Psychotic symptoms in genetic-at-risk and bipolar disorder samples: prevalence and related variables

Iria Mendez

UNIVERSITAT DE BARCELONA

Tesis Doctoral

PSYCHOTIC SYMPTOMS IN GENETIC-AT-RISK AND BIPOLAR DISORDER SAMPLES: PREVALENCE AND RELATED VARIABLES

Iria Mendez Blanco

UNIVERSITAT DE BARCELONA

PSYCHOTIC SYMPTOMS IN GENETIC-AT-RISK AND BIPOLAR DISORDER SAMPLES: PREVALENCE AND RELATED VARIABLES

Doctoral thesis report submitted by Iria Mendez to obtain a doctoral degree by the University of Barcelona

Supervised by:

Dr. Boris Birmaher
University of Pittsburgh
School of Medicine

Dr. Josefina Castro-Fornieles
Department of Medicine
University of Barcelona

Doctoral Program in Medicine and Translational Research

Faculty of Medicine and Health Sciences, University of Barcelona

July 2nd, 2021, Barcelona

Prof. Josefina Castro-Fornieles and Prof. Boris Birmaher certify that they have guided and supervised the doctoral thesis entitled "Psychotic symptoms in genetic-at-risk and bipolar disorders samples: prevalence and related variables", presented by Iria Mendez Blanco. They assert that codes of ethics and good practice have been followed and that they are not aware of any plagiarism. They hereby confirmed that this thesis fulfills the requirements to be defended in order to be awarded the title of Doctor.

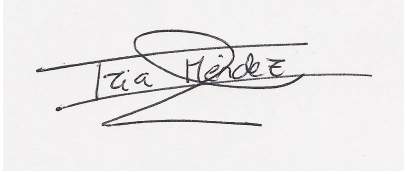
Signature and Data,

Boris Birmaher

Prof. Fina Castro-Fornieles *Prof. Boris Birmaher*

With this document, pre-doctoral stutent Iria Mendez formally declared that this thesis does not include any content that may constitute plagiarism, giving consent for this thesis to be subjected to a procedure to verify its originality.

Signature and Data,



2nd of June 2021, Iria Mendez

ACKNOWLEGMENTS

To my most precious treasures: Aina, Roi & Leo. I love you to the moon and back… *ad infinitum*.

ACKNOWLEGMENTS

This thesis would not have been possible without the incredible support of my directors, Dr. Josefina Castro from the Clinic Hospital, and Drs. Birmaher and Axelson from UPMC. Fina, I really want to express my most sincere gratitude. You never lost faith in me. I met you in my last year of residency, and you have guided me through the world of child and adolescent psychiatry from the very beginning. I may say that you have been an inspiration for me and many other women in our field; you have made our world much easier. Boris and David, being your trainee was one of the greatest opportunities in my life. You were such great professors that I do not possess the words to express my acknowledgement. You were incredibly clever, visionary, demanding and caring all at once. You have given me so much advice that I keep in my working memory every day, and that I am teaching to the new generations in order to honor your wisdom.

Of course, I am indebted to the Koplowitz Foundation for its continued funding, first in my training as a child psychiatrist, and again during the internship for my PhD.

Thank you to my colleagues at the Clinical Hospital. Having the opportunity of working with you has been a great pleasure. We have laughed, fought and laughed again for years, at our "de-briefing Friday meetings", the best coping strategy to deal with the stress of combining our work as clinicians and the PhD. Inma, Sara, Olga, Carlos, Vanessa, Mireia, Elena, and many others. You have been great. Sole, Pilar, Itziar, the DBT team. It seemed impossible in the beginning, but we did it, we found the middle path. Rosa, Luisa, Astrid. Thank you so much for being my advisors. I have listened carefully and mindfully. Maybe I have not always been able to express

my gratitude, let me say that it was with the deepest wish for common good. Please let me make amends with this public declaration of admiration for your work.

I would especially like to congratulate Roger Borras, my statistician, coach and friend in the last few years. There were some really bad days of analyzing data and answering reviewers, but you never gave up. And many thanks to my English teacher, Russell, "my style corrector", and advisor, taking hours at any time of day in order to fit in my busy agenda.

Finally, I would like to thank my family for their support during all these years. My parents, for teaching me the values of perseverance and persistence, and for encouraging me to explore new frontiers without losing my genuine essence. You are my wise mind; it has been a real honor to be your daughter. Thank you to my loving aunt and uncles for kindly laughing with and at me in my neurodevelopmental process to "mature" adulthood. Thank you to my grandparents for showing me how to be generous and respectful with others' beliefs and backgrounds, and how to love without expecting anything in return. Thank you to my dearest cousins, Antia who generously came to the US to babysit an 18-month-old girl while I was writing my first article; and Sabela, who managed this summer with my three children while I was finishing this dissertation. Thank you to my ex-husband for hours and hours of home working, in order to be equal and return my previous investment in his PhD. Thank you to my in-laws for years of support and love. Thank you to Albina for cooking and caring so lovingly these last months. And of course, thank you to my closest friends Sabela, Ana, Anna, Teresa, Montse, Paula, Sole again, and the "old team", Héctor, Victor, … you know who you are. There have been years of complaints about my PhD, and hours and hours of gossiping, even online gossiping. Thank you for always pushing me up, I would like to say, forever.

FUNDING

This work was supported by different sources. First, the BIOS study received funding by grant MH60952 from the National Institute of Mental Health (NIMH). The second study developed in Spain was supported by the Spanish Ministry of Health, Institute of Health Carlos III ISCIII (PI11/01224) and the European Development Fund (ERDF). In addition, Iria Mendez was funded by the Koplowitz Foundation twice, first with a two-year fellowship in child and adolescent psychiatry at the UPMC, while she started this project. Second, with a 3-month internship grant to finish the cleaning data process at the UPMC.

TABLE OF CONTENTS

APS: Attenuated Psychotic Syndrome.

ARMS: At Risk Mental States.

SCH: Schizophrenia/ Schizophrenia and related disorders.

BD: Bipolar Disorder.

MDD: Major Depression Disorder

FEP: First Episode of Psychosis.

BD-psy: Bipolar Disorder with psychotic features.

BD-nonpsy: Bipolar Disorder without psychotic features.

MDD-psy: Major Depression with psychotic features.

DO: Disorder/ Disorders.

CHR: Clinical High Risk.

GHR: Genetic High Risk.

IQ: Intellectual quotient.

PLE: Psychotic-Like Experiences.

UHR: Ultra High Risk.

EIS: Early Intervention Services.

This thesis has been written by the Child and Adolescent Psychiatry and Psychology Department of Clinic Hospital (Barcelona, Spain) and the Child and Adolescent Bipolar Spectrum Services (CABS) at Western Psychiatric Institute and Clinic of UPMC (University of Pittsburgh Medical Center; Pittsburgh, US).

This work is a compilation of the following two papers, both published in international journals with a global impact factor (IF) of 6,39 and 0,79 respectively (ISI Web of Knowledge, Journal Citation Reports 2019). We have included additional unpublished information from the baseline analysis of study 1.

Study 1: **Iria Mendez, MD;** David Axelson, MD; Josefina Castro-Fornieles, MD, PhD; Danella Hafeman, MD, PhD; Tina R. Goldstein, PhD; Benjamin I. Goldstein, MD, PhD; Rasim Diler, MD; Roger Borras, MSc; John Merranko, MSc; Kelly Monk, RN; Mary Beth Hickey, BA; Boris Birmaher, MD. "Psychotic-Like Experiences (PLE) in Offspring of Parents with Bipolar Disorder and Community Controls. A Longitudinal Study". J Am Acad Child Adolesc Psychiatry. 2019 May; 58(5):534-543.e6. doi: 10.1016/j.jaac.2018.09.440. Epub 2018 Nov 3. PMID: 30768403. IF: 6,39; Q1.

Study 2: Iria Mendez, MD; Josefina Castro-Fornieles, PhD, MD; Sara Lera-Miguel, PhD; Marisol Picado, PhD; Roger Borras, MS; Sandra Cosi, PhD; Marc Valenti, PhD, MD; Pilar Santamarina, PhD; Elena Font, PsyA; Soledad Romero, PhD, MD. "Functional and Academic Impairment in Adolescents with Early-Onset Bipolar Disorder Compared to Healthy Controls: a Case-Control Study".J Can Acad Child

Adolesc Psychiatry. 2020 Aug;29(3):149-164. Epub 2020 Aug 1.PMID: 32774398. IF: 0.79, Q2.

ANTECEDENTES: Casi el 20% de la población adulta[1] e infanto-juvenil[2] experimenta síntomas psicóticos en algún momento de su vida. Si bien se había postulado su carácter benigno, estudios recientes señalan su potencial valor predictivo de transición hacia psicosis [3,4]. Tener un familiar de primer grado con un Tr. psicótico no afectivo sería el principal factor de riesgo[5], con resultados no concluyentes para la carga familiar de Tr. Bipolar[6]. Diversos factores ambientales estarían relacionados con el riesgo de desarrollar síntomas psicóticos, y en menor medida en su transición a psicosis franca[7]. La presencia de síntomas psicóticos en el curso del Tr. Bipolar se asociaría a mayor severidad en población adulta[8], aunque disponemos de poca evidencia en población infantil[9].

HIPÓTESIS: La hipótesis principal del proyecto será que la herencia familiar para el trastorno bipolar (TB), y más específicamente el fenotipo con síntomas psicóticos, aumentará el riesgo de síntomas psicóticos sub-umbrales o atenuados en muestras no clínicas infanto-juveniles a lo largo de su evolución, así como su posterior evolución a trastornos psicóticos afectivos. Como hipótesis secundaria, se plantea que otros factores de riesgo ambientales como insultos perinatales, infecciones, o exposición a trauma, aumentarán el riesgo para el desarrollo de síntomas psicóticos sub-umbrales en estas poblaciones. Se plantea así mismo que los hijos de pacientes con TB subtipo psicótico, presentarán más síntomas clínicos y peor nivel de funcionalidad en mayor proporción que los hijos de TB sin psicosis a nivel basal. Ya en poblaciones clínicas con TB, tanto adultas como infanto-juveniles, se plantea que la presencia de síntomas psicóticos umbrales se asociará a mayor severidad clínica y deterioro funcional.

OBJETIVOS: El principal objetivo de este estudio es estudiar el fenómeno de los síntomas psicóticos en el contexto del trastorno bipolar (TB), desde su expresión de menor intensidad, síntomas psicóticos subumbrales ("Psychotic Like Symptoms": PLE) en poblaciones de alto riesgo genético, hasta síntomas psicóticos umbrales en el curso del trastorno bipolar. Utilizando dos muestras diferentes, se analizó la prevalencia de estos síntomas en poblaciones de alto riesgo genético, poblaciones sin riesgo, y pacientes con un TB ya desarrollado. Se analizaron también factores de riesgo genético y ambientales para el desarrollo de los síntomas. Y, por último, su impacto funcional.

METODOLOGÍA: Se han utilizado dos estudios diferentes. Primero, el estudio BIOS, un estudio longitudinal prospectivo con una muestra comunitaria de menores de 6-18 años con alto y bajo riesgo para TB; BIOS incluye una muestra basal de padres con Trastorno Bipolar que también fue analizada, junto con sus hijos. Se complementó con una muestra de adolescentes 12-18años con TB pareados por sexo y edad con controles sanos. Todos los resultados se analizaron siguiendo modelos paramétricos descriptivos, con modelos de regresión logística y modelos de predictivos de supervivencia según fuese necesario.

RESULTADOS: A lo largo de los 11 años de seguimiento de hijos de alto riesgo genético e hijos de controles sanos, la prevalencia de síntomas psicóticos aumentó de forma progresiva hasta un 15%, y 2.5% desarrollaron un trastorno psicótico en ambos grupos. Tener un familiar de primer grado con TB no incrementó el riesgo para síntomas psicóticos sub-umbrales, pero sí la presencia de un trastorno psiquiátrico,

bajo nivel de funcionalidad y una historia previa de abusos físicos o sexuales. Los padres bipolares con síntomas psicóticos difirieron de forma estadísticamente significativa en un predominio del subtipo Bipolar I; mayor comorbilidad, e inferiores resultados a nivel de funcionamiento global. Sus hijos, presentaron mayor prevalencia de Tr. por Estrés Post-traumático, y mayor abuso de sustancias en los hijos de no psicóticos, sin diferencias a nivel funcional. Al analizar los adolescentes con TB y adolescentes sanos, los TB incluso en eutimia presentaron menor nivel de funcionalidad que los controles, siendo la presencia de síntomas psicóticos la variable más correlacionada con pérdida de funcionalidad.

1. INTRODUCTION

1.1. Psychotic disorders vs. psychotic symptoms: evolution from a categorical model toward a continuum model for psychosis.

Since the development of operational diagnostic criteria in the last quarter of the 19th century, the concept of psychosis or psychotic symptoms have been linked to the presence of a severe mental illness, a psychotic disorder, either schizophrenia (SQZ) or affective psychotic disorders (BD or MDD with psychosis)[10,11]. Therefore, once psychotic symptoms are confirmed, the diagnosis is confirmed, following a categorical model for disease with only two possibilities: disease present or disease absent. Starting with DSM-III the existence of pre-psychotic symptoms has been included in the course of the SQZ, and also for BD in DSM-5[12] under the section II: "Conditions for further study". However, there is no possibility for a formal diagnosis of "intermediate phenotypes" other than "schizotypal personality disorder", "unspecified SQZ or BD", or the new category called "other specified BD and related disorders".

Research on the phenomenology and etiology of psychotic experiences has challenged the categorical model for decades. First, genetic studies have shown a shared liability for a variety of mental disorders, and specifically between affective and non-affective psychotic disorders[7,13,14]. Second, longitudinal studies have demonstrated the instability of psychotic disorder diagnoses during the first years after the onset of the first psychotic episode[15–17]. And third, epidemiological studies have shown that psychotic symptoms are much more prevalent in general populations than previously thought[1,18,19]. And, as will be explained later, in addition to representing a feature of psychotic disorders, psychotic experiences also occur in non-psychotic disorders and personality disorders. It is also very prevalent among first-

degree relatives of psychotic patients. It is also an isolated phenomenon in otherwise healthy individuals. Therefore, psychosis is contextualized nowadays as an extended phenotype ranging from benign and transitory experiences to that requiring medical care.

The possibility of intermediate phenotypes or proneness states in non-clinical populations is not new in psychiatry. Clinicians have observed for decades the presence of psychotic symptoms of a lower degree in the months or years previous to the onset of a psychotic disorder, or in patients who would never develop the illness or require hospitalization during follow-up. And note that the majority of authors linked the presence of previous psychotic symptoms only with later risk for SQZ-like disorders, and not with affective psychosis (BD or MDD).

Kraepelin was the first to describe minor changes in mood and behavior months or years before the onset of a mental disorder[20,21]. For example, in the case of *dementia praecox*, the early symptoms would progressively develop from childhood to adolescence[22]:

"Usually, psychosis begins with symptoms of general malaise and uneasiness, headaches, ear noises, dizziness, disagreeable feelings in different parts of the body, insomnia and poor appetite. The sick persons become shy, withdrawn into themselves, down- cast, anxious, stop working, express vague concerns especially with hypochondriac contents" (Kraepelin 1893, 439).

"A latent schizophrenia is already a type of psychosis"[22].

When, sometime later, Bleuler adapted Kraepelin's dementia to the construct of Schizophrenias, he also described the presence of uncharacteristic symptoms such as increased distraction, forgetfulness, reduced emotional reactivity or anhedonia, and avolition before the onset of full-scale hallucinations and delusions. Although initially

However, he included them as part of the core symptoms of the diseases, with no "at risk" or "prodromal state.

However, the notion of "prodrome" gained interest among his contemporaries, with the terms of "depressive prodromes" or "prodromal pseudoneurasthenia" (Pascal, 1906) under debate. In fact, in the 3rd edition of his textbook, Bleuler used Kretschmer's term "schizoid" for the first time to refer to the unresolved dilemma of qualitative versus quantitative boundaries between predisposition and disease:

"As from which level of anomaly on a person should be classified solely as a "schizoid" psychopath or else as schizophrenic and mentally ill, is still not possible to define at all (Bleuler, 1920)."

During the 1920s interest in the early stages of psychosis grew, encouraged by the mental hygiene movement, and reinforced by the success of early diagnoses and interventions in other branches of medicine[22,23]. In 1927 Sullivan noted that, "psychiatrists see too many end states and deal professionally with too few of the pre-psychotic"[24,25], or "early cases" for Mayer-Gross (1938)[22]. But it was not until 1938 that Cannon first used the term "early SQZ"[21] to classify the first retrospective analysis of early symptoms. He based his conclusions on a sample of 100 inpatients, admitted to hospital for the first time, including testimonies from their families and friends[26]. In those with a psychotic disorder, he found two groups of symptoms already present days or years before the hospitalization was necessary: specific symptoms (e.g., ideas of being observed and talked about, hallucinations, odd somatic experiences) associated only with SQZ; and nonspecific symptoms (e.g., nervousness, sleeplessness, lack of concentration, depression), that were diagnostically ambiguous since these symptoms could precede a wide range of disorders.

After World War II, interest shifted to psychoanalysis and psychodynamic

orientations, where psychotic disorders were conceptualized as a psychosocial process[27]. As a result, the borders between character eccentricities and SQZ or other psychotic disorders faded, all of them being considered psychological maladjustment at different levels of severity. Therefore, the idea of a "prodrome" or "pre-psychotic state" was abandoned, although research in the field scarcely continued. The concepts of attenuated or sluggish forms of psychosis were studied in the Soviet Union[22]. While in Germany, Huber and Gross G., from the phenomenology school of Heidelberg and Bonn, returned to the idea of "fundamental, primary or basic symptoms". They defended the idea of preliminary stages of early psychosis, called as "failure states". These were essentially a collection of subjective experiences of subtle cognitive deficits and changes in self-feeling perceptions, present before the onset of the acute episode. Although originally considered as a unified model of psychosis in general, including both SQZ and affective disorders, later it was restricted to the SQZ-like subtype[22].

Furthermore, in 1958, Conrad[28,29], based on his clinical experience in a military hospital, introduced for the first time the idea of a stage model for psychosis, in this case restricted to SQZ. A similar concept was defended years later by Docherty (1978) in the US[22,30]. K. Conrad, based on his observations working with young soldiers in a military hospital, established five phases in the evolution of the illness: Trema, Apophany, Anastrophe, Apocalypsis, and Consolidation. The first three consisted of a series of progressive behavioral changes, initially very unspecific, like increased withdrawal or progressive lack of association, previous to the onset of a full delusional structure.

Jet in the 1960s, clinical psychologists from different backgrounds began to recognize that cognitive deficits in patients with SQZ hindered the process of

psychotherapy. Thus they had to develop a new approach, which progressively turned into the field of experimental psychology, exemplified by the works of Chapman and Freeman in the US, and McGee in the UK. They introduced the idea of basic symptoms, which emcompassed cognitive deficits as a previous phase in schizophrenic patients with less than three years of evolution[22].

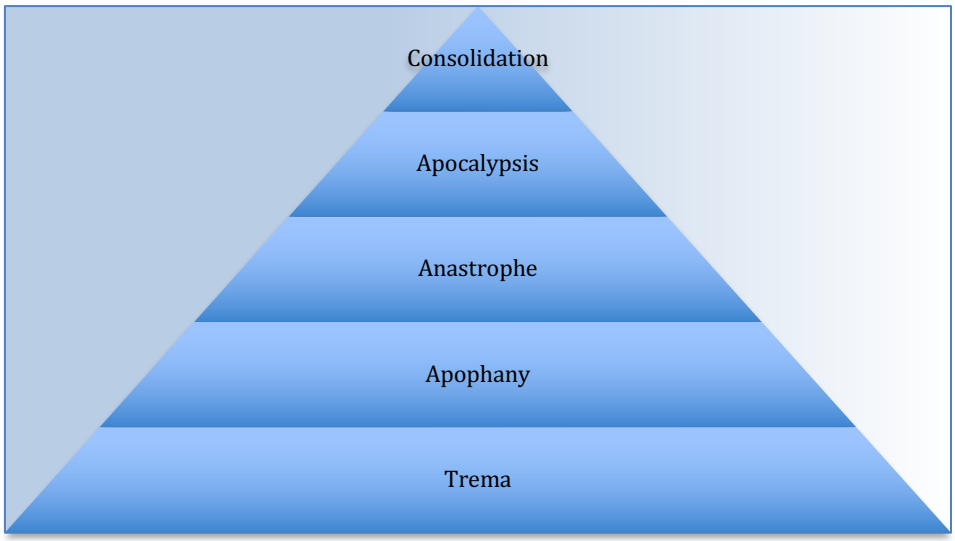


Fig.1: K. Conrad's Five-Stage Model for Schizophrenia (Conrad, 1958)[28].

Trema (stage fright): the patient has the feeling that something very important is about to happen which causes fear;
Apophany: the perception - those random and independent events are -connection- connected and make sense;
Anastrophe: - delusions appear suddenly as a revelation, concerning what had been perplexing during delusional mood and often bring relief;
Apocalypsis: - complete loss of reality and control of self;
Consolidation: the individual can "encapsulate" the delusions or abnormal perceptions.

Meanwhile, retrospective and prospective studies with schizophrenic subjects continued to appear during the 1970s and 1980s, summarized by McGlashan[31,32] in this way:

1) the instability of the first diagnosis, with changes over subtypes during the early years;

2) the heterogeneity in the course of the illness, depending on multiple variables with duration of the untreated illness among others;

3) the course of the illness, rather than relentlessly progressive, appears to plateau after 5-10 years, as well as the response to treatment;

4) the type of symptoms also fluctuates through different phases of the illness.

