las diferencias por sexo desde la hipótesis del neurodesarrollo, afirmando un predominio en varones con inicio precoz del episodio psicótico con síntomas negativos. No obstante, no se ha podido demostrar que este cuadro clínico sea consecuencia de alteraciones en el neurodesarrollo.

Por otro lado, el estudio de las diferencias por sexo en el campo de la psicosis ha suscitado un gran número de investigaciones. Los varones y las mujeres cuando presentan la enfermedad de la esquizofrenia presentan rasgos, características y peculiaridades propias de su sexo que tenemos que tener en cuenta, ya que éstas pueden ayudarnos a conocer más sobre las diferentes formas de inicio que tiene la enfermedad, y poder así mejorar la detección precoz.

Una de las limitaciones del estudio está relacionada con el reducido tamaño de la muestra, por lo que no resulta representativa de la población en estudio. Los resultados obtenidos son, por tanto, preliminares y no nos permiten realizar conclusiones que puedan ser generalizables.

BIBLIOGRAFÍA

1. Weinberger DR. The pathogenesis of schizophrenia: a neurodevelopmental theory. En: Nasrallah HA, Weinberger DR, editor. The Neurology of Schizophrenia. Amsterdam: Elsevier; 1986. p. 387-405.
2. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? BMJ (Clin Res Ed). 1987;295:681-2.
3. Goldstein JM, Santagelo SL, Simpson JC, Tsuang M. The role of gender in identifying subtypes of schizophrenia: a latent class analytic approach. Schizophr Bull. 1990;16:263-76.
4. Castle D, Sham P, Murray R. Differences in distribution of ages onset in males and females with schizophrenia. Schizophr Res. 1998;33:179-83.
5. Angermeyer MC, Khün L. Gender differences in age of onset of schizophrenia: an overwiew. Eur Arch Psychiatry Neurol Sci. 1988;237:351-64.
6. Goldstein JM, Tsuang MT, Faraone SV. Gender and schizophrenia: implications for understanding the nature of the disorder. Psychiatry Res. 1989;28:243-53.
7. Castle DJ, Wessely S, Murray RM. Sex and schizophrenia: effects of diagnostic stringency and associations with premorbid variables. Br J Psychiatry. 1993;162:658-62.
8. Ochoa S, Usall J, Villalta-Gil V, Vilaplana M, Márquez M, Valdelomar M, et al. Influence of age at onset on social functioning in outpatients with schizophrenia. Eur J Psychiatry. 2006;20:157-63.
9. Vázquez-Barquero JL, Cuesta Nuñez MJ, De la Varga M, Herrera Castanedo S, Gaite L, Arenal A. The Cantabria first episode schizophrenia study: a summary of general findings. Acta Psychiatr Scand. 1995;91:156-62.
10. Larsen TK, McGlashan TH, Moe LC. First-episode schizophrenia: I. Early course parameters. Schizophr Bull. 1996;22: 241-56.
11. Häfner H, An Der Heiden W, Behrens S, Gattaz WF, Hambretch M, Löffler W, et al. Causes and consequences of the gender difference in age at onset of schizophrenia. Schizoph Bull. 1998;24:99-113.
12. Folnegovic Z, Folnegovic-Smalc V. Schizophrenia in Croatia: age of onset differences between males and females. Schizophr Res. 1994;14:83-91.
13. Addington D, Addington J, Patten S. Gender and affect in schizophrenia. Can J Psychiatry. 1996;41:265-8.
14. Naqvi H, Khan MM, Faizi A. Gender differences in age of onset of schizophrenia. J Coll Physicians Surg Pak. 2005;15: 345-8.
15. Lewine RRJ. Sex differences in schizophrenia: timing or subtypes? Psychol Bull. 1981;90:432-44.
16. Walker E, Bettes BA, Kain EL, Harvey P. Relationship of gender and marital status with symptomatology in psychotic patients. J Abnorm Psychol. 1985;94:42-50.
17. Riecher-Rössler A, Häfner H. Gender aspects in schizophrenia: bridging the border between social and biological psychiatry. Acta Psychiatr Scand. 2000;102:58-62.

18. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Gur RC. Gender differences in the clinical expression of schizophrenia. Schizophr Res. 1992;7:225-31.
19. Cowell PE, Kostianovsky DJ, Gur RC, Turetsky BI, Gur RE. Sex differences in neuroanatomical and clinical correlations in schizophrenia. Am J Psychiatry. 1996;153:799-805.
20. Linström E, Von Knorring L. Symptoms in schizophrenic syndromes in relation to age, sex, duration of illnes and number of previous hospitalizations. Acta Psychiatr Scand. 1994;89:274-8.
21. Hayashi N, Igarashi Y, Yamashina M, Suda K. Is there a gender difference in a factorial structure of the positive and negative syndrom scale. Psychopathology. 2002;35:28-35.
22. Usall J, Ochoa S, Araya S, Gost A, Busquets E y grupo NEDES. Sintomatología y género en la esquizofrenia. Actas Esp Psiquiatr. 2000;28:219-23.
23. Szymanski S, Lieberman JA, Alvir JM, Mayerhoff D, Loebel A, Geisler S, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry. 1995;152:698-703.
24. Häfner H, Maurer K, Loffler W, Van der Heiden W, Munk-Jorgensen P, Hambrecht M, et al. The ABC Schizophrenia Study: a preliminary overview of the results. Soc Psychiatry Psychiatr Epidemiol. 1998;33:380-6.
25. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261-76.
26. Peralta V, Cuesta MJ. Validación de la escala de los síndromes positivo y negativo (PANSS) en una muestra de esquizofrénicos españoles. Actas Luso-Esp Neurol Psiquiatr. 1994;22:171-7.
27. Villalta-Gil V, Vilaplana M, Ochoa S, Dolz M, Usall J, Haro JM, et al. Four Symptom dimensions in outpatients with schizophrenia. Compr Psychiatry. 2006;47:384-8.
28. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl. 2003;416: 16-23.
29. Nicole L, Lesage A, Lalonde P. Lower incidence and increased male: female ratio in schizophrenia. Br J Psychiatry 1992;161:556-7.
30. Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from metaanalysis. Arch Gen Psychiatry. 2003;60:565-71.
31. Lindamer LA, Lohr JB, Harris MJ, Jeste DV. Gender, estrogen, and schizophrenia. Psychopharmacol Bull. 1997;33:221-8.
32. Salokangas RK, Honkonen T, Saarinen S. Women have later onset than men in schizophrenia —but only in its paranoid form. Results of the DSP project. Eur Psychiatry. 2003;18: 274-81.
33. Ballageer T, Malla A, Manchanda R, Takhar J, Haricharan R. Is adolescent-onset first-episode psychosis different from adult onset? J Am Acad Child Adolesc Psych. 2005;44: 782-9.
34. Schürhoff F, Goldmard JL, Szöke A, Bellivier F, Berthier A, Meary A, et al. Admixture analysis of age at onset in schizophrenia. Schizophr Res. 2004;71:35-41.

Manual of PAS-S:

Escala de Adaptación Premórbida (PAS-S)

(Versión adaptada en español. Mayo 2011)

Basada en la versión de Mastrigt & Addington (2002)

Por Ana Barajas, Susana Ochoa, Judith Usall, Iris Baños, Bernardo Sánchez, Montse Dolz, Helena Huerta, Victoria Villalta, Iria Meléndez, Janina Carlson, & Grupo GENIPE.

CIBERSAM

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

ESCALA DE ADAPTACIÓN PREMÓRBIDA (PAS-S)

Descripción

Escala diseñada **para medir el funcionamiento premórbido** en las diferentes etapas evolutivas del ciclo vital de la persona, donde "premórbido" está definido como el periodo que finaliza 12 meses antes de que haya evidencia de sintomatología psicótica franca.

PAS-S, es la versión española adaptada de la Escala de Adaptación Premórbida (PAS), la cual consta de **26 ítems** que evalúan el nivel de sociabilidad y aislamiento, el tipo de relaciones sociales, la adaptación y comportamiento escolar, así como aspectos socio-sexuales en la adolescencia y vida adulta. Estos ítems están incluidos en 4 secciones correspondientes a las siguientes etapas evolutivas: infancia (4 ítems), adolescencia temprana (5 ítems), adolescencia tardía (5 ítems) y vida adulta (3 ítems). Además, incluye una sección general (9 ítems) que valora diversos aspectos del período premórbido relacionados con el nivel educativo máximo alcanzado, el mantenimiento y rendimiento en la actividad académica ó laboral en un período justo anterior al inicio de los síntomas psicóticos, el establecimiento de la independencia, el nivel máximo de funcionamiento global, la adaptación personal y social, el grado de intereses en la vida y el nivel de energía de la persona.

Cada ítem **se puntúa de 0 a 6**, siendo las puntuaciones más elevadas indicativas de un peor funcionamiento premórbido. Por tanto, a mayor puntuación, mayor disfunción.
En la mayoría de ítems, la escala incluye una definición operativa para cada punto de anclaje con el objetivo de facilitar su valoración. La definición más apropiada y que mejor describa la situación del paciente en el período premórbido será la puntuación que el paciente recibirá en ese ítem.

Se trata de una escala **heteroaplicada**, que debe ser administrada por un clínico utilizando la **técnica de entrevista semiestructurada**. Sólo aquellos períodos de la vida que son premórbidos según la definición indicada anteriormente deberían ser evaluados, independientemente de la edad actual de la persona (por ejemplo: una persona de 39 años que tuvo su primer episodio psicótico a los 17 años no sería evaluada en la sección de adultos pero si en el resto de secciones incluyendo la sección general).

La **edad de aplicación** puede oscilar desde pacientes que se encuentran en la etapa adolescente hasta pacientes en la vida adulta (12-65 años).

Puede ser **administrada tanto al paciente como a familiares** u otros informantes cercanos al mismo (en el caso de que se considere que el paciente no es buen informante o sea necesario completar algunos ítems no contestados por el paciente), así como al clínico referente. En el caso de que la escala sea administrada a varias fuentes de información, la puntuación final será la puntuación ajustada tras tener en cuenta las puntuaciones obtenidas a través de los distintos informantes.

El **tiempo aproximado de administración** variará en función de las secciones que incluya el período premórbido. Se estima que la duración aproximada de valoración de los ítems de cada sección es de 10 minutos, excepto la sección general (15 minutos). Así, en el caso de que el período premórbido únicamente cubra la sección infantil, el tiempo de administración será de 25 minutos (10 minutos para la sección infantil y 15 minutos para la sección general). Por tanto, el tiempo de administración oscilará entre 25 y 55 minutos.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

La versión original de la escala fue diseñada por Cannon-Spoor et al. (1982) y modificada por Mastrigt y Addington (2002).

La escala ha sido traducida en varios idiomas, entre ellos: Polaco (Debowska et al., 1998), Noruego (Larsen et al., 1998), Alemán (Krauss et al., 1998), Español – versión mejicana (Lopez et al., 1996), aunque sólo ha sido validada en población alemana (Krauss et al., 1998), israelí (Brill et al., 2008), mejicana (Lopez et al., 1996) y española (Barajas et al., 2011)*.

Los diferentes análisis de componentes principales que se han realizado de esta escala han puesto de manifiesto la existencia de 2 factores subyacentes denominados: dominio académico y dominio social (Allen et al. 2001; Guerra et al. 2002; Norman et al. 2005).

BIBLIOGRAFIA:

Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Mastrigt S & Addington J. Assessment of premorbid function in first-episode schizophrenia: modifications to the Premorbid Adjustment Scale. J Psych & Neurosc. 2002; 27(2):92-101.

Debowska G, Grzywa A, Kucharska-Pietura K. Insight in paranoid schizophrenia — its relationship to psychopathology and premorbid adjustment. Comp Psychiatry 1998;39:255-60.

Larsen TK, Johannessen JO, Opjordsmoen S. First-episode schizophrenia with long duration of untreated psychosis: Pathways to care. Br J Psychiatry 1998;172:45-52.

Krauss H, Marwinski K, Held T, Rietschel M, Freyberger HJ. Reliability and validity of the premorbid adjustment scale (PAS) in a German sample of schizophreniac and schizoaffective patients. Eur Arch Psychiatry Clin Neurosci. 1998; 248:277-281.

Lopez M, Rodriguez S, Apiquian R, Paez F, Nicolini H. Translation study and validation of the Premorbid Adjustment Scale for Schizophrenia. [Spanish] Salud Mental 1996;19:24-9.

Brill N, Reichenberg A, Wieser M & Rabinowitz J. Validity of the Premorbid Adjustment Scale. Schizophr Bull. 2008; 34(5):981-983.

* Barajas A, Ochoa S, Baños I, Usall J, Dolz M, Autonell J, Sánchez B, Cervilla JA, Foix A, Obiols JE, Haro JM & group GENIPE. Spanish validation of the Premorbid Adjustment Scale. Compr Psychiatry. 2011 (sometido a publicación).

Allen DN, Kelley ME, Miyatake RK, Gurklis JA, Van Kammen DP. Confirmation of a two-factor model premorbid adjustment in males with schizophrenia. Shizophr Bull 2001;27(1):39-46.

Guerra A, Fearon P, Sham P, Jones P, Lewis S, Mata I, Murray R. The relationship between predisposing factors, premorbid function and symptom dimensions in psychosis: an integrated approach. Eur Psychiatry 2002;17(6): 311-20.

Norman RMG, Malla AK, Manchanda R, Townsend L. Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains. Acta Psychiatr Scand 2005;112:30-9.

Modificaciones incluidas en la adaptación española:

La Escala de Adaptación Premórbida adaptada y validada en la población española (PAS-S) incluye las siguientes modificaciones respecto a la versión original, que han sido recogidas de la versión publicada por Mastrigt & Addington (2002):

- Tiempo de fin del período premórbido hasta **12 meses** previos al inicio de los síntomas psicóticos francos, en lugar de hasta los 6 meses que indica la versión original, con el objetivo de evitar valorar en el período premórbido sintomatología prodrómica en episodios de inicio insidioso.

- Todos los ítems de la **sección general** serán valorados en relación al período premórbido, no en relación a la situación actual.

- Inclusión de definiciones en algunos **puntos de anclaje**, que no incluye la versión original, con la finalidad de facilitar y objetivar la puntuación en algunos ítems.