"The course of positive and negative symptoms in SQZ is variable depending on the phase of the disorder. In first or early episodes, positive symptoms are frequent, negative symptoms are infrequent, and both types are unstable, fluctuating, and usually they respond to treatment. In subacute/subchronic stages of the illness, negative symptoms increase in prevalence, they are at least as common as positive symptoms, and fluctuate less. In the later stages of the illness, negative symptoms are quite stable and usually dominate the clinical picture"[33].

McGlashan concluded that in most cases the onset is preceded by a variety of unspecified symptoms as well[32], which were grouped by Birchwood into 4 dimensions[34]: a) anxiety/agitation; b) depression/withdrawal; c) disinhibition, and d) incipient psychotic symptoms.

In 1989 the results of the ABC Study[30,35,36] finally confirmed the progression of SQZ in 5 stages, although not exactly as Conrad and Docherty hypothesized. Based on a total sample of 232 schizophrenics, Häfner et al. confirmed a prodromal stage in 73% (170) of cases, which could be divided into two phases:

A) **Prodromic phase** that lasts 4.8 years on average, and with a predominance of negative symptoms and unspecified symptoms;

B) **Psychotic pre-phase**, only one year previous to the onset of the disease, with mild positive symptoms.

Furthermore, the study also confirmed a progressive residual stage after 5 years of follow-up.

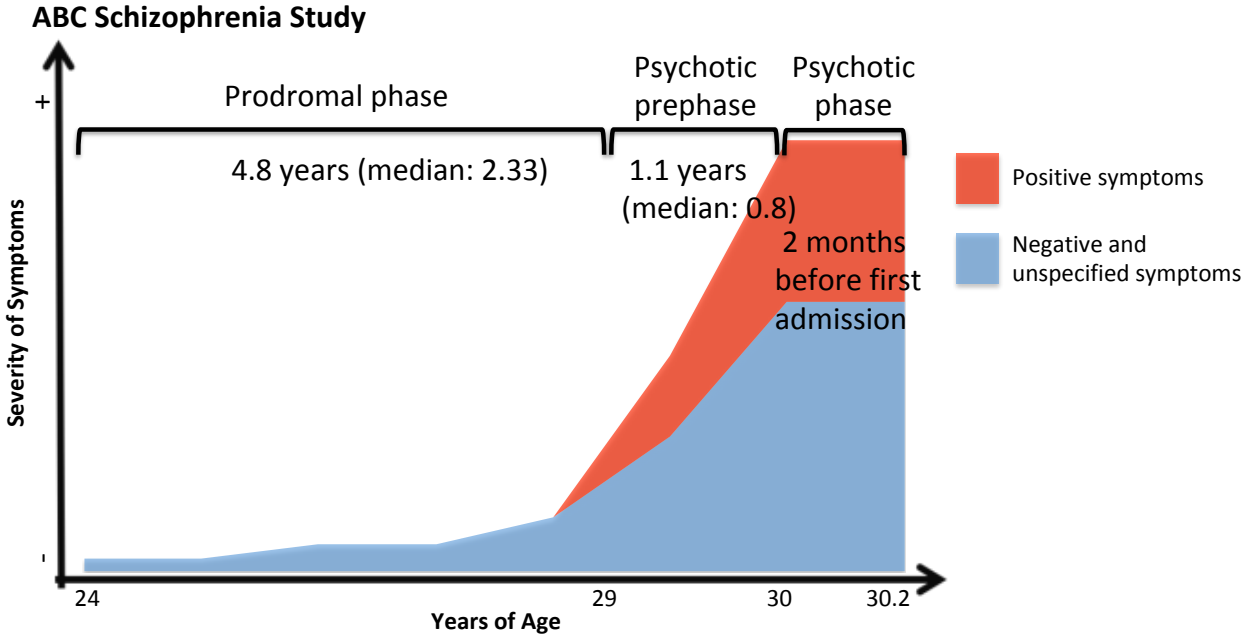


Fig.2. Phases of Progression towards Schizophrenia (Häfner, 2004)[37].

At the same time, the first prospective studies with cohorts of first episode psychosis[24,38,39] confirmed an association between worse response to treatment and longer duration of untreated psychosis (DUP) (first episode)[40,41] or longer duration of untreated illness (DUI) (first episode + prodrome)[42]. They confirmed as well the instability of the diagnosis in first psychotic episodes not only between subtypes of SQZ, but also between SQZ and BD[15,43–46].

In parallel, from the late 1960s, several cohorts from the general population (birth-cohorts, school-based studies, conscript studies) confirmed a progression from cognitive deficits towards the onset of a psychotic disorder[25,47–49]. Morevover, cohorts with first- and second-degree relatives of psychotic patients confirmed not only an increased risk for psychotic disorders[24,50], but also a higher prevalence of negative and positive symptoms in otherwise healthy individuals[51–55]. What partially confirmed the

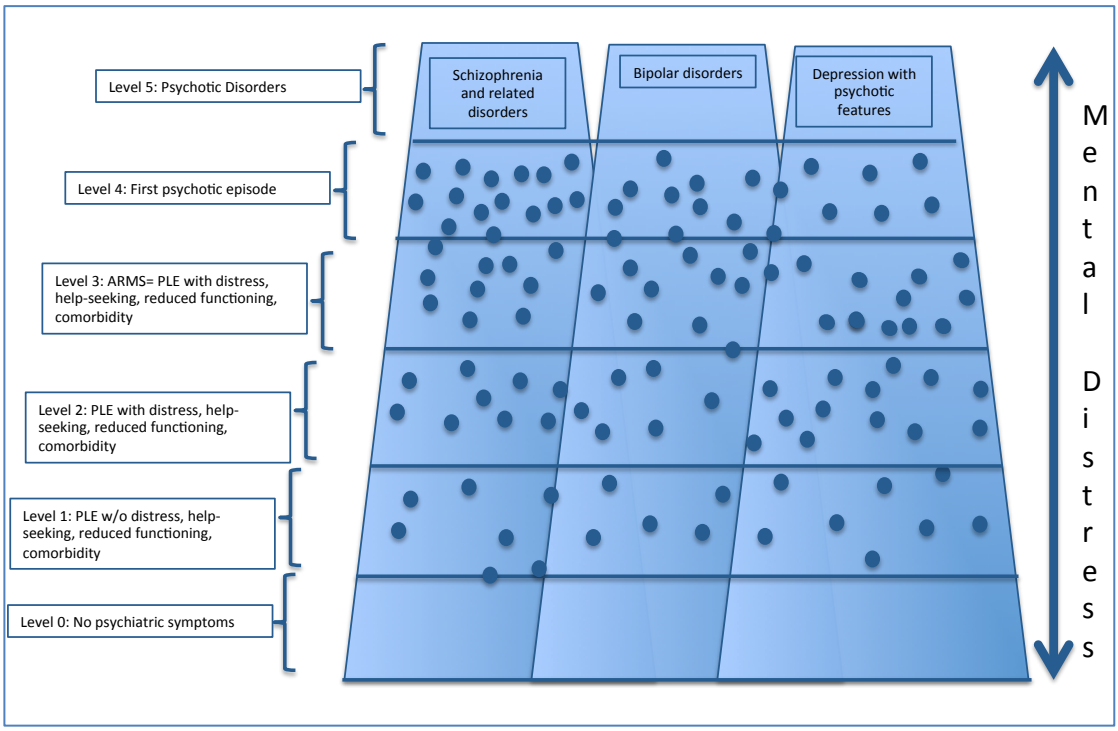
hypothesis of Meehl in 1962[25,56], about the existence of a continuous neurological process from schizotaxia through schizotypy and finally the onset of SQZ.

Encouraged by the large amount of evidence confirming early symptoms in psychosis, and the hypothetical benefits from early intervention, in 1989 in the UK, and in 1996 in Australia[25,57,58] the first Early Intervention Services (EIS) were provided. Both focused on the whole spectrum of psychosis (SQZ-like and affective disorders), and includinged a prodromic stage, called "At Risk Mental State" (ARMS) based on a multi-staging approach[17,59–61] (see section 1.2). These initiatives were soon followed by similar ones in Germany[62–64], Scandinavia[65], and North America[66–69]. In addition, EIS have become very popular in recent years and are spreading across the world[70], organized through the International Early Psychosis Association (IEPA)[64].

1.2. Operational diagnostic criteria for the continuum model for psychosis and levels of care: from psychotic-like symptoms (PLE) toward affective and non-affective psychotic disorders.

The EIS have organized their level of care following a 5-stage model: Yung's Pyramid of Risk (Fig. 3)[71–73]. This PhD project was conceptualized based on Yung's Pyramid, so from now on the dissertation will follow the same stages.

Fig.3: Yung's Pyramid of Risk: 5-Stage Model, adapted from Yung (2006)[71] and Fusar-Poli (2014)[72,73].



At the bottom of Yung's pyramid, **level 0,** is where you would find the majority of the population, with neither psychotic symptoms nor mental disorders.

People with subthreshold psychotic experiences, more commonly known as "psychotic-like experiences" (PLE)[1,74], are included in **level 1** and **level 2**. **Level 1** refers to "PLE without clinical impact". Most of them are sporadic, without any relation to psychiatric disorders, and do not cause distress and do not require help

from mental health services. **Level 2** corresponds to "PLE with clinical impact", PLE that appeared associated with emotional distress, help-seeking behaviors, or reduced functioning. It also includes those PLE that appeared in the context of any psychiatric disorder other than psychotic disorders, most frequently anxiety, reactive depression, drug abuse, and post-traumatic stress disorder.

PLE have received great interest in recent years, as I will explain later (section 1.4), due to its potential transition to level 3 and up. However, the definition of PLE is still unclear. In the majority of studies, PLE are defined based on assessment scales, with a predetermined a priori threshold. However, there is a huge variation between scales, including self-reported scales and face-to-face interviews, and also in the threshold criteria employed[75]. While in some studies PLE were restricted to hallucinations and delusions, in others they included any psychotic symptoms, such as negative symptoms or eccentric behaviors, magic thinking, out-of-body experiences, or social anxiety as well[1,2].

Level 3 corresponds to the Ultra High Risk (UHR) or Clinical High Risk (CHR), in order to differentiate them prodrome/prodromal states, psychosis risk syndrome (PS) or psychotic symptoms[1,76–78]. The Orygen Team proposes three categories at this level (Table 1), two in the form of true hallucinations or delusions as defined by DSM, just below the threshold of what is considered a psychotic disorder: "Attenuated Psychotic Symptoms" (APS), and "Brief Limited Intermittent Psychotic Symptoms" (BLIPS). It includes a third category of decline in functioning in individuals at genetic risk or schizotypal traits, "Genetic-High Risk" (GHR). Add note that DSM-5 includes the concept of APS, although only in section III "conditions for further study" due the current controversy[79–81].

Table 1: Inclusion Criteria for Early Intervention Teams, adapted based on Orygen (McGorry, 1996) (P. D McGorry et al., 1996; Patrick D McGorry et al., 2003).

PRODROMIC STAGE	**ULTRA HIGH-RISK criteria (UHR)**
Attenuated Psychotic Symptoms (APS)	Severity <5-6 CAARMS Frequency <3-6 Period: 1-5 years
Brief Limited Intermittent Psychotic Symptoms (BLIPS)	Frequency 4-6 Severity 5-6 CAARMS <1 week over 1-5 years previous
Genetic High Risk (GHR)	First degree relative with a psychotic disorder or schizotypal personality Significant decrease in mental state or functioning maintained for at least a month and not longer than 5 years (reduction in GAF Scale of 30 percent from pre-morbid level)
PSYCHOTIC Stage	**FIRST PSYCHOTIC EPISODE**
Either Schizophrenia like or Affective Psychosis	Last < 5 years

The UHR criteria have been the most frequently used by EIS across the world. However, they have been criticized for being excessively biased towards the positive symptoms of psychosis, without any mention about the negative or cognitive dimension[72].

Following a different approach, the German Research Network for SQZ introduced the concept of basic symptoms (Huber and Gross)[63,82–84]. Basic symptoms are defined as subjectively experienced disturbances in various domains, including perception, thought processing, language, and attention, that are distinct from classic psychotic symptoms. Working along these lines, they added two more categories to the UHR criteria, the COPER (cognitive-perceptive disturbances) and the COGDIS (cognitive disturbances), which were finally merged into the single category of

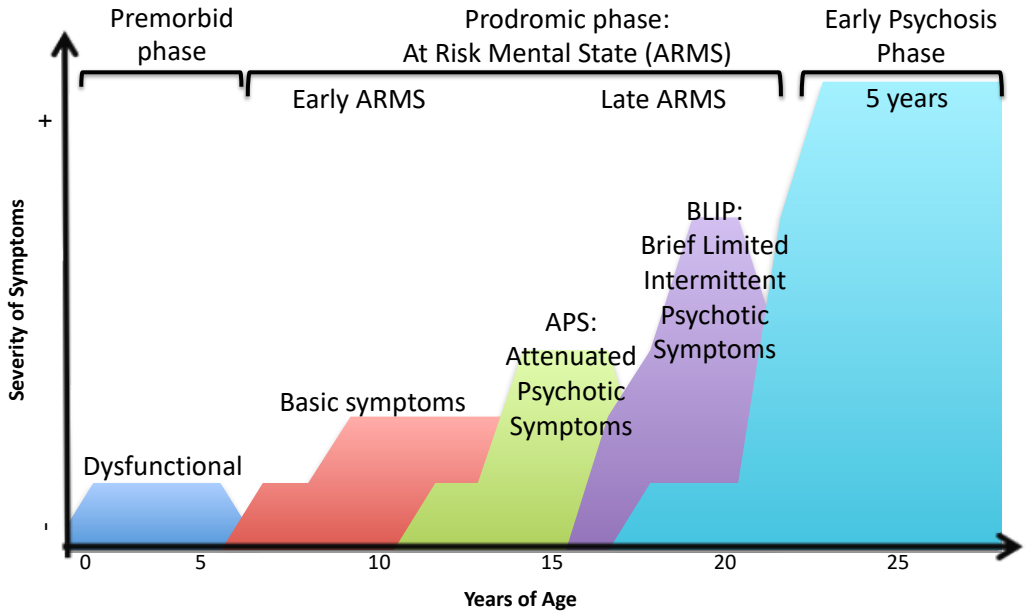
COGDIS[85] (Table 2). In the Recognition and Prevention Program (RaPP), at the Zucker Hillside Hospital (New York), also incorporated a category of Basic symptoms in their CASIS criteria[69,78].

Table 2: Additional Criteria with the Inclusion of Basic Symptoms in the UHR samples.

PRODROMIC STAGE	ULTRA HIGH-RISK criteria (UHR)
COPER **(Cognitive and perceptive disturbances)**	At least any 2 of the following 10 basic symptoms (1) Thought interference (2) Thought perseveration (3) Thought pressure (4) Thought blockages (5) Disturbance of receptive speech (6) Decreased ability to discriminate between ideas/perception, fantasy/true memories (7) Unstable ideas of reference (8) Derealization (9) Visual perception disturbances (excl. hypersensitivity to light or blurred vision) (10) Acoustic perception disturbances (excl. hypersensitivity to sounds) Occurrence of at least 'several times in a month or weekly' within the past 3 months
COGDIS **(Cognitive Disturbances)**	At least any 2 of the following 9 basic symptoms • Unestable ideas of reference • Disturbances of abstract thinking • Inability to divide attention • Thought interference • Thought pressure • Disturbance of receptive speech • Disturbance of expressive speech • Thought blockages • Captivation of attention by details of the visual field Occurrence of at least 'several times in a month or weekly' within the past 3 months

The UHR and basic symptoms criteria relate to contemporary classifications of clinical features, with the basic symptoms criteria perhaps identifying an earlier prodromal state, and the UHR criteria reflecting a somewhat later phase (Fig. 4). There is an increasing tendency to use both when assessing HR individuals[85–88].

Fig. 4: Model of Psychosis Onset from the Clinical High-Risk State, adapted from Fusar-Poli 2013[77].



Level 4 refers to the first episode of psychosis (FEP), regardless of the specific diagnosis. This is a stage where the psychotic disorder may not be completely defined.

The criteria for the formal diagnosis in **levels 4** and **5** are those from DSM-5[12]:

Type of psychotic symptoms: for the diagnosis of SQZ and related disorders, at least 2 symptoms from at least 3 categories are required, summarized in Table 3. There is not any specific mention of the type of psychotic symptoms required for BD or MDD, only a general description of hallucinations and delusions relegated to the section of specifiers. Alterations of speech are recognized as cardinal symptoms both

for mania and depression, but not disorganization. And note that catatonia is considered an independent specifier in the case of BD and MDD.

Severity of symptoms. For a significant proportion of the time since the onset of the disorder, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly affected.

Duration of symptoms. A minimum duration of symptoms is required: one day for brief psychotic episodes; one week for full mania; two weeks for an episode of schizo-affective disorder or depression; and four weeks for acute symptoms plus up to 6 months for SQZ or delusional disorder. In the pyramid of risk, duration marks the division between level 5 and 4: level 5 for those cases that last more than five years; and level 4 for those with less.

Exclusion criteria. It is explicitly necessary to rule out alternative diagnoses that could show a similar phenomenology.

Regarding age of onset, DSM-5 specifies that the three psychotic disorders can be diagnosed at any age, although they are unusual before 10 years of age. It specifies also that BD with psychotic features is slightly more prevalent in adolescents than in adults.

Table 3: The Five Dimensions of Psychotic Features included in DSM-5(American Psychiatric Association, 2013).

Type of psychotic features	
Delusions	· Defined as fixed beliefs that are not amenable to change in light of conflicting evidence. · Their content may include a variety of themes, including: Persecutory, referential, religious, grandiose, erotomanic, nihilistic and somatic delusions. Includes the concept of bizarre delusions, if they are clearly implausible.

	· May also involve thought withdrawal or insertion, or the belief that one is controlled by an outside force
Hallucinations	· Hallucinations are perception-like experiences that occur without an external stimulus, perceived as vivid and clear, and not under voluntary control. · They can occur in any sensory modality. · It is necessary that clear sensorium be preserved.
Disorganized Thinking (Speech)	· Derailment or loosening of associations, tangential or incoherent speech, severe enough to substantially impair communication
Grossly Disorganized Or Abnormal Motor Behavior (Including Catatonia)	· Difficulty in sustaining goal-oriented behavior. · Includes several subtypes of catatonic behaviors: negativism; mutism or stupor; excitement; and others such as stereotyped movements, staring, grimacing, or echoing of speech.
Negative Symptoms	· Explicitly remarked that seems specific of SQZ. · Includes diminished emotional expression, including speech and non-verbal expression. · 4's: Abolition, alogia, and anhedonia, Associability.

Finally, **level 5** corresponds to the fully developed psychotic disorders after 5 years of evolution: 1) SQZ and related disorders; 2) BD with psychotic symptoms (BD-psy); 3) MDD with psychotic symptoms (MDD-psy). Here the psychotic disorders fall into a very discrete category, there can be no doubt as to the diagnosis.

The 5-stage model of Yung's Pyramid implies specific interventions for each level and reorganizations of mental health services with the aim of preventing progression to a higher stage. Following this model, individuals at level 0 do not require any clinical attention, and apparently neither do those at PLE first onset (level 1), other than some form of counseling for the latter. When PLE increase in frequency and intensity (level 2), it is time for standard mental health services in the community to act. Over time, for those who transition to ultra-high risk (UHR) or a first psychotic

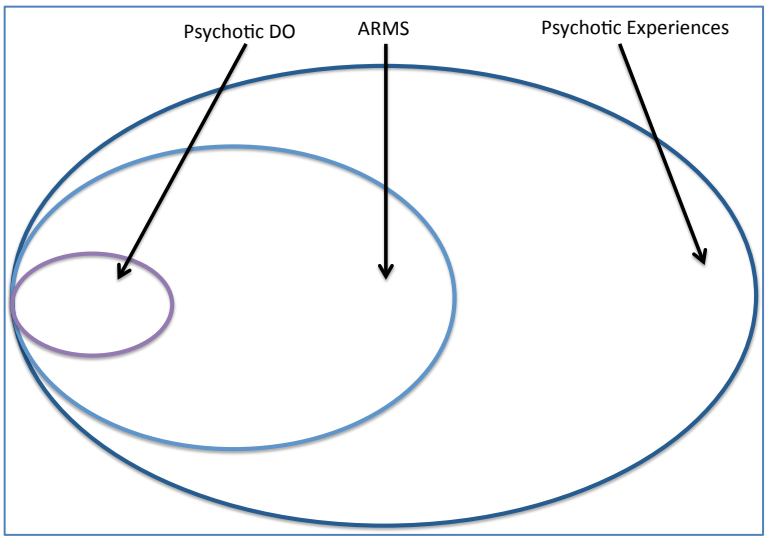
episode (FEP) (levels 3 and 4), early intervention services (EIS) are required, offering an intensive and multi-disciplinary approach. Some cases will reach level 5, at which time they will be returned to standard mental health services or, in a minority of cases, they will enter long-term residential programs.

Over the past two decades there has been a great amount of research and investment in EIS all over the world, encouraged by the ideal of improving the outcome of psychotic disorders with early intervention. Indeed, the level of knowledge about early stages of psychosis has increased substantially (see following sections 1.3-1.5). However, the cumulatie evidence has revealed some deficiencies in the IES model. First, there are some concerns about the feasibility of UHR for clinical approaches. Whereas the first studies with UHR criteria show a transition rate of nearly 40% from level 3 to level 4[89–91], transition rates in more recent samples have dropped to 15-35%[92–96](see section 1.4). In part, this decrease in transition rates could be due to the efficacy of early treatment. But, early interventions may only delay the natural progression to psychotic disorders rather than stop it completely[97–100]. The dilution effect may play a significant role in the lowering of transition rates[101]. The success of EIS has increased the demand for attention for UHR subjects, but also help-seeking subjects who do not fulfill UHR criteria[99,102]. In fact, there are doubts about the capability of EIS to provide early treatment to the highest risk population[103]. In a study based on the EIS of south London catchment area, only 4% of first episodes (level 4) arrived from early intervention programs, whereas the overwhelming majority continued to onset without any previous contact with the system[104]. Moreover, people of low socio-economic status, immigrants and racial minorities were found to be significantly under-represented in the IES compared with standard care[102,105]. Lack of knowledge and fear of stigmatization account partially for this

bias[106,107]. Finally, population-based studies have shown that the prevalence of psychotic symptoms in non-help seeking samples is much higher than previously expected[1,7,19] (see section 1.3), and is therefore impossible to address with the available resources.

Critics have argued that it is time for a paradigm change in terms of early intervention in order to improve its effectiveness[81,106–111]. They have proposed simplifying the interventions to a 3-stage model (fig.5). According to this proposal, stage 1 (sporadic PLE) should be the main target, that can be achieved through public health campaigns that reduce the exposure of the general population to high risk factors (levels 0 and 1 in Yung's Pyramid). Stage 2 (At Risk Mental States, ARMS) combines levels 2 and 3 and would correspond to the standard outpatient mental health services. Finally, stage 3 (psychotic disorders) combines levels 4 and 5, and it would be treated in specific psychosis units, including inpatient and outpatient resources.

Fig.5. The Continuum Model of Psychosis, adapted from Van Os, 2009 [1].



1.3. The magnitude of the problem: prevalence rates from psychotic symptoms toward affective/non-affective psychotic disorders.

As it has been highlighted, the prevalence of PLE in the general population turned out to be much higher than the scientific community had expected. The first epidemiological study that analyzed these phenomena was the Epidemiological Catchment Area Study (ECA)[112], where 10% of men and 14% of women reported experiencing PLE at least once. PLE rates increased up to 28% when it was replicated by the National Comorbidity Survey (NCS)[113], including adolescents from 15 years old or more, however it went down to 9% when replicated ten years later[114]. Similarly, the NEMESIS study [115] found a 17.5% prevalence, and nearly 10% in the UK [116] and 14% in Germany[117], both with a sample age of 16 or older. Following a different approach, Rössler and Werbeloff[118,119] reported in Germany and Israel, respectively, prevalence as high as 50% depending on the type of PLE assessed and the age. In a large meta-analysis of literature on adult samples, Van Os (2009)[1] concluded that PLE in adults had an incidence of 3% per year, with a lifetime prevalence of 5.3%, ranging from 1.9-14.4%. Moreover, when clinical impact was considered, these prevalence rates changed to 1.3% (IQR 0.4%-3%) vs. 8.4% (IQR 3.5%-20.9%) for PLE with or without clinical impact. A prevalence rate of 5.8% was also reported in the last WHO Mental Health Survey[120], based on a sample of more than 30.000 subjects (older than 18 years old), and including 18 countries. Even higher prevalence for PLE have been found in child and adolescent samples, although with high variability of results due to important methodology differences (assessments tools, interview based or self-reported, sample size, age interval, etc.). Whereas

community studies with face-to-face interviews observed PLE prevalence rates ranging from 5-14%[3,121–126], in other studies with self-reported PLE, the prevalence were as high as 21%-50% for some items[127–132]. In a large literature review including community and clinical samples (ages 7-18 years old) with a longitudinal design, Rubio[133] confirmed an incidence rate between 0.7%-1.33% per year, with a baseline-prevalence between 4.9%-9%. The latest meta-analysis available confirmed a PLE prevalence rate of 9%[134]. Furthermore, PLE were persistent over time in 20%-40% of cases and, as expected, higher for longer follow-ups. Interestingly, several longitudinal cohorts with community samples have confirmed a progressive decrease in the reporting of PLE over time[124,125,135–137], except for individuals with higher exposure to stress or already manifesting clinical impact, where PLE reports increased[138]. Taking into account the effect of age, Kelleher[2] ran a new meta-analysis dividing the studies into two groups: a) population-based studies with inclusion criteria 9-12 years old; b) population-based studies with inclusion criteria 13-18 years old. The mean prevalence rate of PLE was 17% for the youngest, with a sharp decrease to 7.5% for the other group.

The prevalence of the ultra-high risk (UHR) group in the general population is unknown. Only two studies have addressed this issue, with contradictory results. Kelleher[139] in a sample of students aged 11-13 years old, using a face-to-face interview design, found that 8% fulfilled the proposed DSM-5 criteria of APS. However, the sample was too small (n=212) to be considered an epidemiological study. More recently, F. Schultze-Lutter[117], using a semi-structured telephone interview in a cohort of 2683 subjects, aged 15-40 years old, reported a prevalence rate of 2.4%. More studies are needed to confirm these preliminary data. There are also few studies regarding the prevalence of UHR in clinical samples, even though it

is well documented that PLE are very prevalent in these at-risk populations. For example, a recent study found that 28% of patients met the UHR criteria in an adult outpatient center[140] and nearly 50% in another outpatient center for children and adolescents[141,142].

Full psychotic disorders are traditionally considered rare diseases, with prevalence rates from 1-1.5% in community samples all over the world[10,11], although we get wide-ranging results depending on the study type and the psychotic disorder subtype. In the US Epidemiological Catchment Area study (ECA)(1991)[112], the lifetime prevalence for SQZ and related disorders was 1.5% of the population; whereas it was 0.8% for BD, and 5.9% for MDD, with no differentiation between those with or without psychotic features. 15 years later, the National Comorbidity Study Replication (NCS-R)[143]found lower rates for affective psychotic disorders with, 0.4% life-time prevalence, with much higher rates for BD and MDD than previously (2.6% and 6.7% respectively), again without considering the presence of psychotic features as an independent category. The Nemesis Study in the Netherlands[115] was the first to analyze the whole spectrum of psychosis. Based on a sample of 7076 subjects (18-64 years old), they found a lifetime prevalence of 1.5% for all psychotic disorders, with 0.37% corresponding to SQZ DO (including schizoaffective disorders in this group), and 1.14% with BD and MDD with psychosis. Even higher prevalence rates were found in the Health 2000 Study[144], specifically designed to study psychosis. Based on a nationally representative sample of 8028 subjects (30 years and above) in US, the lifetime prevalence of all psychotic disorders was estimated to be 3.06% of the population. The SQZ and related disorders category was the most prevalent (0.8%), with the following prevalence rates: 0.8% SQZ; 0.42% substance-induced psychotic disorders; 0.32% schizoaffective disorder;

0.21% for psychotic disorders due to a general medical condition; 0.18% for delusional disorder; and 0.07% for schizophreniform disorders. Regarding affective psychotic disorders, MDD with psychosis (MDD-psy) was the most prevalent at 0.35%; with 0.24% for BD type I disorder with psychosis (BD-psy). Two recent studies in Chinese and European populations confirmed 0.3% of prevalence rate for BD type I with psychosis and MDD-psy[145,146].

Almost 25% of SQZ related disorders and more than half of BD disorders have their onset before 18 years old[17,25,147]. However, in the majority of epidemiological studies with children and adolescents the presence of psychotic disorders has been systematically neglected[148–152]. Only two studies in the 1980s reported prevalence rates for SQZ and related disorders, establishing a range from 0.2 to 0.9 per 10,000 for ages between 13-18 years[153–156]. In the few studies that analyzed the prevalence of pediatric BD, rates ranged from 1% to 3%[157–160], with important differences between the US and Europe[147,161,162]. However, none analyzed the phenotype of BD with psychosis. Based on clinical samples, psychosis is present in at least 50% of BD episodes, up to 90% in some cases[8,11,163,164], especially in children and adolescents[12,165–171]. More recently, two studies have analyzed the incidence of a first psychotic episode (FEP), including SQZ, and BD or MDD with psychosis, level 4 in the 5-stage model (section 1.2). First, Amminger and colleagues[172], estimated the proportion of new cases in their catchment area who were assessed at the EPPIC clinic during a 3-year period. They focused on the broad concept of FEP, from ages 15-29 years. They found an incidence of 16.7 per 10,000 new cases/year for men, and 8.1 per 10,000 for women, the highest incidence was found in the age range 20-24 years old. More recently, Nesvag[173] analyzed data from a Norwegian patient registry

of 13–18-year-olds during a 5-year period. He confirmed an incidence of FEP of 8.9 per 10,000 per year, which increased sharply to 17.9 per 10,000 at the age of 18.

1.4. Clinical meaning of the continuum model for psychosis: from psychotic-like-symptoms (PLE) toward affective-psychotic disorders, the bipolar disorder subcategory.

The clinical significance of PLE in the general population is not yet well established. Due to their high prevalence in community samples, they were initially contextualized as a benign and transitory phenomenon[133,136,174], and placed in level 1 at the pyramid of risk[71–73]. In fact, PLE can be viewed as part of the normal neuro-development during early ages[175,176]. However, when PLE begin during adolescence or adulthood[125,177], there is a strong association with a broad range of psychiatric disorders [3,130–132,178–183]. More recently, PLE have been linked to the presence of self-harming and suicidal thoughts in adolescents, and suicidal behavior in the long term[184–187]. Furthermore, the presence of PLE correlates with a variety of physical complaints, mild impairments in memory and, in general, low levels of functioning and disability[118,175,188–193]. Poulton[3] was the first to observe a relation between the presence of PLE at age 11, and the presence of psychotic disorders at age 26. Several longitudinal cohorts have observed an association between persistence of PLE an increasing risk of more severe pathology and delusional thoughts over time[135–138,182,194,195]. Kaymaz et al.[19] conducted the first meta-analysis of transition from PLE to psychotic disorders in the general population, including both youths and adults. Over a period from 3 to 24 years, the risk of conversion for those who experienced PLE was in the range of 5–25%, substantially higher than the corresponding risk

among those not experiencing PLE (0.1% to 3.7%). A new meta-analysis by Healy 2019 et al.[134] has just confirmed the association between PLE over time and a four-fold higher risk of psychotic disorders, and three-fold higher risk of other major mental disorders. It is important to highlight that transition to psychosis has also been confirmed in PLE recording based on self-reports or screening questionnaires, which could facilitate their use in primary care[137,196,197]. Finally, in a large epidemiological study in Istanbul[7], the incidence of PLE and psychotic disorders was analyzed in 3 sequential sections with adults (n= 4011, 15-65 years), confirming a quasi-continuous progression whose final diagnosis, SQZ type or BD type, would be determined by the presence of additive factors or the absence of protective factors, which will be explained in the next section.

The condition of UHR is in most cases pathological, the majority have already being diagnosed with at least one psychiatric disorder (other than a psychotic disorder), and should be receiving treatment[73,77]. In a recent meta-analysis, Fusar-Poli[73] concluded that an axis I disorder was present in 78% of UHR cases, with depression as the most prevalent (40.7%, 95% CI 32.5%–49.4%), followed by anxiety (15.3%, 95% CI 8.9%–25%). Some studies have observed a lower prevalence of axis I disorders in samples older than 14 years old, although the evidence is scarce[198,199]. Regarding the potential conversion to a full psychotic disorder, the first longitudinal studies with UHR observed a conversion rate of 40% of cases in twelve months[4,71,200]. However, in more recent samples, transition has declined to 15% in 12-months[95], reaching an average of 35% of conversion after 3 years of follow-up[92–94,96]. This could indicate a decline in risk of conversion after the second year of follow-up[105,201]. Alternative explanations could be the dilution effect, or due to the true efficacy of preventive interventions[101,108,202](see section 1.3). Moreover, the available evidence

has reflected different conversion rates among the three UHR proposed categories. The highest risk for psychosis corresponds to BLIPS, intermediate risk corresponds to APS, and the lowest risk corresponds to GHR[203,204]. Moreover, evidence has confirmed that there is a bias towards SQZ, with 70% of cases transitioning to this pole. In comparison, the transition to BD is under 10%[205,206]. It should be noted that those UHR who did not transition to psychosis consistently met diagnostic criteria for a wide range of psychiatric disorders in the long term[105,119,201,207].

Some authors have suggested introducing socio-demographic adjustments by gender and age[208]. UHR were initially developed for adolescents and young adults from 15 to 29 years old, although they have been used for a wider range, e.g., 8 to 40 years [66,77]. However, most assessment tools for UHR must be shortened in length and adapted to the children's language to improve applicability[199,209–212].

Another possibility is the implementation of current clinical criteria, for example by including the degree of impairment. A decline in global functioning was included in UHR but only in the subcategory of UHR-GHR. New evidence confirmed differences in premorbid adjustments between UHR subjects who later became psychotic compared with UHR non-converters, regardless of UHR subcategory[213–219]. Sleep problems[220,221] or symptoms severity[215] could be predictors as well. One study found a positive association between obsessive-compulsive symptoms or aggressive behaviors in UHR subjects and a subsequent onset of Schizophrenia, but not affective disorders during follow-up[222]. Mood swings, subthreshold mania or irritability have been proposed as additional criteria for improving the predictive value of conversion to the BD pole[221,223–225]. Furthermore, the few available BD-offspring studies have shown a predominance of anxiety and depressive symptoms five years before BD onset and a diagnosis of unspecified depression two years before onset[226–231].

A new line of research is focusing on the development of individual calculators of conversion rather than group-level risk estimators[232–235]. These models allow us to continue updating information at each follow-up (joint modelling)[236]. Furthermore, in the near future, their accuracy could improve with the addition of risk biomarkers based on lipids level changes, pro-inflammation and neuroimaging changes[236–239].

Following Yung's pyramid of risk, once hallucinations and delusions reach a threshold level, transition to FEP is completed. Early research in the phenomenology of FEP observed many similarities between SQZ and affective psychotic disorders, and frequent transition from one diagnosis to another during the first years after the onset of psychosis[240–246]. Therefore, level 4 has been conceptualized as a generic category during the 5 year-period of stabilization, before the establishment of a specific diagnosis of psychotic disorder in level 5. The distinction between level 4 and 5 maybe not be necessary, based on evidence from a recent meta-analysis involving 42 studies, nearly 15,000 FEP subjects and an average follow-up of 4.5 years[92]. Contrary to expectations, diagnostic stability for SQZ was found to be very high, 0.93 (95% CI 0.89–0.97), higher than stability for affective spectrum psychoses 0.84 (95% CI 0.79–0.89), and schizoaffective disorder 0.72 (95% CI 0.61–0.73). Shifts from SQZ to affective spectrum psychoses were rare, 0.05 (95% CI 0.01–0.08), slightly higher in the opposite direction, 0.10 (95% CI 0.05–0.15). Among the other psychotic diagnoses there was high diagnostic instability, with frequent conversion to schizophrenia.

The clinical presentation of SQZ and related psychotic disorders are well documented and beyond the scope of this PhD dissertation[10,11]. On the contrary, the

phenomenology of psychotic symptoms in the context of affective disorders, BD and MDD, have been of much less interest until recently[6,11,247–250].

As opposed to SQZ, positive psychotic symptoms in MDD and BD appear only in the context of a mood episode. The presence of psychosis in both MDD-psy and BD-psy is considered a marker of severity in terms of early onset and high hospitalization rates compared with MDD and BD-nonpsy[8,248–254]. They may also be related with higher suicidal ideation and attempts[164,255–258].

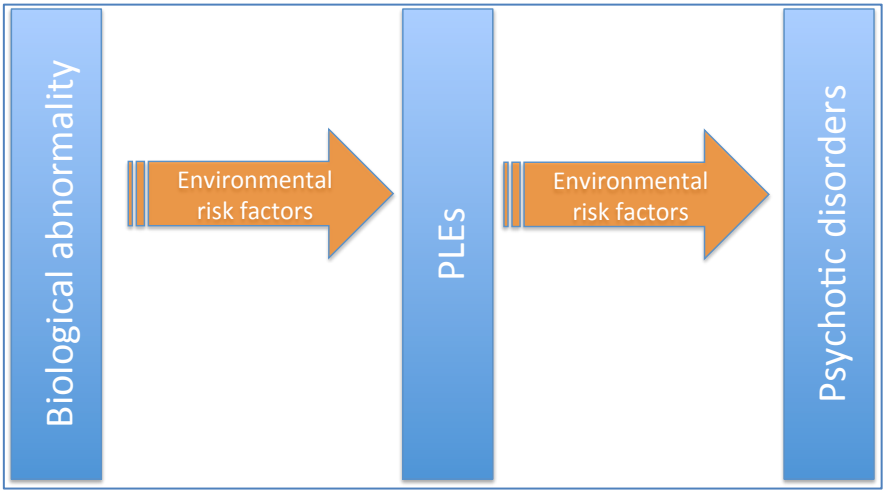
Longitudinal studies with MDD-psy have shown a risk of progression to BD-psy or SQZ, especially with early onset and family loading[201,259,260]. The phenotype BD-psy has been proved to be more stable over time[15].

There is a lack of information comparing MDD-psy vs. MDD-nonpsy over time, whereas several studies have confirmed lower levels of functional recovery for subjects with BD-psy compared to BD-nonpsy or healthy controls[9,164,171,261–263]. Currently there is some evidence that the prognosis may depend on the subtype of psychotic symptoms[256,264,265]. Positive psychotic symptoms (hallucinations and delusions) are present all over the affective psychotic pole, including depression. On the contrary, the negative dimension may be present only in BD-psy and schizoaffective disorders and may be responsible for functional and cognitive impairment[247,266–274]. However, long-term follow-ups confirmed that negative symptoms and impairment of daily functioning is more severe in SQZ and related disorders than BD[262,272,275–277].

1.5. Genetic and environmental risk factors for psychotic-like symptoms (PLE) and affective/non-affective psychotic disorders, the bipolar disorder subcategory.

According to the psychosis proneness-persistence-impairment model (Van Os, 2009)[1], if there is a continuum of psychosis, then it is likely that most of the risk factors associated with overt psychosis will be associated with increased likelihood of developing PLE. In this model, exposure to ongoing stressors would lead to biological and psychological sensitization, which would initially transform sporadic PLE into persistent PLE, and subsequently psychotic disorders in the final stage (Fig. 1). Findings from a recent meta-analysis seem to confirm the need for intermediate phenotypes (UHR subjects) as the main predictor of psychosis conversion[278].

Fig. 6: The Psychosis Proneness-Persistence-Impairment Model of Pychotic Disorders (Van os, 2009)[1].



From the early 1990s genetic risk factors have been found to be the best predictors of psychotic disorders. In the beginning, longitudinal cohorts of genetic high-risk (GHR) studies with offspring and relatives of schizophrenic patients have confirmed heritability rates ranging from 40%-70%[54,279,280]. More recently,

population-based studies have found that first-degree relatives of schizophrenics have an increased risk for BD with psychotic features and, vice versa, first degree relatives of BD have an increased risk for SQZ and related disorders as well[281–285]. However, it is not clear whether the risk is specifically related to the BD psychotic phenotype or to the whole spectrum of BD[51,256].

It has also been confirmed that causality does not depend only on one gene or group of genes, neither on the number of copy variations on one gene (CNV)[14,286]. The neurodevelopmental hypothesis[69,287,288] proposes that a combination of polygenic vulnerabilities and environmental risk factors, probably in the absence of protective factors, would determine the final pathway from intermediate phenotypes to full psychotic disorders. Furthermore, the specific nature of these risks and protective factors would mark the final development toward SQZ or BD psychotic disorders[7,289–291].

In the last few years, several environmental risk factors have been proposed as candidates, but it is unclear whether they are acting directly as pathogens, or as early markers of an underlying process[290,292,293]. Most studies with GHR populations have observed delays in normal child developmental milestones (language, toilet training, coordination, etc.) years previous to the onset of either SQZ or BD with psychosis[47,292]. Mild cognitive impairments are well known as markers of SQZ, although they are minor or not present at all for BD[294–303]. The overall intelligence quotient seems only affected in the SQZ pole[298,301,304], with a u-shape in the case of BD[292,305,306]. Or IQ could be a protective factor, considered as part of cognitive reserve[307]. Social impairment and decline in academic performance are common in both, with social isolation more specifically related to SQZ[218,289,308]. On the contrary, early exposure to traumatic life events has been confirmed in both groups, but it is

more prominent for BD[290,309–311]. Brain injuries seem to be specifically related to SQZ [312], as well as pre-natal conditions (e.g. exposure to toxoplasmosis and other infections, famine, toxins, or other maternal conditions during pregnancy), obstetric complications during delivery, and low weight at birth[55,275,278,290,312,313]. The effect of cannabis reduces the age of onset of any first psychotic episodes[275,278,290,312,314,315]. Migration, ethnicity and urbanicity have been associated mainly with SQZ[275,278,290,312]. Whether cause or consequence of the previous, recent studies highlight changes in the dopamine system previous to the progression from GHR to overt psychosis[316,317], a progressive reduction in cortical thickness as well as abnormalities in the cerebello-thalamo-cortical connectivity[318,319], and high levels of pro-inflammatory cytokines [237,320].