- **Adaptación** de algunos ítems a la situación socio-educativa-laboral actual, en el contexto cultural de la sociedad española:

    - Adaptación del ítem de nivel educativo al sistema educativo español actual.
    - En los ítems que valoran el funcionamiento socio-sexual se valorará del mismo modo las relaciones homosexuales y heterosexuales.
    - Se valora de forma equivalente el matrimonio y la convivencia con pareja estable.
    - El ítem de independencia no será valorado en población adolescente o en estudiantes. No se considerará como disfuncional el no haber establecido la independencia familiar si se es económicamente independiente y no ha habido intentos previos sin éxito.

- Se recomienda que la **puntuación de la sección general** se incluya en el cálculo de la puntuación total de la escala en el caso de un grupo de pacientes con las mismas secciones valoradas. De ese modo, la sección general tendrá un peso equivalente en la puntuación total de la escala. En caso contrario, se recomienda no incluirla en la estimación de la puntuación total de la escala.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Instrucciones de aplicación:

En primer lugar, con la finalidad de determinar si una sección específica debe puntuarse, se debe identificar el período premórbido. Para ello se ha de indicar previamente la fecha de inicio de los síntomas psicóticos a partir de la información registrada en la historia clínica o a través de la información facilitada por el paciente u otros informantes entrevistados. Posteriormente, se deberá indicar el período premórbido, cuyo marco temporal abarca hasta los 12 meses antes del inicio de los primeros síntomas psicóticos.

Una vez identificado el período premórbido se valorarán aquellas etapas evolutivas que cubran tal período y por último se puntuará la sección general, siendo esta última valorable en todos los casos (excepto en pacientes adolescentes, en los que el ítem de independencia no será valorado), todo ello a través de una entrevista semiestructurada.

Indicar la fuente de información: (persona/s a la/s que se le/s realizará la entrevista)

PACIENTE: ☐

FAMILIAR: ☐

CLÍNICO: ☐

OTROS: ☐ (especificar): _____

Antes de iniciar la entrevista completar los siguientes datos:
(a través de la historia clínica, clínico referente, paciente, familiares u otras fuentes de información fiables)

Inicio de los primeros síntomas psicóticos: _____años

*** Período premórbido a evaluar:** hasta la edad de _____ años

*Período que finaliza 12 meses antes de la presencia de síntomas psicóticos francos.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

INFANCIA (hasta los 11 años) SECCIÓN NO APLICABLE ☐

1 SOCIABILIDAD E INTROVERSIÓN

0 No introversión. Busca activa y frecuentemente el contacto social.
1
2 Ligera introversión. Disfruta de la socialización cuando se le implica. Ocasionalmente busca oportunidades para socializarse.
3
4 Introversión moderada.Tendencia a soñar despierto y a ser excesivamente fantasioso. Podría admitir ser incluido pasivamente en una relación con otras personas, pero sin buscarla.
5
6 Introversión. Aislamiento. No se relaciona con los demás. Evita el contacto.

2 RELACIÓN CON COMPAÑEROS

0 Relación con muchos amigos (más de 5). Relaciones cercanas con algunos (con "los mejores amigos" o personas en las que puede confiar).
1 Relación con 2-5 amigos.
2 Relación cercana con pocos amigos (1-2 amigos). Amistad menos cercana con otros.
3 Únicamente relaciones poco cercanas.
4 Patrones de amistad desviados: amistad sólo con más pequeños o mayores que él, o sólo con familiares, o sólo relaciones poco cercanas.
5
6 Ausencia de relaciones con otros. Aislamiento social. No tiene amigos, ni siquiera relaciones superficiales.

3 RENDIMIENTO ESCOLAR

0 Estudiante brillante (con excelentes).
1 Buen estudiante (con excelentes y notables).
2 Buen estudiante (con notables).
3 Estudiante medio (con notables y aprobados).
4 Estudiante aceptable (con aprobados).
5 Estudiante que suspende algunas asignaturas.
6 Estudiante que suspende todas las asignaturas.

4 ADAPTACIÓN ESCOLAR

0 Buena adaptación. Disfruta en la escuela. No hay problemas de comportamiento importantes. Tiene amigos en la escuela. Le gustan la mayoría de los profesores.
1 Ídem al apartado anterior pero con ocasionales problemas de comportamiento.
2 Adaptación aceptable. Problemas ocasionales de comportamiento. No está muy interesado en la escuela, pero no hace novillos o raramente. Tiene amigos en la escuela pero no participa a menudo en actividades extraescolares.
3 Ídem al apartado anterior pero hace novillos con mayor frecuencia.
4 Pobre adaptación. No le gusta la escuela. Hace frecuentemente novillos. Tiene frecuentes problemas de comportamiento.
5 Ídem al apartado anterior pero añade que ha sido expulsado de la escuela en alguna ocasión.
6 Rechaza todo lo que tenga que ver con la escuela. Delincuencia o vandalismo dirigido contra la escuela.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

ADOLESCENCIA (Temprana: 12-15 años)

SECCIÓN NO APLICABLE ☐

1 SOCIABILIDAD E INTROVERSION

0 No introversión. Busca activa y frecuentemente el contacto social.
1
2 Ligera introversión. Disfruta de la socialización cuando se le implica. Ocasionalmente busca oportunidades para socializarse.
3
4 Introversión moderada.Tendencia a soñar despierto y a ser excesivamente fantasioso. Podría admitir ser incluido pasivamente en una relación con otras personas, pero sin buscarla.
5
6 Introversión. Aislamiento. No se relaciona con los demás. Evita el contacto.

2 RELACIÓN CON COMPAÑEROS

0 Relación con muchos amigos (más de 5). Relaciones cercanas con algunos (con "los mejores amigos" o personas en las que puede confiar).
1 Relación con 2-5 amigos.
2 Relación cercana con pocos amigos (1-2 amigos). Amistad menos cercana con otros.
3 Únicamente relaciones poco cercanas.
4 Patrones de amistad desviados: amistad sólo con más pequeños o mayores que él, o sólo con familiares, o sólo relaciones poco cercanas.
5
6 Ausencia de relaciones con otros. Aislamiento social. No tiene amigos, ni siquiera relaciones superficiales.

3 RENDIMIENTO ESCOLAR

0 Estudiante brillante (con excelentes).
1 Buen estudiante (con excelentes y notables).
2 Buen estudiante (con notables).
3 Estudiante medio (con notables y aprobados).
4 Estudiante aceptable (con aprobados).
5 Estudiante que suspende algunas asignaturas.
6 Estudiante que suspende todas las asignaturas.

4 ADAPTACIÓN ESCOLAR

0 Buena adaptación. Disfruta en la escuela. No hay problemas de comportamiento importantes. Tiene amigos en la escuela. Le gustan la mayoría de los profesores.
1 Ídem al apartado anterior pero con ocasionales problemas de comportamiento.
2 Adaptación aceptable. Problemas ocasionales de comportamiento. No está muy interesado en la escuela, pero no hace novillos o raramente. Tiene amigos en la escuela pero no participa a menudo en actividades extraescolares.
3 Ídem al apartado anterior pero hace novillos con mayor frecuencia.
4 Pobre adaptación. No le gusta la escuela. Hace frecuentemente novillos. Tiene frecuentes problemas de comportamiento.
5 Ídem al apartado anterior pero añade que ha sido expulsado de la escuela en alguna ocasión.
6 Rechaza todo lo que tenga que ver con la escuela. Delincuencia o vandalismo dirigido contra la escuela.

5. ASPECTOS SOCIO-SEXUALES (homosexuales o heterosexuales) DE LA VIDA DURANTE LA ADOLESCENCIA TEMPRANA

0 Se han dado las primeras citas. Muestra un "sano interés" por las relaciones socio-sexuales. Puede haber tenido ó tiene una relación "formal" (puede haber iniciado actividad sexual).

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

1 Interés por los otros. Interesado en las relaciones socio-sexuales, sin embargo, no mantiene relaciones cercanas ó flirteos.
2 Interés restringido en las relaciones socio-sexuales.
3 Interés restringido en las relaciones socio-sexuales con intentos inadecuados por relacionarse. Contactos casuales con chicos/as.
4 Ausencia de interés por las relaciones socio-sexuales.
5 Solitario. Ausencia o escasos contactos con chicos/as.
6 Antisocial. Evita y es evitado por los compañeros/as. (A diferencia del apartado anterior, la persona evita activamente a los demás; no se trata de un aislamiento pasivo).

ADOLESCENCIA (Tardía: 16-18 años)

SECCIÓN NO APLICABLE ☐

1 SOCIABILIDAD E INTROVERSIÓN

0 No introversión. Busca activa y frecuentemente el contacto social.
1
2 Ligera introversión. Disfruta de la socialización cuando se le implica. Ocasionalmente busca oportunidades para socializarse.
3
4 Introversión moderada.Tendencia a soñar despierto y a ser excesivamente fantasioso. Podría admitir ser incluido pasivamente en una relación con otras personas, pero sin buscarla.
5
6 Introversión. Aislamiento. No se relaciona con los demás. Evita el contacto.

2 RELACIÓN CON COMPAÑEROS

0 Relación con muchos amigos (más de 5). Relaciones cercanas con algunos (con "los mejores amigos" o personas en las que puede confiar).
1 Relación con 2-5 amigos.
2 Relación cercana con pocos amigos (1-2 amigos). Amistad menos cercana con otros.
3 Únicamente relaciones poco cercanas.
4 Patrones de amistad desviados: amistad sólo con más pequeños o mayores que él, o sólo con familiares, o sólo relaciones poco cercanas.
5
6 Ausencia de relaciones con otros. Aislamiento social. No tiene amigos, ni siquiera relaciones superficiales.

3 RENDIMIENTO ESCOLAR

0 Estudiante brillante (con excelentes).
1 Buen estudiante (con excelentes y notables).
2 Buen estudiante (con notables).
3 Estudiante medio (con notables y aprobados).
4 Estudiante aceptable (con aprobados).
5 Estudiante que suspende algunas asignaturas.
6 Estudiante que suspende todas las asignaturas.

4 ADAPTACIÓN ESCOLAR

0 Buena adaptación. Disfruta en la escuela. No hay problemas de comportamiento importantes. Tiene amigos en la escuela. Le gustan la mayoría de los profesores.
1 Ídem al apartado anterior pero con ocasionales problemas de comportamiento.
2 Adaptación aceptable. Problemas ocasionales de comportamiento. No está muy interesado en la escuela, pero no hace novillos o raramente. Tiene amigos en la escuela pero no participa a menudo en actividades extraescolares.
3 Ídem al apartado anterior pero hace novillos con mayor frecuencia.
4 Pobre adaptación. No le gusta la escuela. Hace frecuentemente novillos. Tiene frecuentes

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

problemas de comportamiento.

5 Ídem al apartado anterior pero añade que ha sido expulsado de la escuela en alguna ocasión.

6 Rechaza todo lo que tenga que ver con la escuela. Delincuencia o vandalismo dirigido contra la escuela.

5 ASPECTOS SOCIO-SEXUALES (homosexuales y heterosexuales) DE LA VIDA DURANTE LA ADOLESCENCIA TARDÍA:

0 Muestra un "sano interés" por las relaciones socio-sexuales. Ha tenido citas. Puede haber tenido (ó tiene) una relación "estable". Puede haber iniciado actividad sexual.

1 Sólo ha tenido (o tiene) una única relación "estable" durante un largo período de tiempo.

2 Relaciones cercanas con chicos/as (Implica ser miembro de un grupo, con interés en relacionarse con los otros pero no en tener una relación de pareja).

3 Interés restringido por las relaciones socio-sexuales.

4 Intentos inadecuados por iniciar relaciones socio-sexuales. Contactos casuales con chicos/as.

5 Ausencia de interés por las relaciones socio-sexuales.

6 No quiere estar con chicos/as. Nunca ha iniciado una relación de pareja.

EDAD ADULTA (A partir de los 19 años)

SECCIÓN NO APLICABLE ☐

1 SOCIABILIDAD E INTROVERSIÓN

0 No introversión. Busca activa y frecuentemente el contacto social.

1

2 Ligera introversión. Disfruta de la socialización cuando se le implica. Ocasionalmente busca oportunidades para socializarse.

3

4 Introversión moderada.Tendencia a soñar despierto y a ser excesivamente fantasioso. Podría admitir ser incluido pasivamente en una relación con otras personas, pero sin buscarla.

5

6 Introversión. Aislamiento. No se relaciona con los demás. Evita el contacto.

2 RELACIÓN CON COMPAÑEROS

0 Relación con muchos amigos (más de 5). Relaciones cercanas con algunos (con "los mejores amigos" o personas en las que puede confiar).

1 Relación con 2-5 amigos.

2 Relación cercana con pocos amigos (1-2 amigos). Amistad menos cercana con otros.

3 Únicamente relaciones poco cercanas.

4 Patrones de amistad desviados: amistad sólo con más pequeños o mayores que él, o sólo con familiares, o sólo relaciones poco cercanas.

5

6 Ausencia de relaciones con otros. Aislamiento social. No tiene amigos, ni siquiera relaciones superficiales.

3 ASPECTOS SOCIO-SEXUALES (homosexuales o heterosexuales) DE LA VIDA DEL ADULTO:

A **CASADO O CONVIVIENDO CON PAREJA ESTABLE (en el pasado o actualmente):**

0 Casado ó conviviendo con pareja estable, sólo un matrimonio/pareja estable (o vuelto a casar/u otra pareja estable como consecuencia de la muerte del cónyuge/pareja). Vida en común. Relaciones sexuales adecuadas.

1 Actualmente casado o conviviendo con pareja estable, con historia de bajo apetito sexual. Períodos de dificultad en las relaciones sexuales o de relaciones extramatrimoniales/infidelidades.

1 Casado más de una vez ó más de una pareja estable (con convivencia). En la actualidad vuelto a casar ó nueva pareja estable (con convivencia). Relaciones sexuales adecuadas durante al menos un matrimonio ó pareja estable (con convivencia).

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

2 Casado ó en convivencia con pareja estable (ó divorciado/separado) y vuelto a casar o emparejar, con una vida sexual inadecuada.
2 Casado o en convivencia con pareja estable y aparentemente separado o divorciado de forma permanente sin volverse a casar ó emparejar, pero mantuvo un hogar en común por lo menos durante 3 años.
3 Como en el caso anterior pero el divorcio/separación ocurrió hace más de 3 años, y mientras estuvo casado/o viviendo en pareja, mantuvo un hogar durante menos de 3 años.

B NUNCA HA ESTADO CASADO O NUNCA HA TENIDO PAREJA ESTABLE Y TIENE MAS DE 30 AÑOS:

2 Ha estado comprometido una o dos veces o ha tenido relación estable (de al menos 2 años). Con relaciones de pareja, o evidencia aparente de una aventura con una persona, pero es incapaz de conseguir un compromiso a largo plazo como el matrimonio o la convivencia con una pareja.
3 Relaciones de pareja estables con una duración de más de 6 meses pero menos de 2 años.
4 Relaciones de corta duración con una o más parejas pero no una relación sexual duradera con una pareja.
5 Relaciones socio-sexuales escasas e infrecuentes.
6 Mínimo interés en relaciones socio-sexuales. Aislado.

C NUNCA HA ESTADO CASADO O NUNCA HA TENIDO PAREJA ESTABLE Y TIENE ENTRE 19-29 AÑOS:

0 Ha tenido al menos una relación estable (mínimo de 6 meses) o un compromiso. Pueden haber vivido juntos.
1 Ha tenido iniciativa para tener citas. Ha tenido varios "novios/as". Algunas relaciones han durado algunos meses pero no son relaciones estables. Relaciones incluso con un compromiso a largo plazo, sin intención de casarse o formalizar la relación.
3 Relaciones de corta duración o "aventuras" con una o más parejas, pero no relaciones duraderas con una única pareja.
4 Relaciones socio-sexuales ocasionales sin lazos emocionales estrechos.
5 Relaciones socio-sexuales escasas o infrecuentes.
6 Mínimo interés en relaciones socio-sexuales. Aislado.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

GENERAL

SECCIÓN NO VALORADA ☐

1 EDUCACION:

0 Educación universitaria finalizada o equivalente.
1 Bachillerato finalizado y algún curso universitario o formación profesional, o equivalente.
2 Bachillerato finalizado (hasta 2º de bachillerato) o equivalente.
3 E.S.O. finalizada (hasta 4º de E.S.O) o equivalente
4 E.S.O. incompleta (hasta 2º de E.S.O) o equivalente
5 Estudios primarios alcanzados (hasta 6º de primaria) o equivalente.
6 Estudios primarios (o equivalente) no alcanzados.

2 DURANTE UN PERIODO DE 3 AÑOS QUE FINALIZA 12 MESES ANTES DE LA 1ª HOSPITALIZACIÓN O DEL INICIO DEL 1er EPISODIO, EL PACIENTE TENIA UN TRABAJO REMUNERADO O RENDÍA ADECUADAMENTE EN EL COLEGIO:

0 Todo el tiempo.
1
2 La mitad del tiempo, aproximadamente el 50% del tiempo.
3
4 Poco tiempo, aproximadamente el 25% del tiempo.
5
6 Nunca.

3 DURANTE UN PERÍODO DE 1 AÑO QUE FINALIZA 12 MESES ANTES DE LA 1ª HOSPITALIZACIÓN O DEL INICIO DEL 1er EPISODIO HA OCURRIDO ALGUN CAMBIO EN EL RENDIMIENTO EN EL TRABAJO O EN LA ESCUELA:

0 Deterioro repentino, brusco.
1
2 Progresivo deterioro durante 3 meses.
3
4 Progresivo deterioro durante 6 meses.
5
6 Es difícil o imposible de determinar el inicio del deterioro.

4 DURANTE UN PERIODO DE 3 AÑOS QUE FINALIZA 12 MESES ANTES DE LA 1ª HOSPITALIZACIÓN O DEL INICIO DEL 1er EPISODIO, CON FRECUENCIA HA CAMBIADO DE TRABAJO, SI TRABAJÓ, O CON FRECUENCIA HA INTERRUMPIDO LA ASISTENCIA A LA ESCUELA:

0 Ha mantenido el mismo trabajo o ha asistido a la escuela de forma continua.
1
2 Ha cambiado de trabajo o ha habido ausencias escolares en 2 o 3 ocasiones.
3
4 Ha permanecido en el mismo trabajo más de 8 meses pero menos de 1 año, o ha asistido a la escuela con regularidad durante el mismo período de tiempo.
5
6 Menos de 2 semanas en el mismo trabajo o en el colegio.

5 ESTABLECIMIENTO DE LA INDEPENDENCIA (no valorable en menores de 18 años o estudiantes)

0 Ha conseguido establecer un hogar fuera del domicilio familiar; independencia económica de los padres. O bien, vive en casa de los padres y paga a los padres la habitación y la manutención. Por lo demás, es económicamente independiente.
2 Realiza intentos, sin éxito, para establecerse en un hogar independiente. Económicamente

independiente.

4 Ídem al anterior pero no es económicamente independiente. Vive en casa de los padres y recibe una paga de los padres. La persona se administra para pagar sus actividades de ocio, ropa, etc.

6 No hace intentos para dejar el hogar o ser económicamente independiente.

6 EVALUACIÓN GLOBAL DEL NIVEL MÁS ALTO DE FUNCIONAMIENTO ALCANZADO EN LA VIDA DEL PACIENTE

0 Completamente capaz de funcionar con éxito y disfrutar con el: (1) colegio o trabajo, (2) amigos, (3) relaciones sexuales íntimas, (4) iglesia, aficiones… Disfruta de la vida y la afronta bien.

2 Es capaz de funcionar bien y disfrutar de algunas áreas de la vida, pero tiene una falta clara de éxito en el funcionamiento de al menos un área.

4 Éxito y placer escaso en 3 áreas de la vida.

6 Incapaz de disfrutar en cualquiera de las áreas de la vida.

7 ADAPTACION SOCIO-PERSONAL:

0 Líder de grupos organizados formalmente (por ej. de equipos deportivos universitarios). Tiene relaciones cercanas e íntimas con otros.

1 Participante activo e interesado, pero no tiene un papel de líder en el grupo de amigos, o en el grupo formalmente organizado, pero tiene relaciones cercanas con otros.

2 Miembro del grupo formal que no tiene implicación o compromiso con el resto del grupo. Ha tenido relaciones cercanas con pocos amigos.

3 Desde la adolescencia y durante la edad adulta temprana ha tenido pocos y casuales amigos.

4 Desde la adolescencia y durante la edad adulta temprana no ha tenido amigos reales, sólo relaciones superficiales.

5 Desde la adolescencia y durante la edad adulta temprana (es decir, después de la infancia), se muestra tímido, aislado (poco sociable), ha preferido estar solo, realizando el mínimo esfuerzo para mantener algún contacto con otros.

6 No quiere estar con sus compañeros u otros. Asocial o antisocial.

8 GRADO DE INTERES EN LA VIDA:

0 Entusiasmo, ambición, interés en el futuro: casa, familia, amigos, trabajo, deportes, arte, animales, jardinería, actividades sociales, música, teatro, etc.

2 Interés moderado en algunas actividades incluyendo reuniones sociales, deportes, música, entre otras.

4 Ligero interés en algunas áreas relacionadas con, por ejemplo, el trabajo, la familia, reuniones sociales reducidas. Apenas puede mantener el interés.

6 Aislado e indiferente hacia los intereses de la vida. No tiene interés por nada.

9 NIVEL DE ENERGIA:

0 Energía adecuada. Entusiasta, activo, alerta, interesado en la vida. Le gusta la vida y tiene energía suficiente para disfrutar de ella. Extrovertido y sin problemas para afrontar la vida.

2 Energía moderadamente adecuada/aceptable. Enérgico, interesado (como se ha descrito anteriormente).

4 Energía moderadamente inadecuada. Tendencia hacia reacciones sumisas y pasivas. Muestra algo de potencial para plantar cara a los problemas de la vida pero le gustaría evitarlos.

6 Reacciones sumisas, inadecuadas, pasivas. Escaso control de la vida, no se enfrenta a los problemas de su vida, no participa activamente. Pasivamente acepta su suerte sin tener la energía para ayudarse a sí mismo.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Puntuación

Los ítems son puntuados entre 0 y 6. Si es imposible evaluar un ítem éste debería estar marcado como N/A (no aplicable) en la hoja de puntuación. La puntuación posible indica la puntuación más alta que puede ser obtenida por la suma de la puntuación máxima de todos los ítems completados; la puntuación alcanzada se consigue sumando las puntuaciones obtenidas en cada uno de los ítems de cada sección. La puntuación total de cualquiera de las secciones está expresada como una puntuación alcanzada divida por la puntuación posible para los ítems evaluados. Por ejemplo: si una persona recibe puntuaciones de 2, 3, 3 y 2 para los 4 ítems de la sección Infancia la puntuación alcanzada es de 10. La puntuación posible es 6+6+6+6=24. La puntuación alcanzada divida por la puntuación posible es 0,42. Si solo 3 ítems se pudieron evaluar entonces la puntuación posible sería de 18 (6+6+6), la puntuación alcanzada sería de 8 (2+3+3) y la puntuación total de la sección sería de 0,44).

La **puntuación total de la escala** se obtiene con el promedio de todas las puntuaciones totales de cada sección.

Las descripciones que incluye cada ítem son únicamente pautas por lo que paciente no tiene que cumplir todos los criterios ofrecidos por un **punto de anclaje** determinado para recibir la puntuación asignada al mismo. Por ejemplo, en el ítem 1 (sociabilidad e introversión) en el punto de anclaje dado por una puntuación de 4, el paciente debe mostrar introversión moderada. Los tipos de comportamiento que pueden estar presentes por un individuo que recibiría una puntuación de 4 serían soñar despierto y ser excesivamente fantasioso. Uno de estos comportamientos sería suficiente para puntuar, a no ser que la gravedad sea mayor y una definición de un punto de anclaje mayor se ajuste más a la situación del paciente.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Tabla resumen de puntuaciones:

Puntuaciones directas:

	INFANCIA				ADOL. TEMPRANA				ADOL. TARDÍA				VIDA ADULTA			
	P	F	C	O	P	F	C	O	P	F	C	O	P	F	C	O
SOC E INTROV.																
REL. COMPAÑ.																
REND. ESCOLAR																
ADAPT. ESCOLAR																
SOCIO-SEXUAL																

	SECCION GENERAL			
	P	F	C	O
EDUCACIÓN				
OCUPACIÓN				
REND. LABORAL/ESCOLAR				
CAMBIO DE TRABAJO/ESCUELA				
ESTABLECIMIENTO DE INDEPEND.				
FUNCIONAM. GLOBAL				
ADAPT. SOCIO-PERSONAL				
INTERESES EN LA VIDAD				
ACTIVIDAD/ "ENERGÍA"				

Fuente de información:
P= PACIENTE
F= FAMILIAR
C= CLÍNICO
O= OTROS

En el caso de tener más de una fuente de información, y por tanto, tener más de una puntuación en los distintos ítems de la escala, se tendrá que calcular la puntuación única (ajustada).

La puntuación única de cada ítem corresponderá a la puntuación ajustada calculada teniendo en cuenta las respuestas de cada informante y su fiabilidad. Será decisión del investigador en función de la información reportada por cada informante.

En el caso de disponer la información de una única fuente de información, las puntuaciones directas corresponderán a las puntuaciones ajustadas.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Puntuaciones directas ajustadas

	INFANCIA	ADOL. TEMPRANA	ADOL. TARDÍA	VIDA ADULTA
	PUNT. AJUSTADA	PUNT. AJUSTADA	PUNT. AJUSTADA	PUNT. AJUSTADA
SOC E INTROV.				
REL. COMPAÑ.				
REND. ESCOLAR				
ADAPT. ESCOLAR				
SOCIO-SEXUAL				

	SECCION GENERAL
	PUNT. AJUSTADA
EDUCACIÓN	
OCUPACIÓN	
REND. LABORAL/ESCOLAR	
CAMBIO DE TRABAJO/ESCUELA	
ESTABLECIMIENTO DE INDEPEND.	
FUNCIONAM. GLOBAL	
ADAPT. SOCIO-PERSONAL	
INTERESES EN LA VIDAD	
ACTIVIDAD/ “ENERGÍA”	

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Corrección:

ÁREAS (ítems)	INFANCIA	ADOL. TEMPRANA	ADOL. TARDIA	VIDA ADULTA
SOCIABILIDAD E INTROVERSIÓN	(/6)	(/6)	(/6)	(/6)
	+	+	+	+
RELACIÓN COMPAÑEROS	(/6)	(/6)	(/6)	(/6)
	+	+	+	+
RENDIMIENTO ESCOLAR	(/6)	(/6)	(/6)	######
	+	+	+	
ADAPTACIÓN ESCOLAR	(/6)	(/6)	(/6)	######
		+	+	+
SOCIO-SEXUAL	######	(/6)	(/6)	(/6) ó (/3)*
TOTAL	Suma de la punt. en cada ítem/nªde ítems en los que puntúa (si puntúa en todos se divide entre 4)	Suma de la punt. en cada ítem/nªde ítems en los que puntúa (si puntúa en todos se divide entre 5)	Suma de la punt. en cada ítem/nªde ítems en los que puntúa (si puntúa en todos se divide entre 5)	Suma de la punt. en cada ítem/nªde ítems en los que puntúa (si puntúa en todos se divide entre 3)

*En el caso de que el ítem correspondiente a puntuar sea el 3A en la etapa adulta.

Puntuación total en Infancia = ((infsoc/6) + (infrel/6) + (infrend/6) + (infadap/6))/4 .

Puntuación total en Adolescencia I = ((adolsoc/6) + (adolrel/6) + (adolrend/6) + (adoladp/6) + (adolsex/6))/5 .

Puntuación total en Adolescencia II = ((adol2soc/6) + (adol2rel/6) + (ado2rend/6) + (ado2adap/6) + (ado2sex/6))/5 .

Puntuación total en Vida Adulta = ((adusoc/6) + (adurel/6) + [(adusexa/3) ó (adusexb/6) ó (adusexc/6)])/3 .