It should be emphasized that only a few studies have analyzed the premorbid phase previous to the onset of PLE in order to establish possible predictive factors. Preliminary evidence has shown that most of the risk factors associated with overt psychosis are also associated with increased likelihood of developping PLE, including neurodevelopmental impairments[321], perinatal complications[322], social difficulties[323], and childhood abuse[324]. Whereas some studies have reported a significant association between GHR families and PLE[123,191,325], longitudinal twin studies have consistently reported a higher contribution from environmental risk factors (49%-67%) than genetics (15-59%)[326,327]. Moreover, Zammit et al[137], in a longitudinal birth cohort study, found that only parental history of depression, and not psychosis, predicted the onset of PLE during adolescence. To our knowledge, there have been no studies evaluating the risk factors associated with PLE in a sample at genetic-high risk (GHR) for BD.

2. HYPOTHESES

2.1. Rationale:

As has been mentioned before, if there is a continuum from isolated PLE in the general population to full psychotic disorders, both phenomena should share similar risk factors. In addition, one would expect them to follow a particular pathway, with a clear differentiation from other mental disorders in their evolution and final stage.

2.2. Main hypothesis:

The main hypothesis of this work is that the same risk factors associated with overt psychosis would be associated with an increased likelihood of developing PLE. For the purpose of this thesis, only the bipolar spectrum pole would be analyzed. Based on the available literature, our a prior hypothesis was that the genetic-risk for bipolar disorder at baseline will be the strongest predictor for the development of PLE both at baseline and longitudinally. Other known environmental risk factors for psychosis and therefore for PLE at baseline will be: obstetric and perinatal complications; early drug exposure; cranio-encephalic trauma; history of infections or other medical complications; sexual or physical abuse; low intellectual level; finally, previous psychiatric pathology.

2.3. Secondary hypotheses:

The secondary hypotheses were:

(1) According to the concept of prodromic status of psychosis, the presence of PLE will correlate with a wide ragne of psychopathologies over time, especially BD- and SQZ-like disorders, and low level of global functioning.

(2) The presence of isolated PLE at an early age will increase the risk of persistent PLE and the final transition to a full psychotic disorder, either affective or non-affective psychosis.

(3) The level of agreement between self-reporting questionnaires for screening PLE and PLE reported in face-to-face interviews will be good/very good.

(4) After the onset of the affective disorder, in our case a bipolar disorder, the presence of psychotic symptoms will be associated with higher severity, higher rates of comorbidity and a higher impact on functioning than bipolar disorders without the psychotic phenotype.

3. OBJECTIVES

3.1. Main objective:

The main objective of this PhD thesis was to study the phenomenon of PLE from two different perspectives: a) bottom-up, by following healthy offspring of BD parents and control parents longitudinally; b) top-down, by analyzing adult with BD and adolescents with early-onset BD and their first-degree relatives cross-sectionally.

3.2. Specific objectives:

The specific objectives in the bottom-up perspective were:

- To analyze genetic and environmental risk factors of PLE in the whole offspring sample (study 1).
- To analyze clinical predictors of PLE in the entire offspring sample (study 1).
- To evaluate the prevalence of PLE at baseline and during follow-up of two cohorts: offspring of BD with and without psychosis, and offspring of healthy parents (study 1).
- To analyze level of functioning and PLE in the entire offspring sample (study 1).
- To study the phenomenology of PLE and rates of conversion to psychotic disorders during the longitudinal follow-up (study 1).
- To compare specificity and sensitivity of face-to-face and self-reported questionnaires for screening PLE in large samples during the follow-up (study 1).

The specific objectives in the top-down perspective were:

- To explore the BD phenotype with psychotic features compared to BD without psychotic features, by evaluating clinical presentations in terms of severity

and comorbidity (based on unpublished information from a baseline analysis of study 1 and study 2).

- To explore the BD phenotype with psychotic features compared to BD without psychotic features in terms of global functionning (baseline analysis of study 1; study 2).
- To analyze the association between environmental and genetic risk factors for psychosis in the BD adolescents' sample (study 2).
- To compare socio-demographics, medical and family history in BD adolescents during euthymia with healthy controls from the community (study 2).
- To compare functional recovery in BD adolescents during euthymia with healthy controls from the community (study 2).
- To analyze the association between psychotic symptoms and other relevant clinical symptoms, and levels of functionality in both BD and HC (study 2).
- To analyze the association between environmental and genetic risk factors and levels of functionality in both BD and HC (study 2).

4. METHODOLOGY

4.1. Type of study.

As has already been mentioned, for the realization of this project, we worked in parallel on two different databases from two different studies:

4.1.1. Study 1: "Psychotic-Like Experiences (PLE) in Offspring of Parents with Bipolar Disorder and Community Controls. A Longitudinal Study". The Bipolar Offspring Family Study (BIOS).

Funded by the National Institute of Mental Health in the US, BIOS is the largest ongoing longitudinal genetic-high-risk (GHR) study of BD, with Dr. Boris Birmaher and Dr. David Axelson as the principal investigators. Dr. Boris Birmaher is currently the director of the Child and Adolescent Anxiety Program, and Co-director of the Bipolar Institute, at the Western Psychiatric Institute and Clinic (WPIC) at the University of Pittsburgh Medical Center (UPMC) (Pennsylvania, US). He serves as a faculty member in the Psychiatry Department of UPMC as well. He has been one of the co-directors of this thesis from the beginning. Dr. David Axelson was the director of the Child and Adolescent Bipolar Service (CABS) when we started this project. He is currently head of the department of psychiatry at the Nationwide Children's Hospital. He is also professor of psychiatry at the Ohio State University College of Medicine and Ohio State's Wexner Medical Center (Colombus, Ohio, US). Although he was one on my co-directors of the thesis, when he moved to Ohio University, he withdrew from the project in favor of Dr. Castro.

BIOS is an observational prospective cohort study, with two cohorts: 1) Exposed or GHR cohort: offspring of parents with BD (either with or without

psychosis); 2) Non-exposed cohort: offspring of healthy parents or with minor psychiatric disorders.

BIOS was started in 2001 and includes baseline interviews (year 1) for each family member, including parents with BD and healthy parents and each of their offspring, and individual follow-up interviews for the offspring every 2 years (years 3, 5, 7, 9, 11, 13 and 15 at the cut-off point for this study). The adherence rate has been estimated at 80%.

During my stay at the WPIC my role in the study was to complete some of the baseline interviews, to be part of the coding and cleaning. I also ran the initial analyses at baseline, first comparing BD parents with and without psychotic symptoms, and second their offspring. Back in Spain, I completed the longitudinal analyses with the collaboration of R. Borras and Dr. Castro. Roger Borras is licensed in Math and Statistics and has a master's in numerical analysis. He works part-time in our department of Child and Adolescent Psychology and Psychiatry, and as associate professor at the Autonomous University of Barcelona (UAB). Dr. Castro is head of the Institute of Neuroscience at the Clinic Hospital, and professor of psychiatry at the University of Barcelona. When I first started this project, she accepted to be my thesis advisor in Spain, a requirement for international theses, and finally became an amazing co-director after Dr. Axelson left the project.

4.1.2. Study 2: "Functional Impairment and Clinical Correlates in Adolescents with Bipolar Disorder Compared to Healthy Controls. A Case-Control Study".

This study was funded by the Carlos III Institute (FIS: PI11 / 01224), with Dr. Soledad Romero as principal investigator. Dr. Romero is a consulting psychiatrist,

working at the Day Hospital of the department of Child and Adolescent Psychiatry, at the Hospital Clinic (Barcelona, Spain).

This is a cross-sectional study, with a classic case-control design matched by sex and age, which includes two groups: 1) Adolescents with BD subtype I or II, with or without psychotic symptoms; 2) Control group: healthy adolescents from the community, without current or past psychiatric history. It was conducted from January 2012 to September 2016.

As one the collaborators in this study, I have been part of the study from the beginning. First, I assisted during the grant application process, then I reviewed the interview's packages, and after that, I conducted part of the face-to-face interviews, and prepared and cleaned the dataset. Finally, I conducted the analyses with the help of our statistician, R. Borras.

4.2. Sample size and recruitment process.

4.2.1. Study 1: "Psychotic-Like Experiences (PLE) in Offspring of Parents with Bipolar Disorder and Community Controls. A Longitudinal Study". The Bipolar Offspring Family Study (BIOS).

Parents with a BD (n=235) were recruited through advertisements (53%), other research studies (31%), and at adult outpatient clinics (16%). The inclusion criteria at baseline were: 1) fulfilled criteria for a DSM-IV diagnosis of BD I or II disorders, lived within a 200-mile radius of Pittsburgh, and had offspring between 6 and 17 years old at the beginning of the study.a Exclusion criteria included a lifetime diagnosis of SQZ, mood disorders due to substance abuse, medical conditions or

a BIOS includes a subset of families with offspring 2-5 years.

medications, and mental retardation (IQ < 70). Control parents (n=140) were recruited from the community using random digit dialing, at a ratio of one control parent to two BD parents, and matched with the BD group by age, sex, and neighborhood. They were either healthy or had a minor psychiatric diagnosis other than BD and had none of the exclusionary diagnoses noted above. In addition, control parents were excluded if they had any first or second-degree relatives with BD. All offspring of BD and control parents (n=637, 390 and 247 respectively) were included with the exception of those with mental retardation, autism, or other impairments that prevented their participation (e.g., severe medical illness). One child from the BD group was diagnosed with tuberous sclerosis during the study and was excluded from the final analysis.

4.2.2. Study 2: "Functional Impairment and Clinical Correlates in Adolescents with Bipolar Disorder Compared to Healthy Controls. A Case-Control Study".

Adolescents with BD type I or II aged 12–19 years old (n=47) were recruited at Hospital Clinic in Barcelona, either from inpatient (35, 74.5%) or outpatient units (12, 25.5%). HC (n=44) were recruited from advertisements from the same geographical area. Similar gender and age and being healthy without any past or current history for a psychiatric disorder were the inclusion criteria. Exclusion criteria for all participants included learning disabilities, major systemic medical illness, serious head injury, pregnancy and imaging counter-indications. None of the controls and one of the eligible participants with BD refused to participate in the study.

4.3. Assessments.

4.3.1. Study 1: "Psychotic-Like Experiences (PLE) in Offspring of Parents with Bipolar Disorder and Community Controls. A Longitudinal Study". The Bipolar Offspring Family Study (BIOS).

This study is ongoing. A team of graduate students specifically trained for this purpose (Kappa reliability coefficient 0.8 or higher), conducted all face-to-face interviews directly at the participant's home. All information was subsequently presented to a child psychiatrist to confirm the diagnosis. If necessary, the information was completed by reviewing the previous records. Each interview lasted between 2.5h and 5h, and included clinical information, family history, general medical history and a wide range of other variables. We have summarized the ones included in the analyses as follows:

1) Categorical DSM-IV diagnoses: For children under 18 years old, the K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version)[328], which includes input from the child, the parents, and the evaluator. Parents and offspring older than 18 years old were evaluated using the SCID interview (Structured Clinical Interview-DSM-IV)[329], supplemented with the sections "Attention Deficit and Hyperactivity Disorder" and "Separation Anxiety Disorder" from the K-SADS-PL.

2) PLE symptoms: we created a dichotomous variable (Yes / No), combining information from the SCID interviews (8 items on delusions, 5 for hallucinations, and 11 for catatonic or negative symptoms, will be chosen if score = 3 definitely present); and the K-SADS-PL (2 items for psychosis, with score = 3). The supplement of the K-SADS for psychosis was also included (5 hallucinatory items,

and 13 deliriums, final score = 3); and the symptomatic scale K-SADS Mania Rating Scale (MRS)[330] (19 items on hallucinations and 20 on delusions, scoring between 3-6, moderate to severe). Some examples of PLE reported are shown in Table 4.

3) Internalizing or externalizing symptoms: based on the CBCL (Child Behavioral Checklist)[331], which includes information on parents, teachers and children over 11 years. In addition, we created a dichotomous variable called *self-reported psychotic symptoms* based on items Q40= "I hear sounds or voices that other people think aren't there", and Q70="I see things that other people think aren't there", rated either 1 or 2 (threshold=2, very often true; subthreshold=1, somewhat or sometimes true).

4) Medical history: using a specific questionnaire with past history of pregnancy and of obstetric complications; weight at birth, and at each follow-up; infections; past and current allergies or other medical disorders; head injuries; past and current medications; past and current physical or sexual abuse.

5) Intelligence Quotient (IQ): based on the Wechsler Adult Intelligence Scale (WISC)[332].

6) Level of functionality: the Child Global Adjustment Assessment (C-GAS)[333] for children under 18; and the Global Assessment of Functioning (GAF)[334] in adults. And for all ages, the LIFE-RIFT summary (LIFE Range of Impaired Functioning Tool), from the Longitudinal Interval Life Evaluation[335].

7) Socio-Economic Status (SES): Hollingshead scale[336].

Table 4: Examples of PLE collected during the Assessments.

1. **Auditory hallucinations:**
   - Hearing commands from the devil; a man inside his head commenting on his behavior.
   - A man in her head, commenting on her behavior; she thinks he is real (her dead father).
   - Authoritative voices telling them to do violent things.
   - An imaginary friend Rob who tells her what to do ("kill your mom", "hurt your sister").
   - Hearing voices from the radiator.
   - Almost every day hears and sees ghosts for the last 4 years; no one else can see or hear them.
   - Hearing his grandma talking in his head, commenting on others' behaviors and crying.
   - Teacher notes that sometimes he talks to himself.
   - He speaks to his dead grandfather, once a week, in a loud voice.
2. **Visual and somatesthetic hallucinations:**
   - Sees demons at school; feels electricity go through his body.
   - He sees dead people at night.
   - Seeing a man standing in their garage with his skin peeling off.
   - Dragons in the sky when he is extremely happy.
   - Sees colors and shadows moving on walls.
   - Sees dogs and spiders all over the room.
   - Sees a boy in her room, several times over the last 10 years, she thinks its a spirit.
   - Thinks people touch her legs at night.
3. **Delusional thoughts:**
   - Mesianic delusion, he is Satan and predicts de future.
   - Paranoid delusion, thinks people want to hurt him.
   - Talking to the TV, the news addresses his family directly.
   - Paranoid about people following him on the street, avoids public places.
   - During depression, people on the street "may" be able to hear what she is thinking.
   - Paranoid about people, afraid they could enter his house and kidnap him.
   - During manic states she thinks the house is haunted, sees evil shadows on the walls (it lasts a few minutes).
4. **Bizarre behaviors:**
   - Awake at nights, scaring her mom with a doll.
   - "Makes nonsense jokes, like babies in the microwave", sarcastic laugh.
   - Bizarre behaviors, killed several animals.
   - Aggressive behavior that required hospitalizations.
   - Lack of associations, incoherence.

4.3.2. Study 2: "Functional Impairment and Clinical Correlates in Adolescents with Bipolar Disorder Compared to Healthy Controls. A Case-Control Study".

All clinical interviews were conducted at the Hospital Clinic, directly by Dr. Mendez or Dr. Soledad Romero, or by a psychologist from our research team specifically trained for this purpose. The final diagnosis was made by consensus following the DSM-V criteria for BD I or II. The interview package included nearly

the same assessment tools as the BIOS, with the following additional self-report scales:

1. Live events: the Stressful Life Events Survey (SLES), translated into Spanish for that purpose[337].
2. Functionality: Besides the C-GAS/GAF, we included the Premorbid Adjustment Scale (PAS)[338] and the Clinical Global Impression Scale (CGI)[339].
3. School performance: based on the first part of the K-SADS-PLE.
4. Symptomatic scales: To be eligible for the study, all BDs had to be in euthymia, defined as the absence of depressive symptoms above a level of 9 in the short version of the Hamilton Depression Scale (HDRS-R17)[340], and the absence of manic symptom greater than 12 on the Young Mania Rating Scale (YMRS)[341]. The information was completed with the Beck Inventory for Depression-II (BDI-II)[342], the Child Mania Rating Scale (CMRS)[343], and the Mood Disorder Questionnaire (MDQ) [344]. Psychosis was evaluated using the Positive and Negative Syndrome Scale (PANNS)[345], and the Evaluation of Symptoms in the Schizophrenic Prodromal Scale (SOPS)[346].

4.4. Statistical analyses.

We ran several exploratory analyses, both cross-sectional and longitudinal. All analyses were carried out using the SPSS software package, version 22, and the R software version 3.3.1 for Windows 7 (R project for Statistical Computing, Vienna, Austria). To assess demographic and clinical differences between groups at baseline or in the cross-sectional study, we used descriptive parametric tests: t-test, chi-square or Fisher's Exact as necessary, with a two-tailed design and a significance level of $p < 0.05$. To analyze the demographic and clinical differences between groups during

follow-up, we used Generalized Linear Mixed Models with the Least Square Mean Method to control for within-family correlations.

4.4.1. Study 1: "Psychotic-Like Experiences (PLE) in Offspring of Parents with Bipolar Disorder and Community Controls. A Longitudinal Study". The Bipolar Offspring Family Study (BIOS).

The longitudinal risk associations between demographic and clinical variables and the event of interest at each follow-up were analyzed from two different perspectives. First, we used a General Linear Mixed Model taking into account within-family and within-subject correlations. This analysis allowed us to estimate the odds ratios between PLE and several variables at each year of assessment. Then we used a Survival Cox Proportional Hazards Regression Model, with time-varying covariates for multiple events, including within-subject dependence[347]. It allowed us to estimate the Hazard Ratio (HR) and 95% confidence intervals of each risk factor for developing PLE later, considering PLE as episodic. Variables that showed group differences at a level of $p < .05$ were included as potential covariates in subsequent multivariate models, with a retention criterion of $p < .10$.

4.4.2. Study 2: "Functional Impairment and Clinical Correlates in Adolescents with Bipolar Disorder Compared to Healthy Controls. A Case-Control Study".

To study the association of risk for BD compared with HC, we used both conditional and simple logistic regression models for analyses among BD subgroups. Variables that showed group differences at $p < 0.05$ in univariate analyses were included as potential covariates in subsequent multivariate models. The final model

was defined based on clinical criteria, and the Akaike information criterion (AIC) scores. The odds ratios and 95% confidence interval were computed for all models.

4.5. Ethical considerations.

4.5.1. Study 1: "Psychotic-Like Experiences (PLE) in Offspring of Parents with Bipolar Disorder and Community Controls. A longitudinal study". The Bipolar Offspring Family Study (BIOS).

BIOS was reviewed and approved by the Ethics Committee of the WIPC-UPMC back in 2001. In all the baseline interviews, both parents and children were verbally informed about the characteristics of the study, allowing them to discuss any doubts that might arise. Information about the process of privacy of the identity, storage and guarantee of use of the information only for the purposes indicated was specifically provided. Prior to baseline and each of the follow-up interviews, written consent was always requested from parents and subjects over 14 years of age. The parents also signed the written consent for children under 14 years of age.

4.5.2. Study 2: "Functional Impairment and Clinical Correlates in Adolescents with Bipolar Disorder Compared to Healthy Controls. A Case-Control Study".

The Ethics Committee of the Clinic Hospital approved our study in 2011. In all the interviews, parents and adolescents were informed of the nature of the study, and all of their doubts were cleared up. In the same way as in BIOS, all parents and adolescents over 14 years of age were asked for written informed consent.

5. RESULTS

The main purpose of the PhD thesis was to analyze the utility of various risk factors as predictors for PLE and to test their consistency with known predictors for the development of a full psychotic disorder. Another objective of this project was to explore the impact of psychosis on the course of BD, in terms of functionality as well as clinical presentation.

Part of my work was published in two papers presented in this thesis. However, I was not able to confirm some of the a priori hypotheses, and these results were not published. Negative findings are very interesting findings as well and are commented briefly in the Results and Appendix section. Some were used for obtaining the title of *Clinical Research Qualification* at the University Autonoma of Barcelona (UAB) in 2010. Others were presented at the 60th congress of the Spanish Association for Child and Adolescent Psychiatry (AEPNYA), unique co-organized with the American Association of Child and Adolescent Psychiatry (AACAP).

5.1. Study 1: "The Pittsburgh Bipolar Psychotic-Like Experiences (PLE) in Offspring of Parents with Bipolar Disorder and Community Controls. A Longitudinal Study". The Bipolar Offspring Family Study (BIOS).

5.1.1. Baseline analyses:

5.1.1.1. Socio-demographics and clinical features.

The baseline sample consisted on 244 BD parents and 419 offspring. 97 (39.7%) BD parents reported current or past history of psychotic symptoms (BD_psy+), and 147 (60.3%) did not. 160 (38.2%) offspring had one or both parents

with BD-psy+ phenotype, and 259 offspring were from BD_psy- families. Neither BD parents with or without psychotic symptoms nor their offspring differed in socio-demographics, other than marginal differences in the proportion of females (75.3% vs. 83.7%, p=0.05) (Table 5).

Table 5: Socio-demographic Characteristics of Bipolar Parents and their Offspring.

Parents	**BD_psy+ (n=97)**	**BD_psy- (n=147)**	**Statistics (τ/χ2)**	***p*-value**
Age (mean, SD)	39.37 ± 7.42	39.23 ± 7.92	0.136	.89
Gender: Female (%)	75.30%	83.7%	2.62	.11
Race: White (%)	87.6%	89.1%	0.13	.72
BMI (mean, SD)	29.51 ± 6.47	29.23 ± 6.66	0.32	.75
Education: college (%)	60.40%	62.30%	0.089	.77
Currently Working	46.2%	55.1%	1.74	.2
SES (mean, SD)	34.51 ± 14.56	34.65 ± 14.19	0.075	.94
Married at intake (%)	49.5%	49.7%	0.001	.98
>4 pregnancies (women)	38.1%	29.9%	1.78	.18
% Offspring with Psy+	6.90%	4.30%	0.8	.37
Offspring	**BD_psy+ parents (n=160)**	**BD_psy- parents (n=259)**	**Statistic (τ/χ2)**	**P-value**
Age (mean, SD)	11.49±3.89	11.41±3.88	0.2	.80
Gender: Female (%)	42.5%	52.5%	3.97	.05
Race: White (%)	78.8%	83.8%	169	.19
Living with both parents (%)	43.8%	43.2%	.01	.92

BD-psy+: Bipolar disorder with psychotic features; BD-psy-: BD without psychosis; SD: Standard deviation; SES: Socioeconomic status

BD_psy+ parents differed significantly from BD_psy- in the prevalence of BD I subtype (78.4% vs. 59.9%, p < **.01**); and number of co-morbid disorders (3.52 ± 2.34 vs. 2.92 ± 1.97, p < **.05**), with a predominance of substance abuse disorders other than alcohol (51.1% vs. 38.1%, p < **.05**), panic disorder (48.5% vs. 33.3%; p < **.05**), and somatization disorder (7.2% vs. 0.0%, p < **.05**). Age of onset was similar in both parent groups, on average at 18 years old.

BD-offspring displayed few clinical differences between groups. 60% of all offspring had a formal Axis I diagnosis at intake, with similar rates of comorbidity, except for more PTSD (6.9% vs. 2.7%, p < **0.05**), and more complaints about lack of energy in those offspring from BD_psy+ parents (26.5% vs. 23.9%, p < **0.05**). Only 2.8% reported PLEs at baseline and 0.5% a psychotic disorder, without differences between groups. IQ was similar in both groups (average 105.81 ± 5.93).

5.1.1.2. Level of General Functioning.

Only half of the BD parents was employed or married. The BD_psy+ phenotype functioned in daily life statistically worse than BD_psy-, as shown by GAF scores either at present (59.19 ± 13.13 vs. 63.56 ± 11.51, p < .01), or in the past (28.98 ± 12.02 vs. 36.43 ± 14.32, p < .01) (Table 6), meaning moderate to serious impairment in daily life for the psychosis group, and slight symptoms to moderate impairment for the non-psychotic group. However, when functionality was measured based on self-reported data from the LIFE-RIFT scale, both BD groups perceived their level of functioning in the areas of work and recreation as good, with only slight impairment in relationships, satisfaction and global social adjustment.

There were almost no differences in functioning between offspring groups. global performance was normal or slightly impaired in both (C-GAS = 74.21 ± 13.3

vs 74.4 ± 13.26 for current, and 62.52 ± 17.7 vs. 65.71 ± 5.58 for past). When we analyzed specific areas of functioning based on the LIFE scale, we found statistically significant differences in the area of relationships, worse for offspring of BD_psy- (2.35 ± 1.1 vs. 2.7 ± 1.3, $p < .01$), but in the range of good to fair. Role functioning and global social adjustment were also self-reported between good to fair, whereas recreation and satisfaction were rated as good in all offspring (Table 6).

Table 6: Functioning in BD Parents with or without Psychosis and their Offspring.

Parents	**Parents with BD-psy+ (n=97)**	**Parents with BD-psy- (n=147)**	**Statistics (τ/χ2)**	**P-value**
C-GAS current (mean, SD)	59.19 ± 13.13	63.56 ± 11.51	2.82	**<.01**
C-GAS most severe past (mean, SD)	28.98 ± 12.02	36.43 ± 14.32	4.34	**<.01**
Summary LIFE-RIFT (mean, SD)	11.64 ± 3.45	14.72 ± 2.89	(-) 1.42	**<.01**
LIFE_ Role Functioning*	1.89 ± .41	1.72 ± .58	(-) 1.82	.07
LIFE_ Relationships*	1.79 ± .56	1.81 ± .89	(-) 0.25	.8
LIFE_ Recreation*	1.78 ± .62	1.82 ± .48	(-) 0.41	.68
LIFE_ Satisfaction*	1.78 ± .55	1.82 ± .52	(-) 0.43	.67
LIFE_ Global Social Adjustment*	1.87 ± .37	1.73 ± .76	(-) 1.50	.13
Offspring	**Parents with BD-psy+ (n=160)**	**Parents with BD-psy- (n=259)**	**Statistics**	**P-value**
C-GAS current (mean, SD)	74.21±13.3	74.4±13.26	(-)0.12	0,9
C-GAS most severe past (mean, SD)	62.52±17.7	65.7±15.58	(-)1.6	0,1
Summary LIFE-RIFT (mean, SD)	8.15±2.55	8.52±2.53	(-)1.38	0,17
LIFE_ Role Functioning*	2.2±1.02	2.3±.9	(-)0.9	0,36
LIFE_ Relationships*	2.7±1.3	2.35±1.1	(-)2.75	**0,006**
LIFE_ Recreation*	1.8±.93	1.7±.83	1.1	0,27
LIFE_ Satisfaction*	1.9±.72	1.9±.78	(-)0.04	0,97
LIFE_ Global Social Adjustment*	2.1±.75	2.1±.85	(-)0.42	0,67

C-GAS<70-51 mild impairment, 50-31 for moderate, and <30 for severe impairment. LIFT-RIFT summ: 4=best f(x)-20=worse f(x). *1= very good; 2=good; 3=fair functioning/slightly impaired; 4=poor/moderately impaired; or 5=very poor/severely impaired

5.1.2. Follow-up analyses:

5.1.2.1. Socio-demographics.

The final sample included in the longitudinal follow-up paper consisted of 637 offspring, 390 offspring from 236 BD parents, and 247 offspring from 139 control parents (Table 7 and 8). At intake, the mean age for both offspring cohorts was 11.9 ± 3.6 years old, with a median age of 11.2 (6-18) years old. BP offspring were less often living with both biological parents (59.5% vs. 74.9%; $t = 2.81$, $p < .01$), were more Caucasian, and had a slightly lower SES (Table 7).

Table 7: Socio-Demographic Factors of Bipolar Offspring and Control Offspring*.

	All offspring (637)	Bipolar Offspring N (390)	Control Offspring N (247)	Statistics (τ)	p-value
Intake*					
Age	11.88 ± 3.59	11.91 ± 3.61	11.81 ± 3.55	0.15	0.88
Gender: Female	50.9%	49.0%	53.8%	0.53	0.59
Race: White	78.2%	81.0%	73.7%	1.99	0.05
Living: both parents	65.5%	59.5%	74.9%	2.81	**<0.01**
SES	35.32 ± 13.62	34.15 ± 13.93	37.18 ± 12.93	1.95	0.05
Nº of children in the family	2.37 ± 1.06	2.35 ± 1.14	2.38 ± 0.93	0.53	0.59
Last follow-up*					
Age	19.91 ± 5.11	20.01 ± 5.24	19.75 ± 4.89	0.24	0.81
Dropouts	8.3%	7.7%	9.3%	0.13	0.89
Years in the study	8.03 ± 3.43	8.08 ± 3.40	7.95 ± 3.48	0.12	0.90
Number of assessments	4.44 ± 1.58	4.43 ± 1.62	4.46 ± 1.52	0.35	0.72
≥2 FU	85.7%	84.9%	87.0%	0.83	0.41
≥4 FU	57.1%	55.6%	59.5%	0.63	0.53
≥6 FU	3.3%	4.6%	1.2%	1.46	0.15
Living: both parents	32.2%	27.9%	38.9%	1.47	0.14
SES	35.18 ± 13.72	34.69 ± 13.99	35.97 ± 13.27	0.91	0.36

SES: Socioeconomic status; FU: follow-up assessments.
****GLMM adjusted for within family correlation. In bold p-values =<0.05.***

BP parents (Table 8) were younger, more likely to be Caucasian (87.7% vs. 72.2%), less often married (49.4% vs. 64.2%), with lower SES (34.0 ± 14.4 vs. 37.4 ± 13.1) and lower psychosocial functioning (all p-values <0.05). As expected, BP parents reported more post-traumatic stress disorder (PTSD), and 50% reported psychotic symptoms. All major depression episodes were included as part of the BP disorder.

Table 8: Bipolar and Community Parents. Socio-Demographic and Clinical Factors at Intake.

	All Parents N (375)	Parents with BP-I/II N (236)	Parents Control group N (139)	Statistics (τ/χ2)	p-value
Socio-demographics at intake					
Age at intake	40.04 ± 7.5	39.5 ± 7.6	40.9 ± 7.3	1.82	0.07
Gender: Female	294 (78.4)	188 (80.7)	106 (77.4)	0.58	0.45
Race: White	308 (82.1)	207 (87.7)	101 (72.2)	13.5	**<0.0001**
Married	203 (54.1)	115 (49.4)	88 (64.2)	7.71	**<0.01**
SES at intake	34.2 ± 14.4	34.2 ± 14.4	37.4 ± 13.1	2.18	**0.03**
Diagnosis at intake					
BP-I		172 (72.9)	NA	NA	NA
BP-II		64 (27.1)	NA	NA	NA
Major Depression		NA	34 (24.5)	NA	NA
PTSD	99 (26.4)	86 (36.4)	13 (9.4)	33.03	**<0.0001**
Overall functioning at intake					
CGAS/GAF current <70	175 (46.7)	157 (66.5)	18 (12.9)	100.88	**<0.0001**
CGAS/GAF most severe past <70	293 (78.1)	231 (97.9)	62 (44.6)	145.33	**<0.0001**
CGAS/GAF highest in the past <70	83 (22.1)	76 (32.2)	7 (5)	37.46	**<0.0001**

BP: Bipolar disorder; SES: Socio-economic status; PTSD: Post-traumatic stress disorder; CGAS: Child Global Adjustment Scale; GAF: Global Assessment Of functioning. In bold p-values <0.05.

Each family had on average two children and was followed up every 2.5 years for a period of 8.3 years (0-13 years). 91.7% (n=585) remained in the study, defined as completing at least one follow-up (Table 9). Those who dropped out were less likely to live with both biological parents (45.3% vs. 67.3%; $t = 2.39$, $p = .02$) and had lower SES (29.01 ± 9.55 vs. 35.85 ± 13.79; $t = 2.67$, $p < .01$) than those who remained in the study (Table 9).

Table 9: Socio-Demographic and Clinical factors at Intake of Offspring With and Without Follow-Up Assessments*.

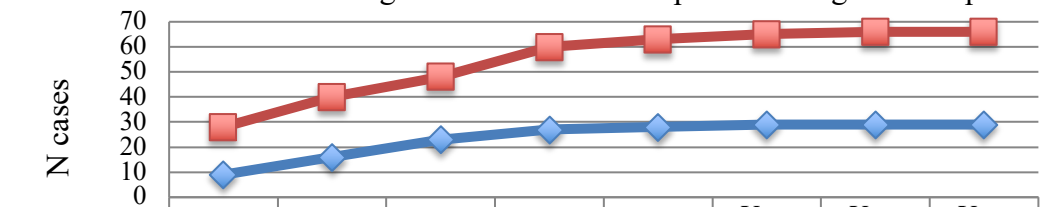
	All offspring (637)	Offspring wo FU (n=53)	Offspring w FU (n=584)	Statistics (τ)	p-value
Socio-demographics at intake					
Age at intake	11.88 ± 3.59	11.41 ± 3.7	11.92 ± 3.58	0.58	0.56
Gender: Female	324 (50.9)	25 (47.2)	299 (51.2)	0.36	0.72
Race: White	498 (78.2)	33 (62.3)	465 (79.6)	1.55	0.12
Living with biological parents	417 (65.5)	24 (45.3)	393 (67.3)	2.39	**0.02**
PLE symptoms	37 (5.8)	2 (3.8)	35 (6)	0.47	0.64
SES	35.32 ± 13.62	29.01 ± 9.55	35.85 ± 13.79	2.67	**<0.01**
N° of kids in the study	2.37 ± 1.06	2.15 ± 0.86	2.39 ± 1.08	1.63	0.1
BD parents vs HC parents	390 (61.2)	30 (56.6)	360 (61.6)	0.06	0.95
Family with Psychotic symptoms	133 (20.9)	15 (28.3)	118 (20.2)	1.06	0.29
Diagnosis at intake					
Any Diagnosis	378 (59.3)	32 (60.4)	346 (59.2)	0.27	0.79
Any Affective DO	81 (12.7)	6 (11.3)	75 (12.8)	0.01	0.99
Any Anxiety DO	212 (33.3)	16 (30.2)	196 (33.6)	0.28	0.78
Any ADHD DO	155 (24.3)	16 (30.2)	139 (23.8)	0.73	0.46
Any CD DO	101 (15.9)	13 (24.5)	88 (15.1)	1.29	0.2
Any PTSD DO	27 (4.2)	2 (3.8)	25 (4.3)	0.13	0.89
Any Psychotic DO	7 (1.1)	1 (1.9)	6 (1)	0.12	0.91
Any Substance Abuse/Dependence DO	23 (3.6)	2 (3.8)	21 (3.6)	0.14	0.88
Any other DO	101 (15.9)	9 (17)	92 (15.8)	0.22	0.82
Hx of abuse at intake					
Physical and Sexual abuse	54 (8.5)	4 (7.5)	50 (8.6)	0.19	0.85
Sexual abuse	30 (4.7)	1 (1.9)	29 (5)	0.72	0..47
Physical abuse	29 (4.6)	4 (7.5)	25 (4.3)	0.82	0.41
Both	5 (0.8)	1 (1.9)	4 (0.7)	0.89	0.37
Overall functioning at intake					
CGAS/GAF current <70	152 (24)	14 (28)	138 (23.6)	0.7	0.48
CGAS/GAF most severe past <70	284 (44.8)	25 (50)	259 (44.3)	0.99	0.32
CGAS/GAF highest in the past <70	122 (19.3)	13 (26.5)	109 (18.7)	1.11	0.27

*W: with; WO: without; FU: follow-up; SES: Socioeconomic Status; BD: bipolar; HC: healthy controls: DO: Disorder; PTSD: Post-Traumatic Stress Disorder; Hx: History; CGAS: Child Global Adjustment Scale; GAF: Global Assessment of Functioning. * Model adjusted for within family correlation. In bold p-values <0.05.*

5.1.2.2. Prevalence of PLE and Psychotic Disorders.

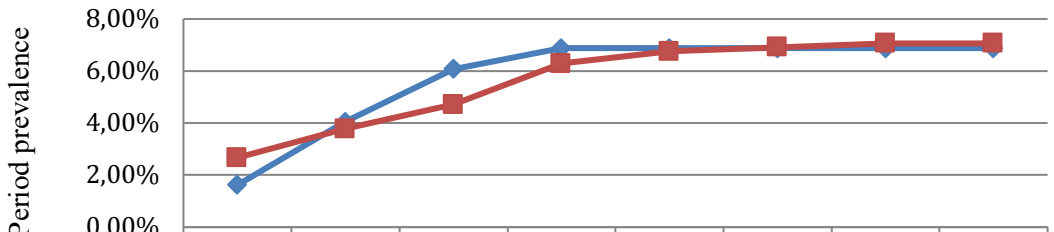
Ninety-five offspring (14.9%, 95/637) reported PLE at some point during the study, 37 (5.8%) at intake and 58 (9.1%) during follow-up (Table 10). Offspring of BD parents reported more PLE than offspring of community control parents (66/390, 16.9% vs. 29/247, 11.7%), both at intake and during follow-up (Fig.7). However, contrary to our hypothesis, this difference was not statistically significant, probably due to the higher proportion of BD offspring (Fig.8). The mean age of onset for PLE was 14.6 ± 4.7 years old, with only 16 cases (16.8%) reporting PLE before age 10 (Fig.9). About 25% of PLE (23/95) were reported more than once during the course of the study. In both cohorts, hallucinations were the most prevalent PLE phenomenon, followed by delusions or a combination of the two (8.5% vs. 2.8% vs. 3%, respectively). The prevalence of psychotic disorders was similar in both groups (offspring of BD parents: 2.6% vs. offspring community control parents: 2.4%).

Fig.7: Number of PLE reported during follow-up



	Year 1	Year 3	Year 5	Year 7	Year 9	Year 11	Year 13	Year 15
Controls	9	16	23	27	28	29	29	29
Subjects	28	40	48	60	63	65	66	66

Fig.8: Percentage of PLE reported during follow-up



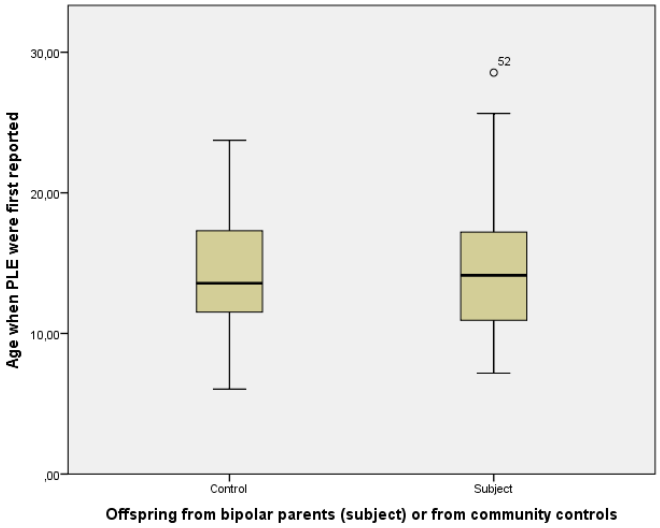
	Year 1	Year 3	Year 5	Year 7	Year 9	Year 11	Year 13	Year 15
Controls	1,62%	4,05%	6,07%	6,88%	6,88%	6,88%	6,88%	6,88%
Subjects	2,67%	3,77%	4,71%	6,28%	6,75%	6,91%	7,06%	7,06%

Table 10: Transactions Across the Psychosis Spectrum in Offspring during Follow-Up.

	All offspring N (637)	Offspring of parents with BPI/II N (390)	Offspring of parents w/o BP I/II N (247)	Statistics (τ)	p-value
Non PLE at intake ●	600 (94.2)	362 (92.8)	238 (96.4)	1.26	0.21
PLE-Threshold and Subthreshold w/o Psychotic DO at Last Assessment	51 (8.5)	34 (9.4)	17 (7.1)	0.43	0.67
PLE-Subthreshold w/o Psychotic DO at Last Assessment	41 (6.8)	28 (7.7)	13 (5.5)	0.54	0.59
PLE-Threshold w/o Psychotic DO at Last Assessment	10 (1.7)	6 (1.7)	4 (1.7)	0.13	0.89
Psychotic DO at Last Assessment	7 (1.2)	4 (1.1)	3 (1.3)	0.18	0.86
Non-affective Psychotic DO	3 (0.5)	1 (0.3)	2 (0.8)	0.66	0.51
Affective Psychotic DO	4 (0.7)	3 (0.8)	1 (0.4)	0.38	0.71
PLE w/o Psychotic DO at intake ●	30 (4.7)	24 (6.2)	6 (2.4)	1.39	0.16
PLE-Subthreshold w/o Psychotic DO at intake ●	21 (3.3)	17 (4.3)	4 (1.6)	1.20	0.23
PLE-Threshold w/o Psychotic DO at Last Assessment	0	0	0		
Psychotic Disorder at Last Assessment	0	0	0		
PLE-Threshold w/o Psychotic DO at intake ●	9 (1.4)	7 (1.8)	2 (0.8)	0.69	0.49
Psychotic Disorder at Last Assessment	2 (6.0)	2 (8.3)	0	0.00	0.99
Non-affective Psychotic DO	1 (3.3)	1 (4.2)	0	0.05	0.96
Affective Psychotic DO	1 (3.3)	1 (4.2)	0	0.05	0.96
Psychotic Disorder at Intake ●	7 (1.1)	4 (1.0)	3 (1.2)	0.02	0.98
Non-affective Psychotic DO	5 (0.8)	2 (0.5)	3 (1.2)	0.51	0.61
Affective Psychotic DO	2 (0.3)	2 (0.5)	0	0.01	0.99

PLE: psychotic-like experiences (Subthreshold and Threshold for low and high intensity respectively); DO: disorder.
● Model adjusted for within family correlation. In bold p-values <0.05.

Fig.9: Age when PLE first reported by cohort group.



5.1.2.3. Predictors of risk for PLE during follow-up.

After a series of survival analyses, including cox proportional hazard regression models with time-varying, and general linear mixed models, three variables remained statistically significant predictors of PLE either at intake or during follow-up: (1) a history of any psychiatric disorders (HR = 3.1; 95% CI 1.3-7.36, p = .01), (2) low psychosocial functioning (HR = 2.94; 95% CI 1.79-4-81, p < .0001), and (3) a history of physical or sexual abuse (HR = 1.85; 95% CI 1.02-3.38, p = .04) (Table 11, figure 10). Similar results were found when only BD offspring were analyzed (Table 12). On the contrary, for control offspring, the only risk factor of PLE identified was low psychosocial functioning (Table 13). Exposure to medication during follow-up was also a risk factor of PLE (HR = 1.78; 95% CI 1.17-2.7, p < .01) in the univariate models for the whole sample and for the BD group, but it wasn't statistically significant in the series of multivariate models. We were not able to find any association between PLE and head injury, endocrine illnesses, pubertal status, or body mass index. None of the perinatal factors were longitudinally associated with PLE, neither for the whole sample nor for any of the offspring groups.

We found that all diagnoses were significantly associated with the likelihood of experiencing PLE at some time during the follow-up, with the exception of other mood disorders and tic disorders. The association between psychiatric diagnoses and PLE was similar with or without considering threshold or subthreshold PLE (Table 14). Although significant in both, the association was stronger for BP offspring than for control offspring (Table 15).