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

ÁREAS (ítems)	SECCIÓN GENERAL
EDUCACIÓN	(/6)
	+
OCUPACIÓN	(/6)
	+
RENDIMIENTO LABORAL/ESCOLAR	(/6)
	+
CAMBIO DE TRABAJO/ESCUELA	(/6)
	+
ESTABLECIMIENTO DE INDEPENDENCIA	(/6)
	+
FUNCIONAMIENTO GLOBAL	(/6)
	+
ADAPTACIÓN SOCIO-PERSONAL	(/6)
	+
INTERESES EN LA VIDA	(/6)
	+
ACTIVIDAD/"ENERGIA"	(/6)
TOTAL	**Suma de la punt. en cada ítem/nªde ítems en los que puntúa** (si puntúa en todos se divide entre 9)

Puntuación total en la Sección General = ((genedu / 6) + (genetreb / 6) + (generend / 6) + (genecanv / 6) + (geneind / 6) + (genefunc / 6) + (geneadp / 6) + (geneint / 6) + (geneactv / 6))/9 .

PUNTUACIÓN TOTAL = ((Punt. total en Infancia) + (Punt. total en Adolesc.I) + (Punt. total en Adolesc.II) + (Punt. total en Vida Adulta) +(Punt. total en Sección General))/5 .

Nota: en el caso de no tener en cuenta la sección general, no se sumaría su puntuación total y se dividiría por 4.

Versión original en: Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470-484.

Errata Sheet:

Errata Sheet:

STUDY 1: Barajas, A., Ochoa, S., Baños, I., Dolz, M., Villalta-Gil, V., Vilaplana, M., ... Usall, J. (2013). Spanish validation of the Premorbid Adjustment Scale (PAS-S). *Comprehensive Psychiatry*, 54(2), 187-194. doi: 10.1016/j.comppsych.2012.07.007

Error (page)	Correction
"adult and general subscales must be reviewed, because the most common modifications to the PAS reported in the literature are not included them" (p. 193)	"adult and general subscales must be reviewed, because the most common modifications to the PAS reported in the literature are excluded from these subscales"

STUDY 3: Barajas, A., Ochoa, S., Obiols, J.E., & Lalucat-Jo Ll. (2015). Gender differences in individuals at high-risk of psychosis: A comprehensive literatura review. *The Scientific World Journal*, 2015, Article ID 430735, 1-13. doi:10.1155/2015/430735

Error (page)	Correction
"The conversion rate to psychosis was 22.95% in the three-year follow-up period without gender statistical gender differences (22.5% men versus 23.8% women)" (Table 1, p. 3)	"The conversion rate to psychosis was 22.95% in the three-year follow-up period without statistical gender differences (22.5% men versus 23.8% women)"
"On the other hand, there are suggestions that deficits in social functioning are often predictors of later social functioning [66]. Besides, prior findings have indicated that social and role (school/work) functioning are key predictors of conversion among UHR youth [67, 68]" (p. 9)	"On the other hand, there are suggestions that deficits in social functioning are often predictors of later social functioning [66]. Besides, recent findings have indicated that social and role (school/work) functioning are key predictors of conversion among UHR youth [67, 68]"

STUDY 5: Barajas, A., Baños, I., Ochoa, S., Usall, J., Huerta, E., Dolz, M., ... Grupo GENIPE. (2010). Gender differences in incipient psychosis. *The European Journal of Psychiatry*, 24(3), 176-194. doi: 10.4321/S0213-61632010000300006

Error (page)	Correction
"although the average number of days was higher in men and than in women" (p. 184)	"although the average number of days was higher in men than in women"
"*Fisher's Exact Test* p = " (p. 185)	"*Fisher's Exact Test* p = 0.225"
"In patients younger than 18 years, signficant differences in PF during early adolescent stage was observed (U = 38.0, p = 0.013), with males showing lower scores" (p. 186)	"In patients younger than 18 years, significant differences in PF during early adolescent stage were observed (U = 38.0, p = 0.013), with males showing higher scores"
"Instead, the group of younger men had worse dysfunctional language than women before the onset of psychotic episode"(p. 190)	"Instead, the group of older men had worse dysfunctional language than women before the onset of psychotic episode"
"No significant differences in gender were observed with respect to onset of the psychotic episode" (p. 191)	"No significant gender differences were observed with respect to age at onset of the psychotic episode"
"Finally, the absence of a control for pharmacological treatment group could influence the analysis of certain variables as well as the symptoms after 8 weeks of evolution of the episode or cognitive functioning " (p. 191)	"Finally, the absence of control for pharmacological treatment could influence the analysis of certain variables, such as severity of symptoms 8 weeks after the onset of FEP or cognitive functioning"

CURRICULUM VITAE

Curriculum vitae

ACADEMIC BACKGROUND

Present:	Currently developing a doctoral thesis by publications. PhD programme in Psychopathology of the Child, Adolescent and Adult. Department of Clinical and Health Psychology. School of Psychology. Autonomous University of Barcelona. Thesis title: *"Premorbid and prodromal functioning as predictors at onset of psychosis: a first-episode study".*
September 2012	COPC (Col·legi Oficial de Psicòlegs de Catalunya) accreditation in specific training for non-specialized psychologist in clinical psychology.
2009 – 2010	Graduate certificates in *Multivariate analysis: regression models,* included in the Master's Degree in *Methodology of Research in Health Sciences*. Autonomous University of Barcelona.
2008 – 2009	Graduate certificates in *Development and Adaptation of Questionnaires in the field of health,* included in the Master's Degree in *Methodology of Research in Health Sciences*. Autonomous University of Barcelona.
July 2008	Certificate of Advanced Studies (DEA) in Personality, Evaluation and Psychological Treatment. PhD programme in Psychopathology of the Child, Adolescent and Adult. Department of Clinical and Health Psychology. School of Psychology. Autonomous University of Barcelona.
2007 – 2009	Master's Degree in *Childhood Clinical Psychopathology.* Autonomous University of Barcelona.
2005 – 2007	Master's Degree in *Adult Clinical Psychopathology.* Autonomous University of Barcelona.
2004 – 2006	Diploma of Higher Specialized Studies. PhD program "Clinical Psychology for Infancy, Adolescence and Adults". Autonomous University of Barcelona.
March 2001:	Pedagogical Aptitude Certificate (CAP). University of Barcelona.
1996 – 2001	Degree in Psychology (Clinical speciality). University of Barcelona.

ADDITIONAL TRAINING

⇒ **Seminars, courses, workshops:**

June 2014:	Course – "Historia Clínica Compartida (HCC3)" (2h). Associació Centre d'Higiene Mental Les Corts.
May 2014:	Workshop – "Actualització dels Programes d'Atenció Específica a la Psicosi Incipient: l'experiència de Birmingham" (2h). Parc Sanitari Sant Joan de Déu i Departament de Salut. Generalitat de Catalunya (Barcelona, Spain).

April 2014: Course – "*Curso de Formación en la Aplicación del Programa de Rehabilitación Cognitiva en Psicosis: REHACOP*" (8h). Universidad de Deusto (Bilbao, Spain).

November 2013: Workshop – "*III Workshop Recerca en Salut Mental i Dona*" (3.5h). Grup de Treball i Recerca en Salut Mental de la Societat Catalana de Psiquiatría i Salut Mental (Barcelona, Spain).

Oct 2012-May 2013: Course – "*Curs d'Entrenament Meta-cognitiu per a pacients amb Psicosi Incipient*" (12h). Centre d'Higiene Mental Les Corts, cofinanced by Fondo Social Europeo (Barcelona, Spain).

May 2012: Workshop – "*V Workshop de la Biblioteca de Instrumentos en Salud Mental i Discapacidad*" (10h). Parc Sanitari Sant Joan de Déu (Sant Boi de Llobregat, Barcelona, Spain).

March 2012: Course – "*Entrenament en les escales d'avaluació del Programa de Metacognició.*" Parc Sanitari Sant Joan de Déu (Sant Boi de Llobregat, Barcelona, Spain).

March 2012: Course – "*Entrenament Metacognitiu (EMC) com a tractament per a persones amb esquizofrènia i primers episodis psicòtics.*" Parc Sanitari Sant Joan de Déu (Sant Boi de Llobregat, Barcelona, Spain).

November 2011: Workshop – "*II Workshop Recerca en Salut Mental i Dona*" (3.5h). Grup de Treball i Recerca en Salut Mental de la Societat Catalana de Psiquiatría i Salut Mental (Barcelona, Spain).

May 2011: Course – "*Curs de reconeixement dels pròdroms del trastorn bipolar*" (5h). Institut d'Estudis de la Salut. Generalitat de Catalunya (Barcelona, Spain).

April - June 2011: Course – "*Curso de exploración neuropsicológica en niños y adolescentes en salud mental*" (34h). Comisión de Formación Continuada de las Profesiones Sanitarias de la Comunidad de Madrid – Sistema Nacional de Salud (Madrid, Spain).

November 2010: Workshop – "*Adiccions i Dona*" (6h). Corporació Sanitària Parc Taulí, supported by Fundació Parc Taulí. Institut Universitari UAB (Sabadell, Barcelona, Spain).

September 2010: Course – "*Método para la elaboración de trayectorias/vías clínicas/rutas asistenciales*" (12h). Agència d'Informació, Avaluació i Qualitat en Salut, supported by Plan de Calidad para el Sistema Nacional de Salud (Barcelona, Spain).

May-June 2010: Course – "*Curs de presentació de pòsters científics en anglès*" (6h). Centre d'Higiene Mental Les Corts, cofinanced by Fondo Social Europeo (Barcelona, Spain).

February 2010: Workshop – "*Taller sobre aspectes cognitius en la psicosi incipient*" (6h). Institut d'Estudis de la Salut. Generalitat de Catalunya (Barcelona, Spain).

Jan-Nov 2010: Course – "*Curs de Tractaments Familiars a la Psicosi Incipient*" (11h). Centre d'Higiene Mental Les Corts, cofinanced by Fondo Social Europeo (Barcelona, Spain).

November 2009: Workshop – *"Taller sobre detecció i maneig del trastorn d'ús de substàncies en el trastorn per psicosi incipient"* (5h). Institut d'Estudis de la Salut. Generalitat de Catalunya (Barcelona, Spain).

October 2009: Course – *"Investigació Qualitativa de Nivell Bàsic"* (12h). Institut Català de la Salut (ICS) (Barcelona, Spain).

October 2009: Workshop – *"¿Cómo sacar el mayor rendimiento a las publicaciones? Pautas para la lectura crítica, la elaboración y la difusión de manuscritos ¿Cómo poner en marcha un proyecto editorial?"* (20h). Fondo de Investigación Sanitaria del Instituto Carlos III (Madrid, Spain).

September 2009: Workshop –*"Models d'intervenció psicoterapèutica als trastorns psicòtics incipients"* (5h). Institut d'Estudis de la Salut. Generalitat de Catalunya (Barcelona, Spain).

June 2009: Course – *"Escales Clíniques de Mesura en Psiquiatría"* (16h). Societat Catalana de Psiquiatria i Salut mental (SCPiSM) (Barcelona, Spain).

May 2009: Workshop – *"II Jornada de Promoció del Programa d'Atenció Especialitzada de Psicosis Incipient. Intervenció precoç en psicosi"* (8h). Institut d'Estudis de la Salut. Generalitat de Catalunya (Barcelona, Spain).

2009/10: Course – *"Análisis Multivariable: Modelos de Regresión"* (250h) (10 ECTS). Autonomous University of Barcelona (Barcelona, Spain).

2008/09: Course – *"Desarrollo y adaptación de cuestionarios en el ámbito de la Salud"* (60h) (2.4 ECTS). Autonomous University of Barcelona (Barcelona, Spain).

May 2008: Course – *"Entrenamiento en Terapia de Resolución de Problemas by Prof. Javier García-Campoyo"* (10h). Autonomous University of Madrid (Madrid, Spain).

May 2008: Workshop – *"Intervención precoz en la psicosis by Oscar Vallina"* (2h). In XXII Jornadas Estatales de la Asociación Española de Neuropsiquiatría (AEN) (Girona, Spain).

September 2007: Course – *"Intervenciones grupales dirigidas"* (10h). Sant Joan de Déu-Serveis de Salut Mental (Sant Boi de Llobregat, Spain).

July 2007: Workshop – *"CBT and Decentering Techniques for Auditory Verbal Hallucinations by Mark van der Gaag"* (7h). Sant Joan de Déu-Serveis de Salut Mental (Sant Boi de Llobregat, Spain).

November 2006: Course – *"Psicofarmacología"* (15h). Sant Joan de Déu-Serveis de Salut Mental (Sant Boi de Llobregat, Spain).

April 2006: Seminar – "Aspectos clínicos, epidemiológicos y etiológicos de la esquizofrenia". University of Barcelona (Barcelona, Spain).

July 2000: Seminar – *"La malaltia neurodegenerativa: del laboratori a la clínic"*- University of Barcelona, (Barcelona, Spain).

⇒ **Attendance of conferences/congresses:**

October 2015: **"**IV Jornada. La salut mental la fem entre tots: eines de prevenció". Corporació Sanitària Parc Taulí (Sabadell, Barcelona, Spain).

October 2015: **"**11th International Conference of the European Network for Mental Health Service Evaluation: Closing the gap between research and policy in mental Health". ENMESH (Málaga, Spain).

May 2015: "European Meeting on Women's Mental Health". Grup de Treball i Recerca de Dona i Salut Mental (GTRDiSM). Societat Catalana de Psiquiatria i Salut Mental (Barcelona, Spain).

November 2014: "V Congreso Internacional de Bioética: Filosofía y Salud Mental." Grupo de Investigación APORIA, Sant Pere Claver- Institut de Docència (Barcelona, Spain).

September 2014: "XVI World Congress of Psychiatry: Focusing on access, quality and humane care." World Psychiatry Association (Madrid, Spain).

June 2014: "1ª Jornada d'Hospitals de Dia de Salut Mental per a nens i adolescents". Societat Catalana de Psiquiatria InfantoJuvenil (Barcelona, Spain).

June 2014: "XVI Jornadas Nacionales de Patología Dual." Sociedad Española de Patología Dual (Valencia, Spain).

June 2014: "Jornada de Cloenda." Societat Catalana de Psiquiatria i Salut Mental (SCPiSM) (Barcelona, Spain).

May 2014: "VI Jornada del Programa d'Atenció al Trastorn Psicòtic Incipient del PDSMIA." Parc Sanitari Sant Joan de Déu i Departament de Salut – Generalitat de Catalunya (Cerdanyola del Vallès, Barcelona, Spain).