Table 11: Demographic and Clinical Predictors from Intake and During Follow-Up for the Onset of PLE in All Offspring* .

	Unadjusted Univariate Analysis, HR (95% CI)	Statistics (z)	p-value	Adjusted Multivariate Analysis HR (95% CI)	Statistics (z)	p-value
Socio-demographics:						
Gender: Female	1.03 (0.66, 1.61)	0.12	0.90	0.96 (0.62, 1.49)	0.18	0.85
Race: White	0.62 (0.35, 1.09)	1.66	0.09			
Living: Both parents	1.03 (0.67, 1.58)	0.13	0.89			
Age at intake	0.93 (0.87, 0.99)	2.33	**0.02**	0.92 (0.87, 0.98)	2.44	**0.01**
Years in the study	0.93 (0.87, 0.99)	2.13	**0.03**			
SES	0.97 (0.95, 0.99)	2.72	**<0.01**	0.99 (0.97, 1.00)	1.49	0.13
Drop out	0.87 (0.22, 3.48)	0.19	0.85			
Parent's Psychopathology (proband or co-parent)						
Bipolar vs. Control parents	1.46 (0.88, 2.24)	1.47	0.14			
Bipolar with Psy	1.06 (0.69, 1.65)	0.28	0.78			
PLE	0.95 (0.59, 1.52)	0.22	0.83			
Affective DO	0.57 (0.26, 1.23)	1.43	0.15			
DSM-IV-TR Psychopathology:						
Axis I DO	6.52 (2.81, 15.16)	4.36	**<0.0001**	3.1 (1.3, 7.36)	2.56	**0.01**
Axis I DO Major	5.93 (2.92, 12.03)	4.94	**<0.0001**			
Axis I DO wo Psy	2.36 (1.32, 4.23)	2.89	**<0.01**			
Axis I DO Major wo Psy	2.48 (1.47, 4.17)	3.42	**<0.001**			
Overall functioning:						
CGAS/GAF min <70	5.09 (2.98, 8.73)	5.94	**<0.0001**	2.94 (1.79, 4.81)	4.30	**<0.0001**
CGAS/GAF current <70	5.31 (3.41, 8.28)	7.37	**<0.0001**			
CGAS/GAF most severe past <70	5.02 (2.93, 8.60)	5.88	**<0.0001**			
CGAS/GAF highest in the past <70	5.49 (3.67, 8.21)	5.49	**<0.0001**			
IQ	0.98 (0.97, 1.00)	1.84	0.06			
Medical History:						
Physical or sexual abuse	2.74 (1.55, 4.85)	3.46	**<0.001**	1.85 (1.02, 3.38)	2.01	**0.04**
Head injury	1.35 (0.68, 2.69)	0.86	0.39			
Medication	1.78 (1.17, 2.70)	2.68	**0.01**			
Endocrine illness	0.61 (0.26, 1.45)	1.12	0.26			

Pubertal Status	0.71 (0.42, 1.22)	1.23	0.22
BMI	1.01 (0.97, 1.06)	0.69	0.49
Perinatal Hx			
Parental age at offspring's birth	0.96 (0.92, 1.01)	1.57	0.12
Infections/injuries during pregnancy	1.34 (0.77, 2.36)	1.04	0.3
Birth weight	0.95 (0.71, 1.27)	0.36	0.72

SES: Socioeconomic status; Major DO: excluded Mood/Anxiety NOS, Tics, or Other. DO w/o Psy: Schizophrenia; Schizophreniform; Psychosis NOS; Brief Psychosis. CGAS: Child Global Adjustment Scale; GAF: Global Assessment of Functioning; IQ: Intellectual Quotient; BMI: Body Mass Index
****Survival Time Varying model, adjusted by gender, age at intake and SES. AIC=1359.23. In bold p-values <0.05 included in the multivariate analysis.***

Fig. 10: Multivariate Adjusted Hazard Ratios (HR) to Develop PLE in all Offspring

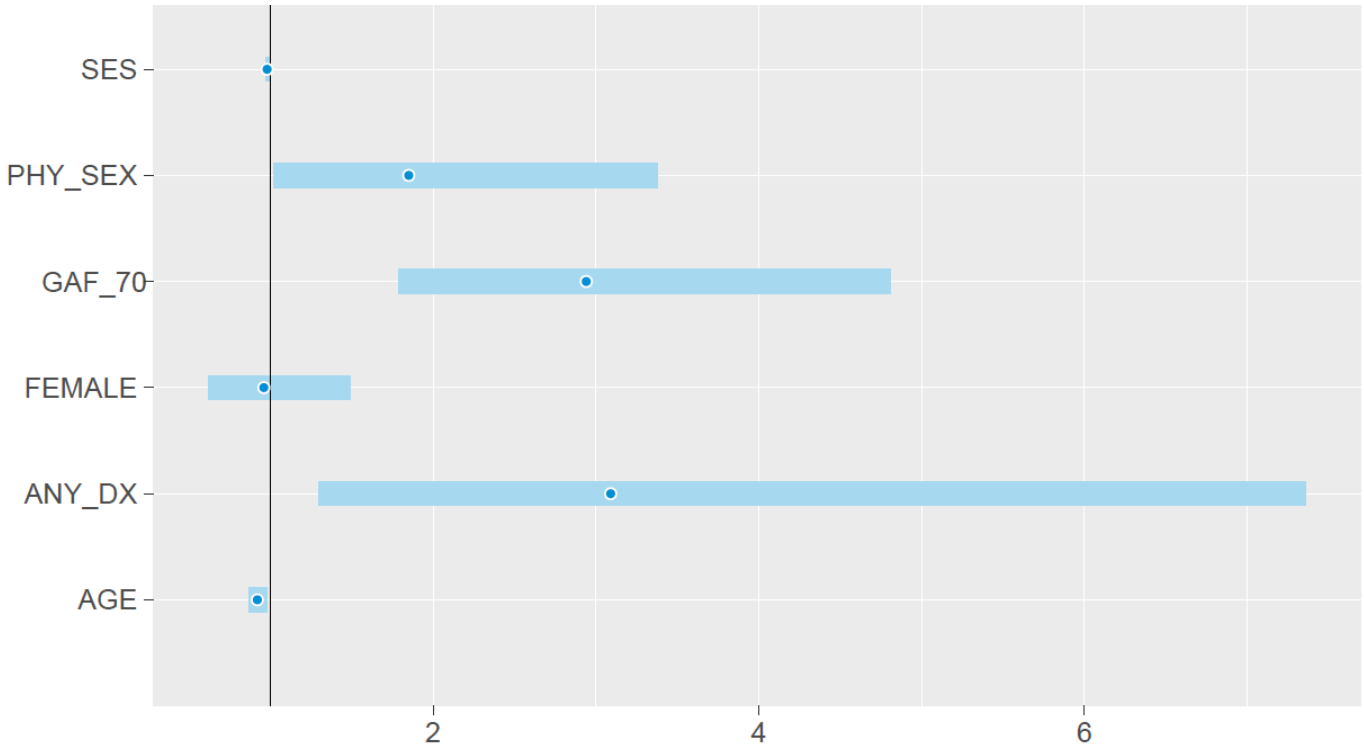


Table 12: Predictors from Intake and During Follow-Up for the Onset of PLE in Offspring Of Bipolar parents.

	Unadjusted Univariate Analysis, HR (95% CI)	Statistics (z)	p-value	Adjusted Multivariate Analysis, HR (95% CI)	Statistics (z)	p-value
Socio-demographics:						
Gender: Female	0.95 (0.36, 1.37)	0.21	0.84	0.85 (0.51, 1.41)	0.62	0.54
Race: White	0.70 (0.36, 1.37)	1.04	0.29			
Living with: Both parents	1.23 (0.75, 2.03)	0.81	0.41			
Age at intake	0.94 (0.87, 1.01)	1.69	0.09	0.94 (0.87, 1.01)	1.75	0.08
Years in the study	0.92 (0.85, 0.99)	1.99	**0.05**			
SES first	0.98 (0.96, 0.99)	2.48	**0.01**	0.99 (0.97, 1.01)	1.22	0.22
Drop out	0.77 (0.11, 5.48)	0.25	0.79			
DSM-IV-TR Psychopathology:						
Lifetime of any Axis I DO	40.78 (5.71, 291.4)	3.69	**<0.001**	17.26 (2.39, 124.37)	2.83	**<0.01**
Lifetime of any Axis I DO Major	14.46 (5.46, 38.34)	5.37	**<0.0001**			
Lifetime of any Axis I DO wo Psy	2.02 (0.93, 4.37)	1.78	**0.07**			
Lifetime of any Axis I DO Major wo Psy	2.49 (1.23, 5.01)	2.55	**0.01**			
Functionality:						
CGAS/GAF min <70	6.89 (3.67, 12.97)	5.99	**<0.0001**	3.05 (1.63, 5.72)	3.49	**<0.0001**
CGAS/GAF current <70	5.16 (3.14, 8.47)	6.48	**<0.0001**			
CGAS/GAF most severe past <70	7.5 (3.89, 14.47)	6.01	**<0.0001**			
CGAS/GAF highest in the past <70	5.73 (3.58, 9.17)	7.29	**<0.0001**			
Medical Hx:						
Lifetime hx of any physical or sexual abuse	2.65 (1.45, 4.86)	3.16	**<0.01**	1.96 (1.05, 3.67)	2.11	**0.03**
Lifetime hx of any head injury	1.31 (0.6, 2.85)	0.69	0.49			
Lifetime hx of any endocrine illness	0.59 (0.21, 1.71)	0.95	0.34			
Lifetime hx of any medication	1.96 (1.15, 3.32)	2.49	**0.01**			
Pubertal Status	0.69 (0.37, 0.94)	1.17	0.24			
BMI	1.02 (0.97, 2.85)	0.71	0.48			

IQ: Intellectual Quotient; CGAS: Child Global Adjustment Scale; GAF: Global Assessment of Functioning; BMI: Body Mass Index; Major DO: excluded Mood Anxiety NOS, Tics, or Other Do.
DO w/o Psy: Schizophrenia DO; Schizophreniform DO; Psychosis NOS DO; Brief Psychosis.
Survival Time Varying model, adjusted by gender, age at intake, and SES at intake.
In bold p-values <0.05 included in the multivariate analysis. AIC=848.92.

Table 13: Predictors from Intake and During Follow- Up for the Onset of PLE in Offspring Of Community Parents.

	Unadjusted Univariate Analysis, HR (95% CI)	Statistic (z)	p-value	Adjusted Multivariate Analysis, HR (95% CI)	Statistics (z)	p-value
Socio-demographics:						
Gender: Female	1.32 (0.58, 3.01)	0.67	0.51			
Race: White	0.47 (0.17, 1.3)	1.44	0.15			
Living with: Both parents	0.76 (0.31, 1.66)	0.15	0.49			
Age at intake	0.9 (0.81, 1.01)	2.12	0.08	0.9 (0.8, 1.01)	1.75	0.08
Years in the study	0.95 (0.83, 1.07)	0.87	0.39			
SES first	0.97 (0.92, 1.02)	1.29	0.19			
Drop out	1.19 (0.17, 8.24)	0.18	0.86			
DSM-IV-TR Psychopathology:						
Lifetime of any Axis I DO	2.91 (1.13, 7.45)	2.22	**0.03**	1.65 (0.66, 4.09)	1.07	0.28
Lifetime of any Axis I DO Major	2.97 (1.14, 7.72)	2.23	**0.03**			
Lifetime of any Axis I DO wo Psy	2.65 (1.08, 6.5)	1.78	**0.03**			
Lifetime of any Axis I DO Major wo Psy	2.18 (0.92, 5.14)	2.55	0.08			
Overall functioning:						
CGAS/GAF min <70	3.49 (1.47,8.29)	2.84	**<0.01**	2.78 (1.24, 6.27)	2.47	**0.01**
CGAS/GAF current <70	5.67 (2.48 12.97)	4.11	**<0.0001**			
CGAS/GAF most severe past <70	3.16 (1.36, 7.32)	2.68	**<0.01**			
CGAS/GAF highest in the past <70	5.18 (2.53, 10.6)	4.51	**<0.0001**			
Medical History:						
Lifetime of any physical or sexual abuse	1.44 (0.19, 10.83)	0.35	0.72			
Lifetime of any head injury	1.19 (0.29, 4.81)	0.25	0.8			
Lifetime of any endocrine illness	0.64 (0.19, 2.15)	0.72	0.47			
Lifetime of any medication	1.18 (0.62, 2.26)	0.5	0.62			
BMI	1.01 (0.93, 1.1)	0.33	0.74			

IQ: Intellectual Quotient; CGAS: Child Global Adjustment Scale; GAF: Global Assessment of Functioning; BMI: Body Mass Index; Major DO: excluded Mood/Anxiety NOS, Tics, or Other. DO w/o Psy: Schizophrenia DO; Schizophreniform DO; Psychosis NOS DO; Brief Psychosis.
Survival Time Varying model, adjusted by gender, age at intake, and SES at intake. In bold p-values <0.05 included in the multivariate analysis. AIC=373.31.

Table 14: Adjusted Prior Diagnoses and Hazard to Develop Subsequent PLE in All Offspring.

	Offspring with PLE (n=95) vs. offspring w/o PLE (n=542)			Offspring with PLE threshold (n=33) vs. w/o PLE (n=542)			Offspring with PLE subthreshold (n=62) vs. offspring w/o PLE (n=542)		
	Hazard ratio	**95% Confidence Interval**	**p-value**	**Hazard ratio**	**95% Confidence Interval**	**p-value**	**Hazard ratio**	**95% Confidence Interval**	**p-value**
Affective DO	3.83	2.48, 5.92	**<0.0001**	4.17	1.97, 8.85	**<0.001**	4.94	2.73, 7.4	**<0.0001**
Major Depression DO	2.76	1.79, 4.27	**<0.0001**	2.82	1.44, 5.55	**<0.01**	3.13	1.77, 5.55	**<0.001**
Bipolar DO (I, II, NOS)	3.99	2.48, 6.41	**<0.0001**	4.74	2.09, 10.79	**<0.001**	4.86	2.71, 8.7	**<0.0001**
Other Mood DO*	1.51	0.92, 2.49	0.10	1.91	0.92, 3.99	0.08	1.29	0.63, 2.61	0.48
Psychotic DO	13.23	9.18, 19.06	**<0.0001**	32.31	18.32, 56.98	**<0.0001**	NA	NA	NA
Non-affective Psychotic DO*	11.15	6.83, 18.2	**<0.0001**	20.95	10.88, 40.36	**<0.0001**	NA	NA	NA
Affective Psychotic DO**	11.34	7.95, 16.17	**<0.0001**	21.81	12.39, 38.38	**<0.0001**	NA	NA	NA
Anxiety DO	3.70	2.41, 5.67	**<0.0001**	5.07	2.48, 10.38	**<0.0001**	3.49	2.07, 5.86	**<0.0001**
Major Anxiety DO	3.78	2.41, 5.93	**<0.0001**	4.13	1.9, 8.97	**<0.001**	4.55	2.78, 7.45	**<0.0001**
Other Anxiety DO***	2.77	1.80, 4.28	**<0.0001**	3.68	1.85, 7.33	**<0.001**	2.81	1.61, 4.89	**<0.001**
Attention Deficit and Hyperactivity DO	2.02	1.28, 3.19	**<0.01**	2.00	0.95, 4.23	0.07	2.83	1.67, 4.82	**<0.001**
Conduct DO/Disruptive Behavioral DO	2.91	1.78, 4.75	**<0.0001**	2.98	1.31, 6.78	**<0.01**	4.21	2.45, 7.25	**<0.0001**
Post Traumatic Stress DO	2.57	1.17, 5.64	**0.02**	2.47	0.63, 9.69	0.19	3.57	1.79, 7.14	**<0.001**
Eating DO	3.25	1.66, 6.37	**<0.001**	2.89	0.9, 9.24	0.07	3.55	1.5, 8.09	**<0.01**
Substance Abuse or Dependence DO	1.8	1.11, 2.91	**0.02**	1.69	0.81, 3.51	0.16	2.11	1.09, 4.01	**0.03**
Tic DO	2.28	0.71, 7.29	0.16	3.24	0.62, 16.85	0.16	1.52	0.26, 8.95	0.64
Other DO****	1.75	1.06, 2.88	**0.03**	2.36	1.11, 5.02	**0.03**	1.18	0.61, 2.28	0.62

Dysthymia, Depression NOS, Adjustment DO, Mood NOS; Schizophrenia, Schizophreniform, Psychosis NOS, and Brief Psychotic; **Bipolar I and Major Depression with psychotic features, Schizoaffective. ***Specific phobia, Anxiety NOS, Adjustment DO with Anxiety, Enuresis, Encopresis; ** learning problems; sleep DO; ADHD or CD NOS; relational problems. Survival Time Varying model, adjusted by gender, age at intake, and SES. In bold p-values <0.05. NA: Not applicable or convergence problems.*

Table 15: Adjusted Prior Diagnoses and Hazard to Develop subsequent PLE in all Offspring, Offspring of Bipolar, and Offspring of Controls.

	Offspring with PLE (n=95) vs. offspring w/o PLE (n=542)			BP Offspring with PLE (n=66) vs. w/o PLE (n=324)			Control Offspring with PLE (n=29) vs. w/o PLE (n=218)		
	Hazard ratio	**95% Confidence Interval**	**p-value**	**Hazard ratio**	**95% Confidence Interval**	**p-value**	**Hazard ratio**	**95% Confidence Interval**	**p-value**
Affective DO	3.83	2.48, 5.92	**<0.0001**	4.57	2.65, 7.88	**<0.0001**	2.5	1.06, 5.91	**0.04**
Major Depression DO	2.76	1.79, 4.27	**<0.0001**	2.51	1.48, 4.26	**<0.001**	3.58	1.54, 8.34	**<0.01**
Bipolar (I, II, NOS)	3.99	2.48, 6.41	**<0.0001**	4.11	2.45, 6.89	**<0.0001**	3.21	0.77, 13.38	0.11
Other Mood DO'	1.51	0.92, 2.49	0.10	1.81	1.07, 3.06	**0.03**	0.59	0.13, 2.66	0.49
Psychotic DO	13.23	9.18, 19.06	**<0.0001**	12.62	8.39, 18.97	**<0.0001**	13.01	6.67, 25.36	**<0.0001**
Non-affective Psychotic DO†	11.15	6.83, 18.2	**<0.0001**	10.53	5.92, 18.74	**<0.0001**	15.15	4.66, 49.19	**<0.0001**
Affective Psychotic DO	11.34	7.95, 16.17	**<0.0001**	10.91	7.35, 16.19	**<0.0001**	12.92	6.21, 26.88	**<0.0001**
Anxiety DO	3.70	2.41, 5.67	**<0.0001**	4.04	2.4, 6.79	**<0.0001**	2.94	1.45, 5.98	**<0.01**
Major Anxiety DO**	3.78	2.41, 5.93	**<0.0001**	3.95	2.22, 7.03	**<0.0001**	3.14	1.48, 6.46	**<0.01**
Other Anxiety DO	2.77	1.80, 4.28	**<0.0001**	2.83	1.69, 4.73	**<0.0001**	2.35	1.16, 4.7	**0.02**
Attention Deficit Hyperactivity DO	2.02	1.28, 3.19	**<0.01**	1.63	0.97, 2.73	0.06	3.19	1.39, 7.31	**<0.01**
Conduct/Disruptive Behavioral DO	2.91	1.78, 4.75	**<0.0001**	2.5	1.4, 4.46	**<0.01**	4.02	1.8, 8.96	**<0.001**
Post-Traumatic Stress DO	2.57	1.17, 5.64	**0.02**	1.79	0.75, 4.28	0.19	4.23	1.29, 13.82	**0.02**
Eating DO	3.25	1.66, 6.37	**<0.001**	3.62	1.87, 7.03	**<0.001**	NA	NA	NA
Substance Abuse/Dependence DO	1.8	1.11, 2.91	**0.02**	1.73	0.97, 3.06	0.06	1.88	0.79, 4.46	0.15
Tic DO	2.28	0.71, 7.29	0.16	2.57	0.86, 7.47	0.09	NA	NA	NA
Other DO●	1.75	1.06, 2.88	**0.03**	1.42	0.81, 2.49	0.22	2.76	1.08, 7.06	**0.03**

'Dysthymia, Depression NOS, Adjustment DO with Depression, other Mood NOS. †Schizophrenia, Schizophreniform, Psychosis NOS, Brief Psychotic; ††Bipolar, Major Depression with psychotic features, Schizoaffective. *Panic, Separation Anxiety, Avoidant, Social Phobia, Agoraphobia, Generalized Anxiety, Obsessive Compulsive; **Specific phobia, Anxiety NOS, Adjustment DO with Anxiety, Enuresis, Encopresis; ● learning problems; sleep DO; ADHD or CD NOS; parent-child relational problems; sibling relational problems.
Survival Time Varying model, adjusted by gender, age at intake, and SES at intake. In bold p-values <0.05. NA: Not applicable or convergence problems.

In a second unpublished analysis, we focused only on those 79 offspring who reported PLE symptoms during the study who did not develop any psychotic disorder (n=16), and we divided the sample into four at-risk groups: BD offspring with (1) or without (2) any psychiatric disorder, and community offspring with (3) or without (4) any psychiatric disorder (Fig. 11, Table 16). Interestingly, offspring of BD with any psychiatric disorder had a 13-fold increased likelihood of PLE (HR = 13.02; 95% CI 12.05, 107.73, $p < 0.01$), as compared with a 2-fold increased risk among community offspring with an existing disorder (HR = 2.04; 95% CI 1.35-76.61, $p = .05$). Being from the group of offspring without any psychiatric disorder did not have any association with an increased risk of PLE. Results were partially confirmed when we focused only on the onset of PLE during follow-up (N=51).

Fig. 11: Four at-risk groups of PLE during follow-up.

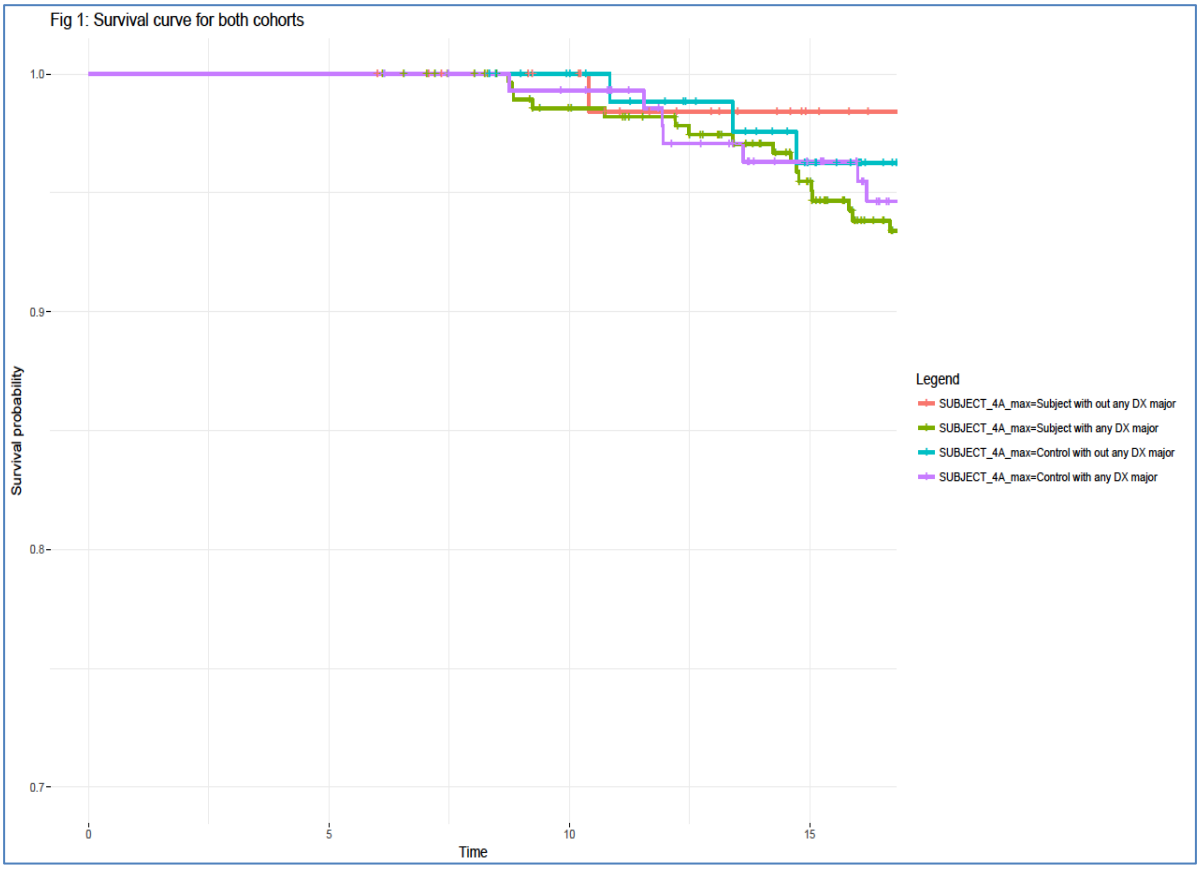


Table 16: Association of Risk for PLE Using BP Offspring without Diagnosis as a Reference.

	Hazard Ratio	95% Confidence Interval	Statistics (z)	p-value
PLE_Reported wo Psy DO (n=79)				
BP offspring with Any Dx	13.02	2.05, 107.73	2.54	**0.01**
Offspring from community w/o Any Dx	5.7	0.67, 48.25	1.62	0.10
Offspring from community Any Dx	2.04	1.35, 76.61	1.97	**0.05**
PLE_FUP wo Psy DO during (n=51)				
BP offspring with Any Dx	8.18	1.11, 60.29	2.06	**0.04**
Offspring from community w/o Any Dx	4.32	0.49, 37.19	1.32	0.19
Offspring from community Any Dx	5.99	0.76, 46.89	1.71	0.09

PLE: Psychotic-Like Experiences; wo: without; Psy DO: psychotic disorder; Dx: Diagnosis.
Cox-mixed effects regression models controlling for within family correlation.

5.1.2.4. Predictors of risk for psychotic disorders during follow-up.

Sixteen offspring (2.5%, 16/637) met diagnostic criteria for a psychotic disorder, 7 at intake (5 non-affective psychoses, 2 affective psychoses) and 9 during follow-up (4 non-affective psychoses, 5 affective psychoses). All offspring who developed a psychotic disorder during follow-up (9) reported PLE in the interviews, 2 at intake and 7 at follow-up (transition rate 7.9%, 0.99%/year). Two risk factors at baseline were found to be associated with the onset of any psychotic disorder during follow-up (Table 17): 1) Low levels of functioning based on current CGAS (HR = 4.37; 95% CI 1.10, 17.15, p = **0.03**); 2) self-reported PLE based on CBCL (HR = 8.97; 95% CI 1.18, 67.27, p =**0.03**). Puberty status at intake was found to be at marginal risk (HR = 5.46; 95% CI 0.82, 35.7, p =0.07).

Table 17: Intake Risk Factors Before Onset of Axis I Psychotic Disorders "de novo" during Follow-Up (n=9).

	Hazard Ratio	95% Confidence Interval	Statistics (z)	p-value
Demographics at intake				
Gender: Female	0.83	0.22, 3.16	0.97	0.79
Race: White	1.05	0.17, 6.25	0.06	0.95
Living with: Both parents	NA	NA	NA	NA
Age at intake	1.14	0.86, 1.49	0.92	0.36
Parent's Psychopathology (proband or co-parent)				
Bipolar parents vs. Community control parents	1.29	0.29, 5.64	0.35	0.73
Family hx for Bipolar with Psychotic Features Subtype	0.80	0.09, 7.07	0.2	0.84
Family hx for PLE symptoms	0.53	0.06, 4.55	0.57	0.57
Perinatal Hx				
Parental age at offspring's birth	0.95	0.84, 1.07	0.9	0.37
Infections or any injury during pregnancy	0.57	0.07, 4.74	0.52	0.6
Medication exposure during pregnancy				
Alcohol or drug exposure during pregnancy	1.14	0.26, 5.05	0.18	0.86
Complications during delivery	0.94	0.22, 4.06	0.08	0.94
Weight at birth	1.14	0.43 2.97	0.26	0.8
Self-reported psychosis at intake				

Self_Reported Psychotic Threshold or Subthreshold Symptoms	8.97	1.18, 67.27	2.12	**0.03**
Self_Reported Psychotic Threshold Symptoms	4.02	0.43, 37.50	1.22	0.22
Self_Reported Psychotic Subthreshold Symptoms	3.59	0.58, 22.26	1.38	0.17
PLE_Reported Threshold or Subthreshold at Intake	NA	NA	NA	NA
Functionality at intake				
CGAS/GAF current_<60	4.37	1.10, 17.15	2.1	**0.03**
CGAS/GAF most severe past_<60	2.60	0.62, 10.92	1.3	0.19
CGAS/GAF highest in the past_<60	6.06	1.53, 23.85	2.56	**0.01**
Any psychiatric diagnosis at intake	0.86	0.21, 3.49	0.2	0.84
Medical history at intake				
Head_Intake	NA	NA	NA	NA
Hormone_Intake	NA	NA	NA	NA
Med_Intake	0.59	0.15, 2.46	0.71	0.48
BMI_Intake	1.03	0.94, 1.15	0.69	0.49
Phy_Sex_Intake	1.27	0.13, 11.87	0.21	0.83
Pubertal_Intake	5.46	0.82, 35.57	1.77	**0.07**

Excluded 7 cases with Axis I Psychotic DO at intake
Hx: History; PLE: psychotic-like symptoms reported at face-to-face interview; CGAS: Child Global Adjustment Scale; GAF: Global Assessment of Functioning.
Cox regression models controlling for within family correlation. NA: not applicable, model failed to converge. Pearson's X-squared test with Yates's continuity correction. In bold p-values <0.1.

5.1.2.5. The validity of self-reported questionnaires for measuring PLE.

Finally, we performed an exploratory analysis of the level of consistency between PLE reported during face-to-face interviews and PLE self-reported in the CBCL/YSR/TRF questionnaires (Achenbach, 1991). For this analysis we focused on the data from baseline to year 7.

178 offspring (27.9%) self-reported psychotic symptoms at some point during the study, compared to 95 (14.9%) when they were interviewed directly. The relation between self-reported PLE and face-to-face PLE was evaluated as "fair agreement" on the kappa scores (K=0.21; 95% CI: 0.12, 0.29; p <0.0001), but not confirmed when threshold and subthreshold scores were compared separately (K=0.16 and 0.06; p <0.03 and 0.15 respectively) (Table 18).

The self-reported psychosis were found associated with any previous Axis I DO (OR = 2.53; 95% CI 1.49, 3.04; p < 0.0001), with a specific association for BP or

Schizoaffective disorders (OR = 26.9; 95% CI:3.36, 444.9; $p < 0.01$), followed by Schizophrenia-like disorders (OR=12.2; 95% CI 3.12, 48.36; $p < 0.001$ (Table 19).

Self-reported PLE did not increase the frequency of face-to-face reported PLE during the follow-up and were not included in the study.

Table 18: Kappa agreement between PLE reported and Self-reported Psychotic Symptoms.

	Cohen's Kappa	95% Confidence Interval	Statistics (z)	P-value	Judgment
Psychosis threshold and subthreshold symptoms	0.205	0.12, 0.29	4.27	**<0.0001**	Fair agreement
Psychosis reported threshold and subthreshold					
Self-psychosis threshold and subthreshold					
Psychosis threshold symptoms	0.16	0.01, 0.31	1.93	**0.03**	Slight agreement
Psychosis reported threshold					
Self-psychosis threshold					
Psychosis threshold and subthreshold symptoms	0.06	0.05, 0.17	1.01	0.15	Slight agreement
Psychosis reported subthreshold					
Self-psychosis subthreshold					

PLE reported: psychotic-like symptoms based on KSADS; Self-reported Psy: psychotic-like symptoms based on CBCL/TRF/YSR.

Table 19: Adjusted Prior Diagnoses and Hazard to Develop Subsequent Self-Psy in All Offspring.

Offspring with Self-Psy (n=178) vs. offspring w/o Self-Psy (n=459)

	Hazard ratio	95% Confidence Interval	p-value
Any Axis I DO	2.12	1.49, 3.04	**<0.0001**
Major Depression DO	1.15	0.74, 1.79	0.54
Bipolar DO (I, II, NOS)	1.6	0.93, 2.76	0.09
Affective Psychotic DO*	26.9	3.36, 444.9	**<0.01**
Non-affective Psychotic DO**	12.2	3.12, 48.36	**<0.001**
Major Anxiety DO	2.18	1.49, 3.17	**<0.0001**
Attention Deficit and Hyperactivity DO	2.17	1.47, 3.19	**<0.0001**
Conduct DO/Disruptive Behavioral DO	2.29	1.47, 3.56	**<0.001**
Post Traumatic Stress DO	1.31	0.6, 2.84	0.49
Eating DO	4.28	1.15, 15.91	**0.03**
Substance Abuse or Dependence DO	0.69	0.42, 1.15	0.16
Any PDD	1.46	0.46, 4.62	0.52
Any Other DO***	1.85	1.19, 2.85	**<0.01**

Self-Psy: Self-reported psychosis based on CBCL scores; DO: disorder; *Bipolar I and Major Depression with psychotic features, Schizoaffective; **Schizophrenia, Schizophreniform, Psychosis NOS, and Brief Psychotic; *** learning problems; sleep DO; ADHD or CD NOS; adjustment DO with Anxiety, Enuresis, Encopresis; relational problems.

Survival Time Varying model, adjusted by gender, age at intake, and SES. In bold p-values <0.05.

5.2. Study 2: "Functional impairment and clinical correlates in adolescents with bipolar disorder compared to healthy controls. A case-control study".

5.2.1. BD adolescents' sample: BD with psychotic symptoms vs. BD without psychotic symptoms.

5.2.1.1. Socio-demographics, medical and family past history.

Our preliminary approach was to focus on analyzing the phenomenon of psychotic symptoms in a clinical presentation and functional performance of the bipolar sample. A total of 47 BD were recruited for the study, the majority (40, 85.1%) from BD type I (Table 20). Most BD recalled an early first contact with mental health services, at a mean age of 10.5±4.1 years, with a formal diagnosis of BD five years later. Comorbidity was very frequent (90%), mainly with anxiety disorders (61.7%) (Table 21). All BP subjects were under pharmacological treatment at the time of the study, with an average of at least two psychotropic medications, antipsychotics (79.5%), followed by lithium (61.9%) (Table 20).

74.5% of BD adolescents (35/47) reported lifetime psychotic symptoms at some point of the history, half of them (22/35, 46.8%) at threshold level based on the DSM-5 classification (Table 20). BD with threshold psychosis compared to BD with subthreshold psychosis or without psychosis at all (Table 21), was significantly associated with a longer duration of hospitalization [53.7 ± 11.1 vs. 20.9 ± 11.1; OR 1.06 (1.0, 1.11), p=**0.03**] and a higher number of medications at present [2.4 ± 0.9 vs.1.8 ± 0.8; OR 2.55 (1.19, 5.43), p=**0.01**], mainly antipsychotics and lithium. On the contrary, BD without psychosis reported more comorbidity with anxiety and had an

earlier first hospitalization [2.4 ± 0.9 vs.1.78 ± 0.8; OR 2.55 (1.19, 5.43), p=**0.01**]. We did not find any statistically significant association between psychosis and number of episodes, or family history of mental disorder.

Table 20: Phenomenology of Bipolar Subjects (N=47)

Mood DO characteristics	
Bipolar subtype: Bipolar I (n, %)	40 (85.1)
Lifetime Psychotic symptoms: Yes (n, %)	35 (74.5)
Psychosis threshold (n, %)	22 (46.8)
Psychosis subthreshold (n, %)	13 (27.7)
Age first diagnosis any Mood DO (mean, SD)	13.66 ± 2.38
Age first diagnosis Bipolar DO (mean, SD)	15.00 ± 1.99
Polarity first Bipolar Episode:	
Mania (n, %)	14 (29.8)
Depression (n, %)	33 (70.2)
Hospitalizations: Yes (n, %)	35 (74.5)
Number hospitalizations (mean, SD)	1.91 ± 1.99
Duration hospitalizations in days (mean, SD)	37.80 ± 60.18*
Age first hospitalization (mean, SD)	14.46 ± 1.77
Psychiatric Hx	
Previous contact with Mental Health: Yes (n, %)	44 (93.6)
Age first contact Mental Health (mean, SD)	10.49 ± 4.12
Reasons for referral (46/47):	
Emotional problems (n, %)	21 (45.7)
Behavioral problems (n, %)	13 (28.3)
Anxiety problems (n, %)	6 (13)
Neurodevelopmental problems (n, %)	3 (6.5)
Other (n, %)	3 (6.5)
Previous psychiatric diagnosis: Yes (n, %)	44 (93.6)
Affective DO (n, %)	15 (31.9)
ADHD (n, %)	8 (17.0)
ODD/CD (n, %)	6 (12.8)
Anxiety DO (n, %)	6 (12.8)
OCD (n, %)	2 (4.3)
AN/BN (n, %)	5 (10.6)
Psychotic DO (n, %)	1 (2.1)
Other DO (n, %)	1 (2.1)
Past treatment	
Previous treatments: Yes (n, %)	37 (78.7)
Number of previous treatments: Yes (n, %)	2.11 ± 0.84
Previous exposure to antipsychotics: Yes (n, %)	29 (61.7)
Mean exposure to Chlorpromazine in the past (mean, SD)	236.80 ± 219.55
Time exposure Chlorpromazine in days (mean, SD)	335.83 ± 351.27
Current treatment	
Current treatment: Yes (n, %)	47 (100)
Number of current treatments: Yes (n, %)	2.09 ± 0.93
Antipsychotics when RMN: Yes (n, %)	38 (80.9)
Doses Chlorpromazine (mean, SD)	262.25 ± 189.86
Time exposure Chlorpromazine in days (mean, SD)	219.08 ± 400.38

Lithium when RMN: Yes (n, %)	29 (61.7)
Doses Lithium (mean, SD)	595.74 ± 494.29
Time exposure Lithium (mean, SD)	107.17 ± 228.14
Antidepressants when RMN: Yes (n, %)	7 (14.9)
Doses (mean, SD)	36.25 ± 33.08
Antiseizures when RMN: Yes (n, %)	12 (25.5)
Doses (mean, SD)	562.5 ± 534.12

SD: standard deviation; DO: disorder; OCD: obsessive-compulsive disorder; AN/BN: anorexia or bulimia nervosa; ADHD: attention deficit/ hyperactivity DO; CD/ODD: conduct or oppositional Defiant DO; PTSD: post-traumatic stress DO.
****1 BD had a diagnosis of TCA with 368 days on inpatient unit.***

Table 21: Socio-demographic, Family, Medical and Psychiatric History of Bipolar with Psychosis vs. without Psychosis.

	Bipolar with Psy N (22)	Bipolar w/o Psy N (25)	Univariate Analysis OR (95%CI)	p-value
Socio-demographics				
Sex: Female (n, %)	11 (50.0)	13 (52.0)	0.92 (0.29, 2.9)	0.89
SES (mean, SD)	42.07 ± 14.67	49.58 ± 12.38	0.96 (0.92, 1.0)	0.07
Age at intake (mean, SD)	15.81 ± 1.79	15.84 ± 2.21	1.08 (0.8, 1.45)	0.62
Family Hx				
1st degree Psychiatric Family Hx (n, %)	15 (68.2)	20 (90.9)	0.21 (0.04, 1.18)	0.08
Mood DO characteristics				
Age first diagnosis any Mood DO (mean, SD)	14.18 ± 2.08	13.02 ± 2.57	1.21 (0.92, 1.6)	0.17
Age first diagnosis Bipolar DO (mean, SD)	15.09 ± 1.85	15.0 ± 1.98	1.03 (0.76, 1.39)	0.87
Hospitalizations: Yes (n, %)	18 (81.8)	17 (68.0)	2.12 (0.54, 8.34)	0.28
Number hospitalizations (mean, SD)	1.72 ± 1.07	2.12 ± 2.67	0.89 (0.62, 1.3)	0.57
Duration hospitalizations in days (mean, SD)	53.72 ± 81.08	20.94 ± 11.13	1.06 (1.0, 1.11)	**0.03**
Age first hospitalization (mean, SD)	15.05 ± 1.62	13.82 ± 1.74	1.55 (1.01, 2.4)	0.05
YMRS (mean, SD)	6.18 ± 5.56	8.08 ± 6.88	0.95 (0.86, 1.05)	0.3
HDRS_17 (mean, SD)	5.86 ± 6.34	7.56 ± 6.24	0.95 (0.87, 1.05)	0.36
BDI (mean, SD)	15.75 ± 13.11	18.48 ± 16.31	0.99 (0.95, 1.03)	0.54
PANSS total (mean, SD)	55.14 ± 19.36	51.63 ± 20.48	1.01 (0.98, 1.04)	0.55
SOPS (mean, SD)	27.23 ± 20.33	22.16 ± 15.88	1.02 (0.98, 1.05)	0.34
SCARED (mean, SD)	26.16 ± 17.88	31.85 ± 20.97	0.98 (0.95, 1.02)	0.36
Conners_total (mean, SD)	63.83 ± 16.29	71.95 ± 17.63	0.97 (0.93, 1.01)	0.15
SIQ (mean, SD)	15.55 ± 19.39	21.1 ± 21.34	0.99 (0.95, 1.02)	0.38
Suicidal ideation (n, %)	8 (36.4)	15 (60.0)	0.38 (0.12, 1.24)	0.11
Suicidal attempt (n, %)	5 (22.7)	10 (40.0)	0.44 (0.12, 1.58)	0.21
Number of suicidal attempt (mean, SD)	1.17 ± 0.75	1.8 ± 0.79	0.29 (0.05, 1.55)	0.15
Self-injurie behavior (n, %)	5 (22.7)	7 (28.0)	0.76 (0.2, 2.85)	0.68
Psychiatric Hx				
Previous contact with Mental Health: Yes (n, %)	20 (90.9)	24 (96.0)	0.42 (0.03, 494)	0.49
Age first contact Mental Health (mean, SD)	11.05 ± 3.85	10.00 ± 4.37	1.07 (0.92, 1.22)	0.38
Past and current psychiatric diagnosis: Yes (n, %)	18 (81.8)	24 (96.0)	2.06 (0.18, 23.16)	0.56
Comorbidity (n, %)	18 (81.8)	24 (96)	0.19 (0.02, 1.82)	0.15
Affective DO (n, %)	22 (100)	25 (100)	NA	NA
ADHD (n, %)	8 (36.4)	6 (24.0)	1.81 (0.51, 6.4)	0.36
ODD/CD (n, %)	4 (18.2)	9 (36.0)	0.39 (0.1, 1.53)	0.18
Anxiety DO (n, %)	9 (40.9)	20 (80.0)	0.17 (0.05, 0.63)	**<0.01**
OCD (n, %)	1 (4.5)	3 (12.0)	0.35 (0.03, 3.63)	0.38

AN/BN (n, %)	5 (22.7)	7 (28.0)	0.76 (0.2, 2.85)	0.68
Other DO (n, %)	4 (18.2)	9 (36.0)	0.39 (0.1, 1.53)	0.18
Hx drugs: abuse/dependence vs. sporadic/absent	9 (40.9)	11 (44)	0.88 (0.28, 2.81)	0.83
Hx drugs: sporadic/abuse/dependence vs. absent	15 (68.2)	15 (60)	1.43 (0.43, 4.75)	0.56
Current treatment				
Current treatment: Yes (n, %)	22 (100)	25 (100)	NA	NA
Number of current treatments: Yes (n, %)	2.45 ± 0.91	1.76 ± 0.83	2.55 (1.19, 5.43)	**0.01**
Antipsychotics when RMN: Yes (n, %)	20 (90.9)	18 (72.0)	3.89 (0.71, 21.19)	0.12
Doses equivalent Chlorpromazine (mean, SD)	343.62 ± 208.23	171.83 ± 116.4	1.01 (1.01, 1.02)	**0.01**
Lithium when RMN: Yes (n, %)	17 (77.3)	12 (48.0)	3.68 (1.04, 13.1)	**0.04**
Doses Lithium (mean, SD)	736.36 ± 442.44	472.0 ± 512.77	1 (1.00, 1.02)	0.07
Antidepressants when RMN: Yes (n, %)	5 (22.7)	2 (8.0)	3.38 (0.58, 19.57)	0.17
Doses Antidepressants (mean, SD)	47.5 ± 35.94	13.75 ± 8.88	NA	NA
Antiseizures when RMN: Yes (n, %)	4 (18.2)	8 (32.0)	0.47 (0.12, 1.86)	0.28
Doses Antiseizures (mean, SD)	656.25 ± 631.92	515.63 ± 519.26	1.01 (0.99, 1.01)	0.65

SES: socio-economic status; SD: standard deviation; Hx: History; DO: disorder; ADHD: Attentional Deficit and Hyperactive DO;
ODD: Oppositional Defiant DO; OCD: Obsessive-compulsive disorder; AN/BN: Anorexia or Bulimia nervosa.
In bold p-values =<0.05

5.2.1.2. Functionality and academic performance.

Contrary to previous studies, the presence of psychotic symptoms was not significantly associated with lower functional impairment, worse academic performance or a higher exposure to stressful life events (Table 22).