November 2013: "IX Jornades de Recerca en Salut Mental." Parc Sanitari Sant Joan de Déu (Sant Boi de Llobregat, Barcelona, Spain).

June 2013: "62ena Reunió Científica de la Societat Catalana de Neuropsicología: Rehabilitació Cognitiva i Noves Tecnologies." Societat Catalana de Neuropsicologia (Barcelona, Spain).

June 2013: "Jornada d'Actualització en Patologia Dual a l'Àrea Integral de Salut Barcelona Esquerra." Àrea Integral de Salut Barcelona Esquerra. Consorci Sanitari de Barcelona (Barcelona, Spain).

April 2013: "V Jornada dels programes d'atenció específica al trastorn psicòtic incipient (PAE-TPI): L'atenció a les addiccions en el Trastorn Psicòtic Incipient." Fundació Pere Mata Terres de l'Ebre (Amposta, Tarragona, Spain).

February 2013: "I Jornada Científica BiblioPro." Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) & CIBER en Epidemiología y Salud Pública (CIBERESP) (Barcelona, Spain).

October 2012: "8th International Conference on Early Psychosis." International Early Psychosis Association (San Francisco, CA, USA).

October 2012: 3er Congrés Català de Dona i Salut Mental. Grup de Treball i Recerca en Salut Mental de la Societat Catalana de Psiquiatría i Salut Mental (Barcelona, Spain).

February 2012: "IV Jornada dels programes d'atenció específica al trastorn psicòtic incipient (PAE-TPI): L'atenció al trastorn psicòtic incipient en les experiències del Regne Unit i de Catalunya." Centre d'Higiene Mental Les Corts & Departament de Salut – Generalitat de Catalunya (Barcelona, Spain).

December 2011: "Jornada Trimestral de Formació del Institut Pere Mata: Trastorns Psicòtics Incipients." HPU Institut Pere Mata (Reus, Tarragona, Spain).

October 2011: "IX Reunión Internacional sobre las fases tempranas de las enfermedades mentales: servicios e intervenciones para las fases tempranas de la psicosis." Unidad de Investigación en Psiquiatría de Cantabria. Servicio de Psiquiatría. Hospital Universitario Marqués de Valdecilla (Santander, Spain).

September 2011: "3rd European Conference on Schizophrenia Research." Competence Network on Schizophrenia (CNS) (Berlín, Germany).

May 2011: "III Jornada del Programa d'Atenció Específica per a les persones amb un Trastorn Psicòtic Incipient. "Estratègies per facilitar l'adherència i la prevenció de recaigudes." Institut d'Assistència Sanitària. Institut d'Estudis de la Salut – Generalitat de Catalunya (Girona, Spain).

March 2011: The Research & Innovation Showcase Event & Exhibition. Birmingham & Solihull Mental Health NHS Foundation Trust (Birmingham, UK).

February 2011: Jornades Internacionals Baetulae: la atención integral a las psicosis. Fundació Privada Llegat Roca i Pi & Ajuntament de Badalona (Badalona, Spain).

November 2010: "7th International Conference on Early Psychosis." International Early Psychosis Association (Amsterdam, The Netherlands).

July 2010: "Jornada de Presentació de la Guía de Desenvolupament del Programa d'Atenció Específica per a les persones amb un Trastorn Psicòtic Incipient (PAE-TPI) del Pla Director de Salut Mental i Addiccions." Centre d'Higiene Mental Les Corts & Departament de Salut – Generalitat de Catalunya (Barcelona, Spain).

April 2010: "III Jornades anuals dels Programes d'Atenció Específica als Trastorns Psicòtics Incipients a Catalunya: avaluació i línees de recerca." HPU Institut Pere Mata (Reus, Tarragona, Spain).

November 2009: "7ª Reunión Internacional sobre las Fases Tempranas de las Enfermedades Mentales. Curso Evolutivo y Outcome en los Primeros Episodios de Psicosis." Unidad de Investigación en Psiquiatría de Cantabria. Servicio de Psiquiatría. Hospital Universitario Marqués de Valdecilla (Santander, Spain).

November 2009: The 15th Biennial Winter Workshop in Psychoses (Barcelona, Spain).

September 2009: 2on European Conference on Schizophrenia Research. Competence Network on Schizophrenia (CNS) (Berlín, Germany).

June 2009: "44 Reunión de la Asociación Española de Psiquiatría del Niño y del Adolescente (AEPNYA)." AEPNYA (Pamplona, Spain).

Febrer 2009: "Taules rodones. II Congrés Català de Dona i Salut Mental". Grup de Treball i Recerca en Salut Mental de la Societat Catalana de Psiquiatría i Salut Mental (Barcelona, Spain).

Febrer 2009: "Sessions plenàries. II Congrés Català de Dona i Salut Mental". Grup de Treball i Recerca en Salut Mental de la Societat Catalana de Psiquiatría i Salut Mental (Barcelona, Spain).

November 2008: "XII Congreso Nacional de Psiquiatría." Sociedad Española de Psiquiatría y Sociedad Española de Psiquiatría Biológica (Valencia, Spain).

May 2008: "XXII Jornadas Estatales de la Asociación Española de Neuropsiquiatría (AEN)." Asociación Española de Neuropsiquiatría (Girona, Spain).

February 2008: "14th Biennial Winter Workshop on Schizophrenia and Bipolar Disorder." Organized by Professors Tim Crow and Steven Hirsch in association with World Federation of Societies of Biological Psychiatry (Montreux, Switzerland).

November 2007: "2on Congrés Català de Dona i Salut Mental." Grup de Treball i Recerca en Salut Mental de la Societat Catalana de Psiquiatría i Salut Mental (Barcelona, Spain).

September 2007: "1st European Conference on Schizophrenia Research." Competence Network on Schizophrenia (CNS) (Dusseldorf, Germany).

July 2007: "V World Congress of Behavioral & Cognitive Therapies." The European Association for Behavioural and Cognitive Therapies (EABCT) (Barcelona, Spain).

June 2007: "IV Curso Fases iniciales de trastornos psicóticos." Universidad de Oviedo (Asturias, Spain).

May 2007: "V Simposi de Neuropsicología y Neuropsiquiatría." Sociedad Catalana de Psiquiatría y Salud Mental (Barcelona, Spain).

March 2007: "XXII Jornadas de Terapia del Comportamiento y Medicina Conductual en la práctica clínica." Sociedad Catalana de Psiquiatría (Barcelona, Spain).

March 2007: "IV Simposio Internacional Psiquiatría Global. Tratamiento de las Psicosis: avances clínicos y terapéuticos en psiquiatría." (Barcelona, Spain).

December 2006: "1er Congrés Català de Dona i Salut Mental." Grup de Treball i Recerca en Salut Mental de la Societat Catalana de Psiquiatría i Salut Mental (Barcelona, Spain).

June 2006: "La atención al trastorno psicótico incipiente: investigación, detección, intervención." Fórum Salud Mental (Barcelona, Spain).

June 2004: "I Jornada de Riesgos Psicosociales y Gestión de RRHH." Universidad Politécnica de Cataluña (Barcelona, Spain).

May 2004: "II Jornadas Estatales de Violencia y Mujeres." Colegio Oficial de Psicólogos de Catalunya (Tarragona, Spain).

STAYS IN OTHER RESEARCH CENTERS

INSTITUTION: Birmingham and Solihull Mental Health NHS Foundation Trust. YouthSpace – The Early Intervention Service
CLINICAL DIRECTOR: Max Birchwood, PhD., DSc. Professor of Mental Health.
DURATION: 4 months
DATES: December 2010 – April 2011
COUNTRY (STATE): Birmingham (United Kingdom)
PROJECT: Assessment of effectiveness of an early specific psychosis intervention programme: comparison with international performance measures.

INSTITUTION: Department of Research – Adolescent Psychiatry Unit. University Hospital Gregorio Marañón (Madrid, Spain). Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM).
DIRECTOR: Celso Arango.
DURATION: 2 months
DATES: March - April 2008
COUNTRY (STATE): Madrid, Spain
PROJECT: Diferencias de género en personas con un primer episodio psicótico.

FELLOWSHIPS

12/2010 – 06/2011 Bolsas de Ampliación de Estudios (BAE) by the "Fondo de Investigación Sanitaria del Instituto Carlos III (Ministerio de Investigación e Innovación)".

03/2008 – 04/2008 Researcher at Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) (Barcelona, Spain).

03/2007 – 03/2009 PhD fellowship awarded by the "Fondo de Investigación Sanitaria del Instituto Carlos III (Ministerio de Investigación e Innovación)".

PROFESSIONAL EXPERIENCE

09/2014- present Consultant on the subject "Adult Psychopathology". School of Psychology, Open University of Catalonia (Universitat Oberta de Catalunya - UOC).

12/2010 – 04/2011 Psychologist Researcher at Birmingham and Solihull Mental Health NHS Foundation Trust. YouthSpace – The Early Intervention Service, supervised by Prof. Max Birchwood.

03/2009 – present Psychologist and Researcher at Centre d'Higiene Mental Les Corts (Barcelona, Spain).

03/2011 – present: Level II in the profesional category as indicated in "VII Convenio Colectivo de los Hospitales de la XHUP y de los centros de atención primaria concertados."

01/2013 – present: Level A (Associate) of 1st group of the "VII Convenio Colectivo de los Hospitales de la XHUP y de los centros de atención primaria concertados."

03/2008 – 03/2009 Researcher member of the Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) (Barcelona, Spain).

03/2008 – 04/2008 Psychologist Researcher at Department of Research, Adolescent Psychiatry Unit, University Hospital Gregorio Marañón (Madrid, Spain), supervised by Dr. Celso Arango.

2006 – 03/2009 Psychologist Researcher at Parc Sanitari Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), (Sant Boi de Llobregat, Barcelona, Spain).

PARTICIPATION IN RESEARCH PROJECTS

PROJECT TITLE: Eficacia del Entrenamiento Metacognitivo Individualizado (EMC+) en personas con psicosis de breve evolución – PI14/00044
PRINCIPAL INVESTIGATOR: Susana Ochoa Güerre
FINANCIAL ENTITY: Instituto de Salud Carlos III - Fondo de Investigación Sanitaria (Spain).
LENGHT: FROM: January 2015 TO: December 2017

PROJECT TITLE: Eficacia del programa d'Entrenament Metacognitiu per a millorar la inclusió social i laboral de les persones amb un primer episodi psicòtic
PRINCIPAL INVESTIGATOR: Susana Ochoa Güerre
FINANCIAL ENTITY: Programa Recercaixa: Obra Social "La Caixa" & Associació Catalana d'Universitats Públiques (ACUP). Convocatòria 2013.
LENGHT: FROM: January 2014 TO: December 2015

PROJECT TITLE: EU Gene-Environment Interaction study (London) [EUGEI]
PRINCIPAL INVESTIGATOR: Dr Craig Morgan/Dr. Miquel Bernardo (Spain)
FINANCIAL ENTITY: The European Community's Seventh Framework Programme under grant agreement no. HEALTH-F2-2010-241909 (Project EU-GEI).
LENGHT: FROM: May 2012 TO: May 2015

PROJECT TITLE: Evaluación del proceso de recuperación de la psicosis
PRINCIPAL INVESTIGATOR: Mercedes Paino Piñeiro
FINANCIAL ENTITY: Subprograma de proyectos de investigación fundamental no orientada. Convocatoria 2011. Programa Nacional de Proyectos de Investigación Fundamental. Ministerio de Ciencia e Innovación I+D+I Ref. PSI2011-23818.
LENGHT: FROM: 2012 TO: 2014

PROJECT TITLE: Eficacia del Entrenamiento Meta-Cognitivo (EMC) sobre los síntomas, la metacognición, el funcionamiento social y neuropsicológico en personas con psicosis de breve evolución – PI11/01347
PRINCIPAL INVESTIGATOR: Susana Ochoa Güerre
FINANCIAL ENTITY: Instituto de Salud Carlos III - Fondo de Investigación Sanitaria (Spain)
LENGHT: FROM: 2011 TO: 2014
PROJECT TITLE: Programa de Atención Específica para los Trastornos Psicóticos Incipientes (PAE-TPI): Promoción y adecuación de la valoración integral y de las intervenciones psicológicas, psicoterapéuticas y psicosociales
PRINCIPAL INVESTIGATOR: Lluís Lalucat i Jo
FINANCIAL ENTITY: Fondos de cohesión 2010 del Ministerio de Sanidad, Política Social e Igualdad, y el Departamento de Salud – Generalitat de Catalunya (Spain)
LENGHT: FROM: January 2011 TO: December 2011

PROJECT TITLE: Estudio de validación de la escala de adaptación premórbida (PAS) en una muestra de pacientes psicóticos
PRINCIPAL INVESTIGATOR: Judith Usall Rodie
FINANCIAL ENTITY: Plataforma del Banco de Instrumentos en Salud Mental. Centro de Investigación Biomédica en Red de Salud Mental (CIBERsam)
LENGHT: FROM: 2010 TO: 2011

PROJECT TITLE: Evaluación de la efectividad de un Programa de Atención Específica para las personas con un Trastorno Psicótico Incipiente (PAE-TPI) desarrollado en Cataluña
PRINCIPAL INVESTIGATOR: Ana Barajas Vélez
FINANCIAL ENTITY: Fondos de cohesión 2010 del Ministerio de Sanidad, Política Social e Igualdad, y el Departamento de Salud – Generalitat de Catalunya (Spain)
LENGHT: FROM: January 2010 TO: December 2010

PROJECT TITLE: Transición de los estados de alto riesgo a la psicosis: Factores determinantes y eficacia del programa P3
PRINCIPAL INVESTIGATOR: Serafín Lemos Giráldez
FINANCIAL ENTITY: Subprograma de proyectos de investigación fundamental no orientada. Convocatoria 2008. Programa Nacional de Proyectos de Investigación Fundamental. Ministerio de Ciencia e Innovación I+D+I Ref. PSI2008-06220/PSIC.
LENGHT: FROM: 2009 TO: 2011

PROJECT TITLE: Traducción y validación de la versión española de la entrevista ERIraos para la evaluación de la sintomatología prodrómica en trastornos psicóticos incipientes
PRINCIPAL INVESTIGATOR: Susana Ochoa Güerre

FINANCIAL ENTITY: Plataforma del Banco de Instrumentos en Salud Mental. Centro de Investigación Biomédica en Red de Salud Mental (CIBERsam)
LENGHT: FROM: 2009 TO: 2011

PROJECT TITLE: Adaptación y validación de la versión española abreviada de la entrevista IRAOS para la evaluación retrospectiva de la fase prodrómica en pacientes con esquizofrenia
PRINCIPAL INVESTIGATOR: Judith Usall Rodie
FINANCIAL ENTITY: Fondo Investigación Sanitaria. Evaluaciones de Tecnologías Sanitarias y Servicios de Salud (ETES) - PI08/90804
LENGHT: FROM: 2009 TO: 2011

PROJECT TITLE: Interacción genotipo-fenotipo y ambiente. Aplicación a un modelo predictivo en primeros episodios psicóticos
PRINCIPAL INVESTIGATOR: Miquel Bernardo
FINANCIAL ENTITY: Fondo Investigación Sanitaria (FIS) – PI08/1053
LENGHT: FROM: 2009 TO: 2011

PROJECT TITLE: Traducción en catalán y validación en lengua española de la entrevista semiestructurada Comprehensive Assessment of At Risk Mental States (CAARMS) para la identificación de estados mentales de alto riesgo
PRINCIPAL INVESTIGATOR: Lluís Lalucat i Jo
FINANCIAL ENTITY: Fondos de cohesión del Ministerio de Sanidad, Política Social e Igualdad, y el Departamento de Salud – Generalitat de Catalunya (Spain)
LENGHT: FROM: 2009 TO: 2010

PROJECT TITLE: Estrategias terapéuticas en trastorno depresivo mayor resistente a tratamiento con inhibidores selectivos de la recaptación de la serotonina. Ensayo clínico pragmático, paralelo, aleatorizado con evaluación enmascarada.
PRINCIPAL INVESTIGATOR: Judith Usall Rodie
FINANCIAL ENTITY: Fondo Investigación Sanitaria. Evaluaciones de Tecnologías Sanitarias y Servicios de Salud (ETES) - EC07/90008
LENGHT: FROM: 2009 TO: 2010

PROJECT TITLE: Estudio del consumo de drogas de abuso en personas con un primer episodio psicótico.
PRINCIPAL INVESTIGATOR: Susana Ochoa Güerre
FINANCIAL ENTITY: Fundación Caja de Ahorros de Navarra (CAN)
LENGHT: FROM: 2007 TO: 2009

PROJECT TITLE: Diferencias de género en personas con un primer episodio psicótico
PRINCIPAL INVESTIGATOR: Susana Ochoa Güerre
FINANCIAL ENTITY: Fondo Investigación Sanitaria (FIS) – PI05/1115
LENGHT: FROM: 2006 TO: 2009

PUBLICATIONS

⇒ **Refereed Scientific Journal Articles:**

Barajas, A., Ochoa, S., Obiols, J.E., & Lalucat-Jo Ll. (2015). Gender differences in individuals at high-risk of psychosis: a comprehensive literature review. *The Scientific World Journal*, Volume 2015, Article ID 430735, 1-13. doi:10.1155/2015/430735. Impact Factor: 1.22; Subject category: Psychiatry; Quartile: Q2

Ciocca, G., Usall, J., Dolz, M., Limoncin, E., Giovanni, L., Gravina, G.L., Carosa, E., Sánchez, B., **Barajas, A.**, Baños, I., Huerta, E., Farreny, A., Franchi, C., GENIPE group., & Ochoa, S. (2015). Sexual dysfunctions in people with first-episode psychosis assessed according to a gender perspective. *Revista di Psychiatria*, 50(5), 239-244. Impact Factor: 0.72; Subject category: Psychiatry; Quartile: Q4

Lemos-Giráldez, L., García-Álvarez, L., Paino, M., Fonseca-Pedrero, E., Vallina-Fernández, O., Vallejo-Seco, G., Fernández-Iglesias, P., Ordóñez-Camblor, N., Solares-Vázquez, J., Mas-Expósito, L., **Barajas, A.**, & Andresen, R. (2015). Measuring stages of recovery from psychosis. *Comprehensive Psychiatry*, 56, 51-58. doi: 10.1016/j.comppsych.2014.09.021. Impact Factor: 2.25; Subject category: Psychiatry; Quartile: Q2

Rubio-Abadal, E., Ochoa, S., **Barajas, A.**, Baños, I., Dolz, M., Sánchez, B., Del Cacho, N., GENIPE group., & Usall, J. (2015). Birth weight and obstetric complications determine age at onset in first episode of psychosis. *Journal of Journal of Psychiatric Research*, 65, 108-114. doi: 10.1016/j.jpsychires.2015.03.018. Impact Factor: 4.09; Subject category: Psychiatry; Quartile: Q1

Rubio-Abadal, E., Usall, J., **Barajas, A.,** Carlson, J., Iniesta, R., Huerta-Ramos, E., Baños, I., Dolz, M., Sánchez, B., GENIPE group., & Ochoa, S. (2014). Relationship between menarche and psychosis onset in women with first episode of psychosis. *Early Intervention in Psychiatry*, doi:10.1111/eip.12194. Impact Factor: 1.95; Subject category: Psychiatry; Quartile: Q2

Barajas, A., Ochoa, S., Baños, I., Dolz, M., Villalta-Gil, V., Vilaplana, M., Autonell, J., Sánchez, B., Cervilla, J.A., Foix, A., Obiols, J.E., Haro, J.M., GENIPE group., & Usall, J. (2013). Spanish validation of the Premorbid Adjustment Scale (PAS-S). *Comprehensive Psychiatry*, 54(2), 187-194. doi: 10.1016/j.comppsych.2012.07.007. Impact Factor: 2.26; Subject category: Psychiatry; Quartile: Q2

Barajas, A., Usall, J., Baños, I., Dolz, M., Villalta-Gil, V., Vilaplana, M., Autonell, J., Sánchez, B., Cervilla, J.A., Foix, A., Obiols, J.E., Haro, J.M., GENIPE group., & Ochoa, S. (2013). Three-factor model of premorbid adjustment in a sample with chronic schizophrenia and first-episode psychosis. *Schizophrenia Research*, 151(1-3), 252-258. doi: 10.1016/j.schres.2013.10.027. Impact Factor: 4.43; Subject category: Psychiatry; Quartile: Q1

Ochoa, S., Huerta-Ramos, E., **Barajas, A.,** Iniesta, R., Dolz, M., Baños, I., Sánchez, B., Carlson, J., Foix, A., Pelaez, T., Coromina, M., Pardo, M., GENIPE group., & Usall, J. (2013). Cognitive profiles of three clusters of patients with a first-episode psychosis. *Schizophrenia Research*, 150(1), 151-156. doi: 10.1016/j.schres.2013.07.054. Impact Factor: 4.43; Subject category: Psychiatry; Quartile: Q1

Barajas, A., Baños, I., Ochoa, S., Usall, J., Huerta, E., Dolz, M., Sánchez, B., Villalta-Gil, V., Foix, A., Obiols, J.E., Haro, J.M., & GENIPE group. (2010). Gender differences in incipient psychosis. *The European Journal of Psychiatry*, 24(3), 176-194. doi: 10.4321/S0213-61632010000300006. Impact Factor: 0.46; Subject category: Psychiatry; Quartile: Q4

Barajas, A., Baños, I., Ochoa, S., Usall, J., Villalta-Gil, V., Dolz, M., Sánchez, B., Haro, J.M., & Grupo GENIPE. (2007). ¿Existen diferencias clínicas en el inicio del primer episodio psicótico entre hombres y mujeres? *Psiquiatría Biológica*, 14(4), 136-141. Retrieved from http://www.elsevier.es/es-revista-psiquiatria-biologica-46

⇒ **Submitted Articles:**

Barajas, A. , Pelaez, T., González, O., Usall, J., Iniesta, R., Arteaga, M., Jackson, Ch., Baños, I., Sánchez, B., Dolz, M., Obiols, J.E., Haro, J.M., GENIPE group, & Ochoa, S. Predictive capacity of prodromal symptoms in first-episode psychosis of recent onset. *Comprehensive Psychiatry*, 2015 (submitted to publication, under review).

Butjosa, A., Gómez-Benito, J., Huerta-Ramos, E., Del Cacho, N., **Barajas, A.**, Baños, I., Usall, J., Dolz, M., Sánchez, B., Carlson, J., Ochoa, S. Incidence of stressful life events and the influence of sociodemographic and clinical variables on the onset of first-episode psychosis. *Stress*, 2015 (submitted to publication).

Dachs, I., Irazábal, M., Usall, J., **Barajas, A.**, Dolz, M., Sánchez, B., Baños, I., Coromina, M., GENIPE group, & Ochoa, S. Family impact on caregivers of people with a first-episode psychosis and its relation to symptoms and social functioning. *Schizophrenia Research*, 2015 (submitted to publication).

Ochoa, S., López-Carrilero, R., Barrigón, M.L., Pousa, E., **Barajas, A.**, Lorente, E., González-Higueras, F., Grasa, E., Ruiz-Delgado, I., Cid, J., Birulés, I., Esteban-Pinos, I., Casañas, R., Luengo, A., Torres-Hernández, P., Corripio, I., Montes-Gámez, M., Beltran, M., de Apraiz, A., Domínguez-Sánchez, L., Mas-Expósito, L., Llacer, B., Pelaez, T., Bogas, J.L., Moritz, S., & the Spanish Metacognition Study Group. (2015). Efficacy of Metacognitive Training compared with a psycho-educational group in people with a recent-onset of psychosis. *Schizophrenia Bulletin*, (submitted to publication).

Rubio-Abadal, E., Grau, N., Usall, J., **Barajas, A.**, Butjosa, A., Dolz, M., Baños, I., Sánchez, B., Rodríguez, M.J., Peláez, T., Sammut, S., Rubio-Abadal, E., Carlson, J., Huerta-Ramos, E., GENIPE group, & Ochoa, S. Influence of cognition, premorbid adjustment and psychotic symptoms on social functioning in first-episode psychosis. *Journal of Psychiatric Research*, 2015 (submitted to publication).

⇒ **'In preparation' Articles:**

Barajas, A., Mauri, Ll., Cid, J., Lalucat-Jo, Ll., & on behalf of the Spanish CAARMS group. Reliability and validity of the Spanish version of the Comprehensive Assessment of At-Risk Mental States (CAARMS).

Barajas, A., Ochoa, S., Farreny, A., Rodriguez-Jimenez, R., Moreno, M., Landin, J.R., Bayon, C., Ibañez, A., Cabrera, B., Quintanilla, M.A. & Usall, J., on behalf of the Spanish ERIraos group. Assessment of prodromal symptoms in incipient psychotic disorders: reliability and validity measures of the Early Recognition Inventory-Spanish Version (ERIraos-SV).

Barajas, A., San Emeterio, M., Teixidó, M., PAE-TPI-CHMLC group & Lalucat-Jo, Ll. Programa de atención específica para jóvenes con un trastorno psicótico incipiente: un nuevo modelo de intervención.

Barajas, A., et al. Developing and implemeting early intervention programme for psychotic spectrum disorders in mental health network of Catolonia (Spain).

CONGRESS COMMUNICATIONS

⇒ **Oral Communications:**

October 2015	**A Barajas**, "Prevenció de la psicosis. Funcionamiento premórbido y prodrómico como predictores de inicio de la psicosis". IV Jornada. La salut mental la fem entre tots: eines de prevenció (Sabadell, Barcelona, Spain).
October 2015:	**A Barajas**, "Epidemiological and performance measures in a care programme for incipient psychosis developed in Catalonia: comparison to international experiences". 11th International Conference of the European Network for Mental Health Service Evaluation – ENMESH: Closing the gap between research and policy in mental health (Málaga, Spain).
March 2015:	J Usall, E Rubio-Abadal, S Ochoa, **A Barajas**, E Huerta-Ramos. "Relationship between menarche and psychosis onset in women with first episode of psychosis." 6th World Congress on Women's Mental Health: Trauma, Depression and Resilience (Tokyo, Japan).
September 2014:	**A Barajas.** "Gender differences in first-episode psychosis." XVI World Congress of Psychiatry: Focusing on access, quality and humane care (Madrid, Spain).
June 2014:	**A Barajas.** "Rendimiento cognitivo diferencial en psicosis incipiente y patología dual." XVI Jornadas Nacionales de Patología Dual (Valencia, Spain).

June 2014: **A Barajas.** "Curs evolutiu dels Trastorns Psicòtics Incipients: una perspectiva de gènere." Jornada de Cloenda de la Societat Catalana de Psiquiatria i Salut Mental (SCPiSM) (Barcelona, Spain).

May 2014: **A Barajas**. "Estudi multicèntric sobre l'efectivitat del PAE-TPI: comparativa amb experiències internacionals." VI Jornada del Programa d'Atenció al Trastorn Psicòtic Incipient del PDSMIA (Cerdanyola del Vallès, Barcelona, Spain).

November 2013: **A Barajas**, S Ochoa, A Farreny, L Mas, M Pardo, R Rodríguez-Jiménez, M. Moreno, JR Landín, C Bayón, A Ibañez, B Cabrera, MA Quintanilla, Grupo ERIraos & J Usall. "Diferencias de género en la sintomatología prodrómica de los trastornos psicóticos incipientes." III Workshop Recerca en Salut Mental i Dona (Barcelona, Spain).

February 2013: **A Barajas**, S Ochoa, A Farreny, L Mas, M Pardo, R Rodríguez-Jiménez, M. Moreno, JR Landín, C Bayón, A Ibañez, B Cabrera, MA Quintanilla, Grupo ERIraos & J Usall. "Traducción y validación de la versión española de la entrevista ERIraos-SV para la evaluación de la sintomatología prodrómica en trastornos psicóticos incipientes." 1ª Jornada Científica BiblioPro (Barcelona, Spain).

February 2013: G Giocca, J Usall, M Dolz, E Limoncin, GL Gravina, E Carosa, B Sánchez, **A Barajas**, I Baños, E Huerta, A Farreny, EA Jannini, S Ochoa. "Gender differences in sexual dysfunctions in a group of first-episode psychosis patients." Gender & Science (Rome, Italy).

October 2012: E Rubio, J Usall, **A Barajas**, J Carlson, R Iniesta, E Huerta, I Baños, M Dolz, B Sánchez, S Ochoa. "Relació entre edad de pubertad i debut de psicosi en dones amb primer episodi psicòtic." 3er Congrés Català de Dona i Salut Mental (Barcelona, Spain). **PREMIO MARTA BARCELÓ A LA MEJOR COMUNICACIÓN** (published in C. Med. Psicosom, Nº 105 – 2013, 15)

October 2012: **A Barajas**, J Usall, M Dolz, I Baños, B Sánchez, E Huerta, J Carlson, S Ochoa & Grupo GENIPE. "Diferències de gènere en símptomes prodròmics: estudi retrospectiu de psicosis incipients." 3er Congrés Català de Dona i Salut Mental (Barcelona, Spain) (published in C. Med. Psicosom, Nº 105 – 2013, 19).

May 2012: **A Barajas**, S Ochoa, A Farreny, L Mas, M Pardo, R Rodríguez-Jiménez, M. Moreno, JR Landín, C Bayón, A Ibañez, B Cabrera, MA Quintanilla, J Usall & Grupo ERIraos. "Traducción y validación de la versión española de la entrevista ERIraos-SV para la evaluación de la sintomatología prodrómica en trastornos psicóticos incipientes: resultados preliminares." Workshop de la Biblioteca de Instrumentos en Salud Mental y Discapacidad. CIBERsam (Barcelona, Spain).

December 2011: **A Barajas**. "Intervención Temprana en Psicosis: Programa Especializados vs. Programas Estándar. Experiencia en Cataluña." Jornada Trimestral de Formación del Institut Pere Mata: Trastornos Psicóticos Incipientes (Reus, Spain).

November 2011: **A Barajas**. "Evaluación de la Efectividad del programa de Atención Específica para las personas con un Trastorno Psicótico Incipiente (PAE-TPI) desarrollado en Cataluña vs. el Programa Estándar (PE)." II Workshop Recerca en Salut Mental i Dona. Grup de Treball i Recerca en Salut Mental i Dona (Barcelona, Spain).

October 2011: S Ochoa, J Usall, M Dolz, **A Barajas**, I Baños, B Sánchez. "Evaluación de las necesidades de personas con un primer episodio psicótico y su relación con variables sociodemográficas, clínicas y de funcionamiento." 9ª Reunión Internacional sobre las fases tempranas de las

enfermedades mentales. Servicios e Intervenciones para las Fases Tempranas de las Psicosis (Santander, Spain).

October 2011: **A Barajas**, M Carbonero, A Escudero, E Sánchez, E Conesa, N Mantecón, I Álvarez, MA Argany, M Teixidó, M San Emeterio, L Lalucat. "Effectiveness of an early intervention programme for psychotic spectrum disorders in community mental health centers: 1-year outcome." 9ª Reunión Internacional sobre las fases tempranas de las enfermedades mentales. Servicios e Intervenciones para las Fases Tempranas de las Psicosis (Santander, Spain).

May 2011: **A Barajas** & Ll Lalucat. "Presentació del Projecte de Recerca PAE-TPI." III Jornadas del PAE-TPI. Estratègies per facilitar l'adherència i la prevenció de recaigudes (Girona, Spain).

April 2010: M San Emeterio & **A Barajas**. "Duration of Untreated Psychosis (DUP)." III Jornades dels Programes de Catalunya d'Atenció Específica als Trastorns Psicòtics Incipients (Tarragona, Spain).

June 2009: B Sánchez, M Pardo, **A Barajas**, A Torres, D Muñoz, M Dolz, I Baños, S Ochoa, J Usall & L San. "Tratamiento antipsicótico en población infanto-juvenil: estudio de eficacia y tolerabilidad en primeros episodios psicóticos." 44 Reunión de la Asociación Española de Psiquiatría del Niño y el Adolescente (AEPNYA) (Pamplona, Spain).

June 2008: M Fusté & **A Barajas**. "*Existen diferencias en el inicio del episodios psicótico entre adolescentes y adultos*." Societat Catalana de Psiquiatría i Salut Mental. Jornades de Cloenda (Girona, Spain).

November 2007: **A Barajas** & I Baños. "*Primeros episodios psicóticos: consumo de cannabis y diferencias en adaptación premórbida."* V Jornades de Recerca en Salut Mental (Barcelona, Spain).

May 2007: I Baños & **A Barajas**. *"Psicosis y Cannabis."* Jornadas de Cloenda La Catalana (Girona, Spain).

March 2007: I Baños, **A Barajas**, S Ochoa, JB Navarro, C Medina, G Martinena, J Usall, JE Obiols.*"Efectos del consumo de cannabis sobre el nivel de insight en pacientes con un primer brote psicótico."* XXII Jornada de Terapia del Comportamiento y Medicina Conductual en la práctica clínica (Barcelona, Spain).

December 2006: **A Barajas**. "*¿Existen diferencias en el inicio del primer episodio psicótico entre hombres y mujeres?*" 1er Congrés Català de Dona i Salut Mental (Barcelona, Spain).

⇒ **Posters:**

November 2013: **A Barajas**, S Ochoa, A Farreny, R Rodriguez-Jimenez, M Moreno, R Landin-Romero, C Bayon, A Ibanez, B Cabrera, MA Quintanilla, J Usall. "*Assessment of prodromal symptoms in incipient psychotic disorders: reliability and validity measures of the Early Recognition Inventory-Spanish Version (ERIraos-SV).*" IX Jornades de Recerca en Salut Mental. Parc Sanitari Sant Joan de Déu (Barcelona, Spain).

September 2013: E Huerta-Ramos, A Butjosa, C Núñez, J Usall, **A Barajas**, A. Foix, M Dolz, S Ochoa. "*Influence of gender on the primacy and recency effect in patients with a first-episode psychosis and*

schizophrenia patients." 4th European Conference on Schizophrenia Research Together for better treatment and care (Berlin, Germany).

September 2013: **A Barajas**, S Ochoa, A Farreny, R Rodriguez-Jimenez, M Moreno, R Landin-Romero, C Bayon, A Ibanez, B Cabrera, MA Quintanilla, J Usall. "*Assessment of prodromal symptoms in incipient psychotic disorders: reliability and validity measures of the Early Recognition Inventory-Spanish Version (ERIraos-SV).*" 4th European Conference on Schizophrenia Research Together for better treatment and care (Berlin, Germany).

September 2013: M Dolz, J Tor, J Carlson, B Sánchez, M Pardo, D Muñoz, **A Barajas**, I Baños, J Usall, S Ochoa. "*Comparative of adolescent and adult onset psychosis: one year follow up.*" 4th European Conference on Schizophrenia Research Together for better treatment and care (Berlin, Germany).

February 2013: G Ciocca, J Usall, M Dolz, E Limoncin, GL Gravina, E Carosa, B Sánchez, **A Barajas**, I Baños, E Huerta, A Farreny, EA Jannini, S Ochoa. "*Gender differences in sexual dysfunctions in a group of first-episode psychosis patients.*" Gender & Science (Rome, Italy).

November 2012: G Ciocca, J Usall, M Dolz, E Limoncin, GL Gravina, E Carosa, B Sánchez, **A Barajas**, I Baños, E Huerta, A Farreny, EA Jannini, S Ochoa. "*Sexual dysfunctions, psychopathological symptoms and the role of prolactin in a group of first-episode psychosis patients.*" X National Congress of the Italian Society of Andrology and Sexual Medicine (Lecce, Italy) (abstract published in: Journal of Endocrinological Investigation, 2012, 35, Supl 8, 115).

October 2012: **A Barajas**, M Teixidó, M San Emeterio, E Conesa, M Carbonero, N Mantecón, MA Argany, E Sánchez, I Álvarez, A Escuder, L Lalucat. "*Symptomatic remission in incipient psychosis at 1-year follow-up: relationship with severity of symptoms, global functioning and disability.*" 8th International Conference on Early Psychosis (San Francisco, CA, USA).

October 2012: J Tor, M Dolz, J Carlson, **A Barajas**, B Sánchez, D Muñoz, M Pardo, J Usall, I Baños, M Huerta, L San, S Ochoa. "*Estudi comparatiu de psicosis d'inici precoç i psicosis d'inici adult: diferències en el rendiment cognitiu.*" Reunió Anual Societat Catalana Psiquiatria Infanto-Juvenil (Barcelona, Spain).

October 2012: I Dachs, M Irazábal, J Usall, **A Barajas**, I Baño, M Dolz, B Sánchez, M Coromina, S Ochoa. "*Perfil i càrrega familiar dels cuidadors/es de persones amb un primer episodi psicòtic.*" 3er Congrés Català de Dona i salut Mental (Barcelona, Spain) (published in C. Med. Psicosom, Nº 105 – 2013, 28).

September 2012: G Ciocca, S Ochoa, M Dolz, E Limoncin, B Sánchez, **A Barajas**, E Huerta, A Farreny, EA Jannini, J Usall. "*Gender differences in sexual dysfunctions in a group of first-episode psychosis patients.*" 11th Congress of the European Federation of Sexology (Madrid, Spain).

September 2012: M Pardo, M Dolz, B Sánchez, **A Barajas**, I Baños, J Usall, S Ochoa & Grupo GENIPE. "*Perfil neuropsicológico en primeros episodios psicóticos: diferencias entre psicosis afectivas y no afectivas."* XVI Congreso Nacional de Psiquiatria (Bilbao, Spain).

July 2012: M Dolz, J Carlson, J Tor, **A Barajas**, B Sánchez, M Pardo, J Usall, I Baños, M Huerta, L San, S Ochoa. "*Child and adolescent psychosis: Neurodevelopmental markers as a key point in the pattern of presentation.*" 20th IACAPAP World Congress (Paris, France).

May 2012: I Dachs, S Ochoa, J Usall, **A Barajas**, I Baño, M Dolz, B Sánchez, M Coromina. "*Aspectos claves de la carga familiar en cuidadores de pacientes con un primer episodio psicótico.*" Jornadas Internacionales Baetulae (Badalona, Spain).

April 2012 S Ochoa, J Usall, E Huerta-Ramos, M Dolz, **A Barajas**, I Baños, B Sánchez, J Carlson, A Foix, T Pelaez, M Coromina, M Pardo & GENIPE group. "*A cluster approach for determining groups of patients with first psychotic episode and their relationship with symptoms, social and neuropsychological functioning.*" 3rd Biennial Schizophrenia International Research Conference (Florence, Italy).

November 2011: J Merchán-Naranjo, **A Barajas**, M Rapado-Castro, C García-Mouriño, I Bombín, J Castro-Fornieles, A González-Pinto, M Graell, C Arango, M Parellada. "Conciencia de enfermedad y gravedad de los síntomas en psicosis de inicio temprano." XV Congreso Nacional de Psiquiatría (Oviedo, Spain).

October 2011: **A Barajas**, M Carbonero, A Escudero, E Sánchez, E Conesa, N Mantecón, I Álvarez, MA Argany, M Teixidó, M San Emeterio, L Lalucat. "*Assessment of an early intervention programme for psychotic spectrum disorders in community mental health centers: 1-Year outcome.*" 9ª Reunión Internacional sobre las fases tempranas de las enfermedades mentales. Servicios e Intervenciones para las Fases Tempranas de las Psicosis (Santander, Spain).

October 2011: M Pardo, J Matalí, M Dolz, B Sánchez, S Ochoa, J Usall, I Baños, **A Barajas**. "*Uso de substancias en una muestra de pacientes con un primer episodio psicótico: Diferencias según la edad de inicio.*" 9ª Reunión Internacional sobre las fases tempranas de las enfermedades mentales. Servicios e Intervenciones para las Fases Tempranas de las Psicosis (Santander, Spain).

October 2011: T Pelaez, S Ochoa, J Usall, **A Barajas**, I Baños, M Dolz, B Sánchez. "*Antedecedentes familiars en primeros episodios psicóticos.*" 9ª Reunión Internacional sobre las fases tempranas de las enfermedades mentales. Servicios e Intervenciones para las Fases Tempranas de las Psicosis (Santander, Spain).

September 2011: **A Barajas**, M San Emeterio, M Teixidó, N Mantecón, A Escudero, E Conesa, M Carbonero, MA Argany, E Sánchez, I Álvarez, L Lalucat. "*Clinical and Social Correlates of Untreated Psychosis Duration (DUP): Results from the Catalan Early Psychosis Specific Intervention Programme (EPSIP).*" 3rd European Conference on Schizophrenia Research (Berlin, Germany).

March 2011 S Ochoa, J Usall, **A Barajas**, I Baños, M Dolz, B Sánchez, J Cervilla, E Huerta, A Foix, JM Haro. "*Gender differences in premorbid adjustment functioning in people with a psychotic disorder."* 4th World Congress on Women's Mental Health (Madrid, Spain).

November 2010: M Dolz, **A Barajas**, M Pardo, S Ochoa, B Sánchez, J Usall, I Baños, A Torres, D Muñoz, L San. "*Early onset psychosis: are there two different patterns of presentation?*" 7th International Conference on Early Psychosis (Amsterdam, The Netherlands).

November 2010: E Sánchez, I Álvarez, MA Argany, M Carbonero, E Conesa, A Escudero, N Mantecón, **A Barajas**, M San Emeterio & M Teixidó. "Evaluation of an early specific psychosis intervention *programme (EPSIP) using consensus and performance measures.*" 7th International Conference on Early Psychosis (Amsterdam, The Netherlands).

November 2010: **A Barajas**, M San Emeterio, E Conesa, A Escudero, E Sánchez, I Álvarez, M Carbonero, MA Argany, M Teixidó, L Lalucat. "*Assessment of accessibility to an early specific psychosis intervention programme (EPSIP): comparison with international performance measures.*" 7th International Conference on Early Psychosis (Amsterdam, The Netherlands).

June 2010: A Aznar, **A Barajas**, L Mas, N Puigdellívol, R Rubio, M Vidiella. . "*Estimación del coeficiente intelectual premórbido en una muestra de pacientes con diagnóstico psicótico.*" III Congreso de la Federación Española de Asociaciones de Rehabilitación Psicosocial (Valladolid, Spain).

June 2010: A Aznar, **A Barajas**, L Mas, N Puigdellívol, R Rubio, M Vidiella. "*Estimación del coeficiente intelectual premórbido en una muestra de pacientes con diagnóstico psicótico.*" XXIII Jornadas Nacionales de la Asociación Española de Neuropsiquiatría (Palma de Mallorca, Spain).

November 2009: **A Barajas**, M Teixidó, M San Emeterio, F Villegas, E Sánchez, L Mas, M Carbonero, R Casañas, MA Argany, I Álvarez, L Lalucat. "*Early Intervention in Psychosis: a descriptive study of current international programs.*" The 15th Biennial Winter Workshop in Psychoses (Barcelona, Spain).

November 2009: I Baños, **A Barajas**, J Usall, J Bertsch, R Iniesta, ME Huerta, M Dolz, B Sánchez, S Ochoa. "*Influencia del consumo de cannabis sobre el insight y la sintomatología psicótica en pacientes con un primer episodio psicótico.*" Reunión Internacional sobre las Fases Tempranas de las Enfermedades Mentales "Curso Evolutivo y Outcome en los Primeros Episodios Psicóticos" (Santander, Spain).

September 2009: **A Barajas**, M San Emeterio, M Teixidó, I Álvarez, MA Argany, M Carbonero, A Escudero, E Sánchez, L Lalucat. "*Catalan experience an Early Psychosis Specific Intervention Program (EPSIP): a descriptive study.*" 2nd European Conference on Schizophrenia Research (Berlin, Germany).

August 2009: M Dolz, **A Barajas**, M Pardo, S Ochoa, B Sánchez J Usall, I Baños, A Torres, D Muñoz, L San. "*Early Onset Psychosis: are there two different patterns of presentation?*" International Conference Sponsored by ESCAP: Quality of Life in Child and Adolescent Mental Health (Budapest, Hungary).

June 2009: **A Barajas**, E Serrano, S Peruzzi, L Vaquero, J Matalí & L San. "*Tratamiento Cognitivo Conductual de la Fobia a la Deglución en población infantil.*" 44 Reunión de la Asociación Española de Psiquiatría del Niño y el Adolescente (AEPNYA) (Pamplona, Spain).

April 2009: **A Barajas**, I Baños, E Huerta, A Miñambres, M Pardo, M Planella, J Usall, B Sánchez, M Dolz, S Ochoa. "*Cannabis use in first psychotic episode: differences in premorbid adjustment and early symptoms.*" Thematic Meeting "Major Psychoses and Substance Abuse" (Edinburgh, Scotland).

February 2009: M Fusté, **A Barajas**, M Sánchez, L Miquel, I Baños, E Huerta, J Usall, S Ochoa & Grupo GENIPE. "*Funcionament global en primers episodis psicòtics en funció del gènere.*" 2on Congrés Català de Dona i Salut Mental (Barcelona, Spain).

February 2009: I Baños, **A Barajas**, J Aguado, E Huerta, D Gómez-Ballesteros, C Solís, J Portos, M Castro, S Ochoa, J Usall, JE Obiols & Grupo GENIPE. "*Diferències de gènere en el nivel d'insight en pacients amb un primer episodi psicòtic.*" 2on Congrés Català de Dona i Salut Mental (Barcelona, Spain).

February 2009: **A Barajas**, I Baños, S Ochoa, J Usall, E Huerta, M Dolz, B Sánchez, V Villalta-Gil, A Foix, JM Haro & Grupo GENIPE. "*Diferències de gènere a les psicosis incipients: característiques premòrbides, prodròmiques i simptomatologia d'inici.*" 2on Congrés Català de Dona i Salut Mental (Barcelona, Spain).

November 2008: S Ochoa, **A Barajas**, I Baños, J Usall, V Villalta-Gil, M Dolz, B Sánchez, J Cervilla, M Vilaplana, A Foix, JM Haro, J Autonell. *"¿Existen diferentes tipos de necesidades en función de la evolución del trastorno psicótico?"* Congreso Nacional de la Asociación Española de Psicología clínica y psicopatología (Huelva, Spain).

November 2008: M Fusté, **A Barajas**, I Baños, J Usall, M Dolz, S Ochoa. "*Estudio de primeros episodios psicóticos: diferencias sociodemográficas y clínicas en función del género."* XII Congreso Nacional de Psiquiatria (Valencia, Spain).

May 2008: I Baños, **A Barajas**, V Carral, S Ochoa, O Gónzalez, B Sánchez, R Nogueroles, M Dolz, J Usall, JE Obiols & Grupo GENIPE. *"Primeros episodios psicóticos: consumo de cannabis y diferencias en adaptación premórbida."* XXII Jornadas Estatales AEN (Girona, Spain).

March 2008: **A Barajas**, J Usall, I Baños, S Ochoa, M Dolz, B Sánchez, JA Alda, JM Haro. *"Gender differences in First Psychotic Episode: Symptomatology and insight."* 3rd International Congress on Women's Mental Health (Melbourne, Australia).

February 2008: I Baños, **A Barajas**, V Carral, S Ochoa, O Gónzalez, B Sánchez, R Nogueroles, M Dolz, J Usall, JE Obiols & Grupo GENIPE. "*Primeros episodios psicóticos: consume de cannabis y adaptación premórbida."* XXII Jornadas Asociación Española de Neuropsicología (Barcelona, Spain).

February 2008: **A Barajas**, I Baños, M Pardo, V Villalta-Gil, M Dolz, B Sánchez, J Usall, S Ochoa. "*Early onset of psychosis: neurological soft signs, psychopathology and cognitive functioning."* 14th Biennial Winter Workshop on schizophrenia and bipolar disorder (Montreux, Switzerland).

November 2007: M Sánchez, **A Barajas**, I Baño, A Fargas, J Usall, S Ochoa & Grupo GENIPE. *"Diferencias de género en presentación clínica en primeros episodios psicóticos."* Congreso Nacional de Psiquiatría (Santiago de Compostela, Spain).

September 2007: **A Barajas**, I Baños, S Ochoa, J Usall, V Villalta-Gil, A Fargas, M Dolz, B Sánchez, JA Alda, JM Haro. "S*ocial and academic premorbid adjustment in first psychotic episode."* 1st European Conference on Schizophrenia Research (Düsseldorf, Germany).

August 2007: M Dolz, **ABarajas**, B Sánchez, J Usall, I Baños, A Fargas, A Torres, JA Alda, S Ochoa. "*There are differences in Neurological Soft Signs between adolescent and adult onset episode psychosis*." 13th International Congress European Society for Child and Adolescent Psychiatry (ESCAP) (Florence, Italy).

June 2007: **A Barajas**, M Pardo, M Dolz, I Baños, J Usall, S Ochoa. "*Estudio de primeros episodios psicóticos: características de inicio en la adolescencia. Resultados preliminares."* VII Simposium – Inicios en la infancia de los trastornos psiquiátricos 'adultos' (Córdoba, Spain).

TEACHING EXPERIENCE

09/2014 – present: Consultant on the subject "Adult Psychopathology". School of Psychology. Open University of Catalonia (Universitat Oberta de Catalunya - UOC).

2013 – present: Collaborating professor in the "Máster en Rehabilitación Psicosocial en Salut Mental". Fórum Salut Mental & Universitat Autonòma de Barcelona.

March 2001: Diploma Certificado de Aptitud Pedagógica (CAP). Universidad de Barcelona.

2000-2001: Teaching assistant. School of Nursing. University of Barcelona.

Training sessions in psychometric instruments:

- October 2013: Entrevista semi-estructurada Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) (1.5h)
- May – Nov. 2011:"Formació en escales utilizades en l'estudi: Avaluació de l'efectivitat del Programa d'Atenció Específica per a les persones amb un Trastorn Psicòtic Incipient (PAE-TPI) desenvolupat a Catalunya vs. el Programa Estàndard (PE)" (20h)
    - Positive and Negative Syndrome Scale (PANSS)
    - Social Functioning Scale (SFS)
    - Global Assessement Functioning (GAF)
    - Young Mania Rating Scale (YMRS)
    - Hamilton Depression Rating Scale (HDRS)
    - Quality of Life Scale (EuroQol-5D)
    - Side Effects Scale (UKU)
- May – Set. 2011:"Fiabilitat interobservadors en el marc de l'estudi: Avaluació de l'efectivitat del Programa d'Atenció Específica per a les persones amb un Trastorn Psicòtic Incipient (PAE-TPI) desenvolupat a Catalunya vs. el Programa Estàndard (PE)" (16h)
- May 2010: Early Recognition Inventory based on IRAOS (ERIraos) (3h)
- July 2009: Comprehensive Assessment of At Risk Mental States (CAARMS) (2h)

Clinical sessions:

February 2015: "Disseny del procés d'avaluació i rehabilitació cognitiva en un primer episodi psicòtic." Secció de Neuropsicologia. COPC (Barcelona, Spain) (1.5h).

February 2015: "Programa d'Atenció Específica a les persones amb Trastorns Psicòtics Incipients (PAE-TPI)." Grup BCN Salut Mental (Barcelona, Spain) (1.5h).

December 2014: *"Intervención Temprana en los Trastornos Psicóticos."* X Edición - Máster en Rehabilitación Psicosocial en Salud Mental. Fórum Salut Mental & Universitat Autonòma de Barcelona (Barcelona, Spain) (2h).

Oct. – Nov. 2014: "Valoració integral de necessitats en persones amb Trastorn Mental Sever." Grup BCN Salut Mental (Barcelona, Spain) (6h).

December 2013: *"Intervención Temprana en los Trastornos Psicóticos."* IX Edición - Máster en Rehabilitación Psicosocial en Salud Mental. Fórum Salut Mental & Universitat Autonòma de Barcelona (Barcelona, Spain). (2h).

November 2013: "Presentacions clíniques: Simptomatologia prodròmica en els trastorns psicòtics incipient: identificació a través de l'ús d'entrevistes semi-estructurades." Centre d'Higiene Mental Les Corts (Barcelona, Spain) (1.15h).

Jan. – Feb. 2012: "Supervisió de casos en el marc de l'estudi: Avaluació de l'efectivitat del Programa d'Atenció Específica per a les persones amb un Trastorn Psicòtic Incipient (PAE-TPI) vs. el Programa Estàndard (PE)." Centre d'Higiene Mental Les Corts (Barcelona, Spain). (5h).

October 2010: "*Detección temprana de la psicosis: un enfoque preventivo.*" Parc Sanitari de Sant Joan de Déu – Serveis de Salut Mental (Barcelona, Spain). (1h).

AWARDS

⇒ Best poster
REUNIÓ ANUAL DE LA SOCIETAT CATALANA DE PSIQUIATRÍA INFANTO-JUVENIL.
Title: "Estudi comparatiu de psicosis d'inici precoç i psicosis d'inici adult: diferències en el rendiment cognitiu."
Date: October, 2012 – Barcelona (Spain)

⇒ Best oral communication
3er CONGRÉS CATALÀ DE DONA I SALUT MENTAL.
Title: "Relació entre edad de pubertad i debut de psicosi en dones amb primer episodi psicòtic."
Date: October, 2012 – Barcelona (Spain)

⇒ Best poster
9ª REUNIÓN INTERNACIONAL SOBRE LAS FASES TEMPRANAS DE LAS ENFERMEDADES MENTALES. SERVICIOS E INTERVENCIONES PARA LAS FASES TEMPRANAS DE LAS PSICOSIS.
Title: "Assessment of an early intervention programme for psychotic spectrum disorders in community mental health centers: 1-Year outcome."
Date: October, 2011 – Santander (Spain)

⇒ Best poster
II CONGRÉS DE DONA I SALUT MENTAL.
Title: "Diferències de gènere en el nivell d'insight en pacients amb un primer episodi psicòtic."
Date: February, 2009 – Barcelona (Spain)

⇒ Best research work
SOCIETAT CATALANA DE PSIQUIATRIA I SALUT MENTAL. JORNADES DE CLOENDA
Title: "Gender differences in Psychosis."
Date: June, 2009 – Tossa de Mar – Girona (Spain)

⇒ Best research work
MASTER: *ADULT CLINICAL PSYCHOPATHOLOGY*. AUTONOMOUS UNIVERSITY OF BARCELONA.
Title: "Fases Temrpanas de la Psicosis: estudio del ajuste premórbido y la sintomatología premórbida."
Date: September, 2007 – Barcelona (Spain)

OTHER RELEVANT INFORMATION

⇒ MAIN RESEARCH AREAS

- Evidence of the effectiveness of cognitive rehabilitation in schizophrenia and other psychotic disorders.
- Psychometric instrument validation for detection of incipient psychosis.
- Gender differences in incipient psychosis.
- Epidemiology, course and outcome of incipient psychosis.
- Effectiveness of early specific intervention programmes in incipient psychosis.

⇒ REVIEWER OF JOURNALS

- I have performed reviews of articles for the journals Schizophrenia Research and Treatment, Psychiatry Research & Schizophrenia Research.

⇒ MEMBERSHIP IN ASSOCIATIONS

- Member of the Comissió de Recerca del Grup BCN Salut Mental, since January 2015.
- Member of the Sociedad Española de Patología Dual, since April 2014 (nº 2.029).
- Member of the Comitè Operatiu de Salut Mental i Addiccions de l'Àrea Integral de Salut Barcelona Esquerra, since January 2014.
- Member of the Secció de Neuropsicologia del Col·legi Oficial de Psicòlegs de Catalunya, since June 2013.
- Member of the Comité Ético de Investigación Clínica de la Unión Catalana de Hospitales, since September 2012.
- Member of the Fundació Acadèmia de Ciencies Mèdiques i de la Salut de Catalunya i Balears, since October 2009.
- Member of the Grup de Treball i Recerca de Dona i Salut Mental (GTRDiSM) within on the Societat Catalana de Psiquiatría, since 2007. Member of the scientific committee of the conferences organized since November 2013.
- Member of the Colegi Oficial de Psicòlegs de Catalunya (collegiate psychologist nº: 13,769, since March 2004).

⇒ LANGUAGES

- Spanish (mother tongue)
- Catalan (advanced level)
- English (Official Language School–studying advanced level - 5th). Intermediate level exceeded.

⇒ IT SKILLS

- Windows operating system.
- Office software: Microsoft Office (Word, Excel, Power Point, Access, Outlook); Adobe Acrobat.
- Statistical software: Statistical Product and Service Solutions (SPSS, v.20).
- Bibliographic software: Reference Manager, RefWorks and EndNote.
- Audiovisual software: Adobe Photoshop.
- Database of international journals in psychology and medicine: PubMed, Psycinfo, Cochrane database, etc.