Table 22: Functionality of Bipolar with Psychosis vs. Threshold Psychosis.

	Bipolar with Psy N (22)	Bipolar w/o Psy N (25)	Univariate Analysis OR (95%CI)	p-value
Live events and functionality				
CGAS (mean, SD)	59.86 ± 12.81	59.96 ± 11.72	0.99 (0.95, 1.05)	0.98
PAS (mean, SD)	4.0 ± 1.83	4.5 ± 3.54	0.94 (0.75, 1.17)	0.57
Overall academically performance: good (n, %)	10 (45.5)	11 (44.0)	1.06 (0.33, 3.36)	0.92
SLES_number of events (adolescents) (mean, SD)	13.79 ± 10.63	14.7 ± 11.22	0.99 (0.93, 1.05)	0.79
SLES_impact (adolescents) (mean, SD)	39.16 ± 35.09	46.8 ± 42.91	0.99 (0.99, 1.01)	0.54

CGAS: Child Global Adjustment Scale; SLES: stressful live events schedule. In bold p-values =<0.05

5.2.2. BD adolescents vs. Healthy Control adolescents.

5.2.2.1. Socio-demographics and clinical presentation of both groups: bipolar disorder and healthy adolescents.

A total of 47 BD and 44 HC were originally included in the study. However, due to limitations of conditional regression models, 3 BD had to be excluded from the case-control comparison tables in order to match the two groups 1:1. In addition, matched-pairs were of similar age ± 2 years and of the same gender. The sample that was finally selected (n=88, 44 BD and 44 HC) was mostly Caucasian (88, 96.7%), and lived with both biological parents (62, 68.1%). Only three (3.3%) BD and none of the HC were adopted. A lower socioeconomic status was significantly associated with BD [46.1 ± 13.9 vs. 53.3 ± 11.1; OR 0.95 (0.91, 0.99), p=**0.01**], and was adjusted for in the final models (Table 23).

BD and HC were similar in terms of previous medical history, except for a higher proportion of medical hospitalizations in the past [40.9% vs. 18.2%; OR 2.67 (1.04, 6.81), p=**0.04**]. Most participants were pubertal at the time of inclusion (91.2%). As expected, BD was significantly associated with a family history of mental disorders in first-degree relatives (p<**0.001**), and the strongest association was with affective disorders [61.4% vs. 9.1%; OR 9.75 (2.59, 36.61), p<**0.001**]. Only one BD and no HC had a family history of psychosis (Table 23).

As expected, none of the controls had a major psychiatric diagnosis. However, sporadic or recreational drug use was quite prevalent in both groups (70%), with alcohol as the most popular drug, followed by tobacco and cannabis. Full criteria for substance abuse or dependence was clearly associated with BD [42.6% vs. 16.3%; 3.5 (1.15, 10.63), p=**0.03**] (Table 24).

Table 23: Socio-demographic, Family and Medical History of Bipolar vs. Healthy Control subjects.

	Whole sample N (88)	Bipolar I/II group N (44)	Control group N (44)	Univariate Analysis OR (95% CI)	p-value
Socio-demographics					
Age at intake (mean, SD; max and minimum)	16.07 ± 1.82 (12, 19)	16 ± 1.9	16.14 ± 1.75	MV	MV
Sex: Female (n, %)	48 (54.5)	24 (54.5)	24 (54.5)	MV	MV
Race: White (n, %)	85 (96.6)	41 (93.2)	44 (100)	NA	NA
Adopted: No (n, %)	86 (97.7)	42 (95.5)	44 (100)	NA	NA
Living with biological parents at intake (n, %)	60 (68.2)	29 (65.9)	31 (70.5)	0.83 (0.36, 1.93)	0.67
SES at intake (mean, SD; max and minimum)	49.66 ± 12.94 (13, 66)	46.07 ± 13.77	53.26 ± 11.08	0.94 (0.89, 0.98)	**0.01**
Psychiatric Family Hx					
1st degree Psychiatric Family Hx (n, %)	43 (48.9)	33 (75)	10 (22.7)	9 (2.63, 29.67)	**<0.001**
Family Hx of Psychotic DO (n, %)		1 (2.3)	0	NA	NA
Family Hx of Affective DO (n, %)	30 (34.1)	26 (59.1)	4 (9.1)	12.5 (2.96, 52.77)	**<0.001**
Family Hx of Anxiety DO (n, %)	6 (6.8)	2 (4.5)	4 (9.1)	0.5 (0.09, 2.73)	0.42
Family Hx of Drug Abuse DO (n, %)	2 (2.3)	1 (2.3)	1 (2.3)	1 (0.06, 15.99)	0.99
Family Hx of Other DO (n, %)	4 (4.5)	3 (6.8)	1 (2.3)	3 (0.31, 28.84)	0.34
1st degree Suicidal Family Hx (n, %)		6 (13.6)	0	NA	NA
Medical Hx					
Perinatal complications: Yes (n, %)	21 (23.9)	12 (27.3)	9 (20.5)	1.6 (0.52, 4.89)	0.41
Weight at birth (mean, SD; max and minimum)	3.24 ± 0.53 (1.9, 4.5)	3.23 ± 0.55	3.24 ± 0.52	0.91 (0.34, 2.47)	0.86
Past medical Hx: Yes (n, %)	65 (73.9)	35 (79.5)	30 (68.2)	2.0 (0.68, 5.85)	0.21
Past hospitalizations: Yes (n, %)	26 (29.5)	18 (40.9)	8 (18.2)	2.67 (1.04, 6.81)	**0.04**
Allergies: Yes (n, %)	18 (20.5)	10 (22.7)	8 (18.2)	1.33 (0.46, 3.84)	0.59
Autoimmune DO: Yes (n, %)		4 (9.1)	0	NA	NA
Pubertal: Yes, Tanner 4-5 (n, %)	82 (93.2)	41 (93.2)	41 (93.2)	1 (0.21, 4.95)	1

OR: odds ratio; CI: confidence interval; SD: standard deviation; SES: socioeconomic status; Hx: history; DO: disorder; MV: Matching variable; NA: Not applicable.

- *All cases and controls matched by gender and age. In bold p-values =<0.05.*

Table 24: Psychiatric History of Bipolar vs. Healthy Control Subjects.

	Bipolar I/II group N (44)	Control group N (44)	Univariate Analysis OR (95% CI)	p-value
Past Psychiatric Hx				
Previous contact with Mental Health: Yes (n, %)	41 (93.2)	17 (38.6)	13 (3.09, 54.77)	**<0.001**
Age first contact (mean, SD)	10.86 ± 3.99	7.76 ± 3.21	1.75 (0.99, 3.09)	0.06
Previous psychiatric diagnosis: Yes (n, %)	40 (90.9)	3 (6.8)	12 (2.84, 50.77)	**<0.001**
Lifetime Psychiatric DO (past and current)				
Number of current Diagnostics (mean, SD)	2.3 ± 1.47	0.16 ± 0.37	NA	NA
Lifetime comorbidity hx: Yes (n, %)	39 (88.6)	0	NA	NA
Lifetime Psychotic DO (n, %)	0	0	NA	NA
Lifetime Affective DO (n, %)	44 (100)	0	NA	NA
Lifetime Anxiety DO w/o (n, %)	26 (59.1)	0	NA	NA
Lifetime OCD DO (n, %)	3 (6.8)	0	NA	NA
Lifetime AN/BN DO (n, %)	11 (25)	0	NA	NA
Lifetime ADHD DO (n, %)	12 (27.3)	0	NA	NA
Lifetime CD/ODD DO (n, %)	12 (27.3)	0	NA	NA
Lifetime PTSD DO (n, %)	3 (6.8)	0	NA	NA
Lifetime Elimination DO (n, %)	3 (6.8)	0	NA	NA
Lifetime Other DO* (n, %)	11 (25)	2 (4.5)	10 (1.28, 78.12)	**0.03**
Lifetime Drug Abuse/Dependence DO (n, %) (past/current)				
Hx drugs abuse: abuse/dependence vs. sporadic/absent	20 (45.5)	7 (15.9)	5 (1.45, 17.27)	**0.01**
Hx drugs any: sporadic/abuse/dependence vs. absent	29 (65.9)	35 (79.5)	0.3 (00.8, 1.09)	0.07
Hx OH	22 (50)	25 (56.8)	0.69 (0.3, 1.62)	0.4
Hx caffeine	8 (18.2)	29 (65.9)	0.05 (0.01, 0.34)	**<0.01**
Hx cannabis	17 (38.6)	12 (27.3)	1.62 (0.67, 3.92)	0.28
Hx hallucinogens	0	0	NA	NA
Hx inhalants	0	0	NA	NA
Hx opioids	0	0	NA	NA
Hx sedatives, hypnotics, and anxiolytics	0	0	NA	NA
Hx stimulants (amphetamines, cocaine and other)	9 (20.4)	0	NA	NA
Hx tobacco	19 (43.2)	5 (11.4)	7.5 (1.72, 32.8)	**<0.01**
Hx other	0	0	NA	NA

OR: odds ratio; CI: confidence interval; SD: standard deviation; NA: Not applicable; DO: disorder; Hx: History; OCD: obsessive-compulsive; AN/BN: anorexia or bulimia nervosa; ADHD: attention deficit/ hyperactivity; CD/ODD: conduct or oppositional Defiant; PTSD: post-traumatic stress.* Other DO: elimination; tics; learning; borderline personality traits; subthreshold autistic traits.

- ***All cases and controls matched by gender and age. In bold p-values =<0.05.***

In line with previous results, in terms of a dimensional approach, being in the bipolar group was associated with higher scores on all symptoms scales (Table 25). Despite the fact than some healthy adolescents and their parents reported mild symptoms, they did not reach the threshold level required for a formal diagnosis.

Table 25: Self-Reported and Face-to-Face Reported Symptoms Scales of Bipolar vs. Healthy Control Subjects.

	Bipolar I/II group N (44)	Control group N (44)	Univariate Analysis, OR (95% CI)	p-value
Evaluator's reported:				
YMRS (mean, SD; max/min)	6.77 ± 6.17	0.34 ± 0.78	2.13 (1.1, 4.1)	**0.02**
HDRS_17 (mean, SD; max/min)	6.95 ± 6.4	1.20 ± 1.66	1.54 (1.18, 2)	**<0.01**
PANSS total (mean, SD; max/min)	53.79 ± 20.12	31.45 ± 1.61	1.25 (1.06, 1.49)	**0.01**
SOPS total (mean, SD; max/min)	25.14 ± 18.31	1.55 ± 1.98	1.89 (0.82, 4.34)	0.14
Adolescent's self-reported:				
BDI (mean, SD; max/min)	16.63 ± 13.83	4.11 ± 3.63	1.18 (1.04, 1.33)	**<0.01**
SIQ (mean, SD; max/min)	17.31 ± 18.97	3.39 ± 4.16	1.16 (1.03, 1.31)	**0.01**
MDQ (mean, SD; max/min)	9.11 ± 3.06	2.5 ± 2.67	1.76 (1.4, 2.2)	**<0.001**
Scale of morningness (mean, SD; max/min)	31.43 ± 6.23	31.79 ± 5.84	1.01 (0.92, 1.1)	0.91
SCARED (mean, SD; max/min)	28.05 ± 19.24	17.03 ± 9.33	1.05 (1.01, 1.09)	**0.01**
Suicidal ideation (n, %)	22 (50)	0	NA	NA
Suicidal attempt (n, %)	14 (31.8)	0	NA	NA
Number of suicidal attempt (mean, SD; max/min)	1.6 ± 0.83 (0, 3)	0	NA	NA
Self-injurie behavior (n, %)	11 (25)	1 (2.3)	11 (1.42, 85.2)	**0.02**
Parents' self-reported:				
Conners p>70: Yes (n, %)	19 (43.2)	0	NA	NA
Conners_total (mean, SD; max/min)	67.71 ± 17.25	45.71 ± 7.86	1.11 (1.03, 1.2)	**<0.01**
CMRS (mean, SD; max/min)	13.82 ± 13.17	1.39 ± 2.28	1.3 (1.03, 1.63)	**0.03**
P-YMRS (mean, SD; max/min)	10 ± 10.06	3.38 ± 3.19	1.13 (1.02, 1.26)	**0.02**

YMRS: Young mania rating scale; HDRS_17: Hamilton depression rating scale; PANSS: Positive and negative symptom scale; SOPS: prodromal symptoms scale; BDI: Beck Depression Inventory; SIQ: Suicidal ideation questionnaire; MDQ: Mood disorders questionnaire; SCARED: Screen for child anxiety related disorders; CMRS: Child mania rating scale; P-YMRS: Parent's Young mania rating scale.
**** All cases and controls matched by gender and age. In bold p-values =<0.05. NA: Not applicable.***

5.2.2.2. Functional and academic performance.

Being from the BD group was significantly associated with both a higher number and more severe life events, in both adolescents' and parents' reports (Table 26). As hypothesized, the BD group was associated with lower levels of functionality on CGAS scores [0.65 vs. 85.44 (0.48, 0.87), p<**0.01**], and PAS scores [CI 4.98 (1.39,

17.83), p=**0.02**]. In addition, the BD group correlated with worse performance at school [0.03 (0.01, 0.67), p=**0.03**] compared with HC, and reported a lower level of post-secondary education, although it was only marginally statistically significant.

Table 26: Stressful Life Events and Levels of Functionality of Bipolar vs. Healthy Control Subjects.

	All sample N (88)	Bipolar I/II group N (44)	Control group N (44)	Univariate Analysis OR (95% CI)	p-value
Previous exposure to life events					
Adolescent report:					
SLES_number of events (mean, SD; max and minimum)	10.88 ± 9.53 (0, 42)	14.03 ± 10.72	7.9 ± 7.18	1.1 (1.01, 1.2)	**0.02**
SLES_impact (mean, SD; max and minimum)	30.42 ± 32.27 (0, 139)	41.81 ± 38.09	19.62 ± 20.85	1.04 (1, 1.07)	**0.03**
Parents report:					
SLES_number of events (mean, SD; max and minimum)	7.05 ± 7.2 (0, 35)	10.54 ± 8.05	3.74 ± 4.23	1.23 (1.04, 1.45)	**0.02**
SLES_impact (mean, SD; max and minimum)	22.41 ± 26.36 (0, 137)	35.19 ± 30.7	10.29 ± 13.03	1.07 (1.01, 1.13)	**0.02**
Functionality					
CGAS (mean, SD; max and minimum)	72.52 ± 15.59 (35, 95)	59.89 ± 12.1	85.44 ± 4.03	0.65 (0.48, 0.87)	**<0.01**
PAS general (mean, SD; max and minimum) (N=83)	3.01 ± 2.32 (1, 16)	4.23 ± 2.86	1.88 ± 0.5	4.98 (1.39, 17.83)	**0.02**
Academically performance					
Overall performance: good (n, %)	63 (71.6)	21 (47.7)	42 (95.5)	0.05 (0.01, 0.34)	**<0.01**
Some problems or repeated one grade	21 (23.9)	19 (43.2)	2 (4.5)		
Repeated more than one grade or dropped of school		4 (9.1)	0		
Post-secondary education: yes (n, %) (N=48)	17 (35.4)	5 (20)	12 (52.2)	0.22 (0.05, 1.03)	**0.05**

OR: odds ratio; CI: confidence interval; SD: standard deviation; NA: Not applicable; SLES: stressful live events schedule; CGAS: children's global assessment scale; PAS: premorbid adjustment scale. ■ All cases and controls matched by gender and age. In bold p-values =<0.05.

5.2.2.3. The impact of psychosis and other clinical variables on functionality.

Our next step consisted in analyzing the relation between psychosis and functionality in the whole sample of 44 BD and 44 HC. This time we followed a dimensional approach for measuring psychosis based on scores from the PANSS

and SOPS scales and their level of correlation with CGAS scores. Higher scores on either PANSS or SOPS were found to be inversely correlated with lower scores on the CGAS scale, and the intensity of this correlation was strong (rho=-0.83 and -0.81 respectively; p<**0.001**) (Table 27, Fig.12).

Additionally, we found a strong negative correlation between high scores in depression or mania based on the YMRS and HDRS-17 scales and low CGAS scores, but to a lesser degree than for psychosis (Rho=0.72 and 0.65 respectively; p<**0.001**). Attentional problems (measured based on the Conner's Scale) (rho=-0.66; p<**0.001**) and early exposure to stressful life events (both in number and in intensity) were negatively correlated with CGAS as well (rho=-0.58-0.32; p<**0.01**-<**0.01**), followed by anxiety symptoms based on the SCARED scales (rho=-0.34; p<**0.01).**

5.2.2.4. The impact of other environmental and genetic variables on functionality.

In a series of multivariate analyses, we studied the association between functionality and other environmental and genetic variables in both groups. First, we analyzed the impact of socio-demographic levels on CGAS and academical performance. Despite controlling for SES and family psychiatric history, lower CGAS scores continued to be significantly associated with the BD group. This association remained ever after controlling for current history of drug abuse/dependence. Furthermore, being in the BD group was persistently associated with lower CGAS scores after controlling for the presence of clinical symptoms, either psychosis or depression or mania (Table 28).

Table 27: Correlations between CGAS and Psychiatric Symptoms.

		CGAS	
PANSS Total	Coefficient correlation	(-)0.83	**Rho: Large effect (>0.5)**
	Sig.(2-tailed)	**<0.001**	
	N	85	
SOPS Total	Coefficient correlation	(-)0.81	
	Sig.(2-tailed)	**<0.001**	
	N	87	
HDRS-17	Coefficient correlation	(-)0.72	
	Sig.(2-tailed)	**<0.001**	
	N	87	
YMRS	Coefficient correlation	(-)0.65	
	Sig.(2-tailed)	**<0.001**	
	N	87	
CONNERS_tot	Coefficient correlation	(-)0.66	
	Sig.(2-tailed)	**<0.001**	
	N	75	
Live events_impact_B	Coefficient correlation	(-)0.58	
	Sig.(2-tailed)	<0.001	
	N	73	
Live events_num_B	Coefficient correlation	(-)0.55	
	Sig.(2-tailed)	**<0.001**	
	N	75	
SCARED	Coefficient correlation	(-)0.34	**Medium effect (0.3-0.49)**
	Sig.(2-tailed)	**<0.01**	
	N	73	
Live events_num_A	Coefficient correlation	(-)0.32	
	Sig.(2-tailed)	**<0.01**	
	N	75	
Live events_impact_A	Coefficient correlation	(-)0.32	
	Sig.(2-tailed)	**<0.01**	
	N	75	

PANSS: Positive and negative symptom scale; SOPS: prodromal symptoms scale; HDRS_17: Hamilton depression rating scale; YMRS: Young mania rating scale; Conners: attentional deficit scale; SCARED: Screen for child anxiety related disorders; Live events_A: adolescents self-report; B: parent's report; Num: number of events.

Fig. 12. Correlations between CGAS and Psychiatric Symptoms.

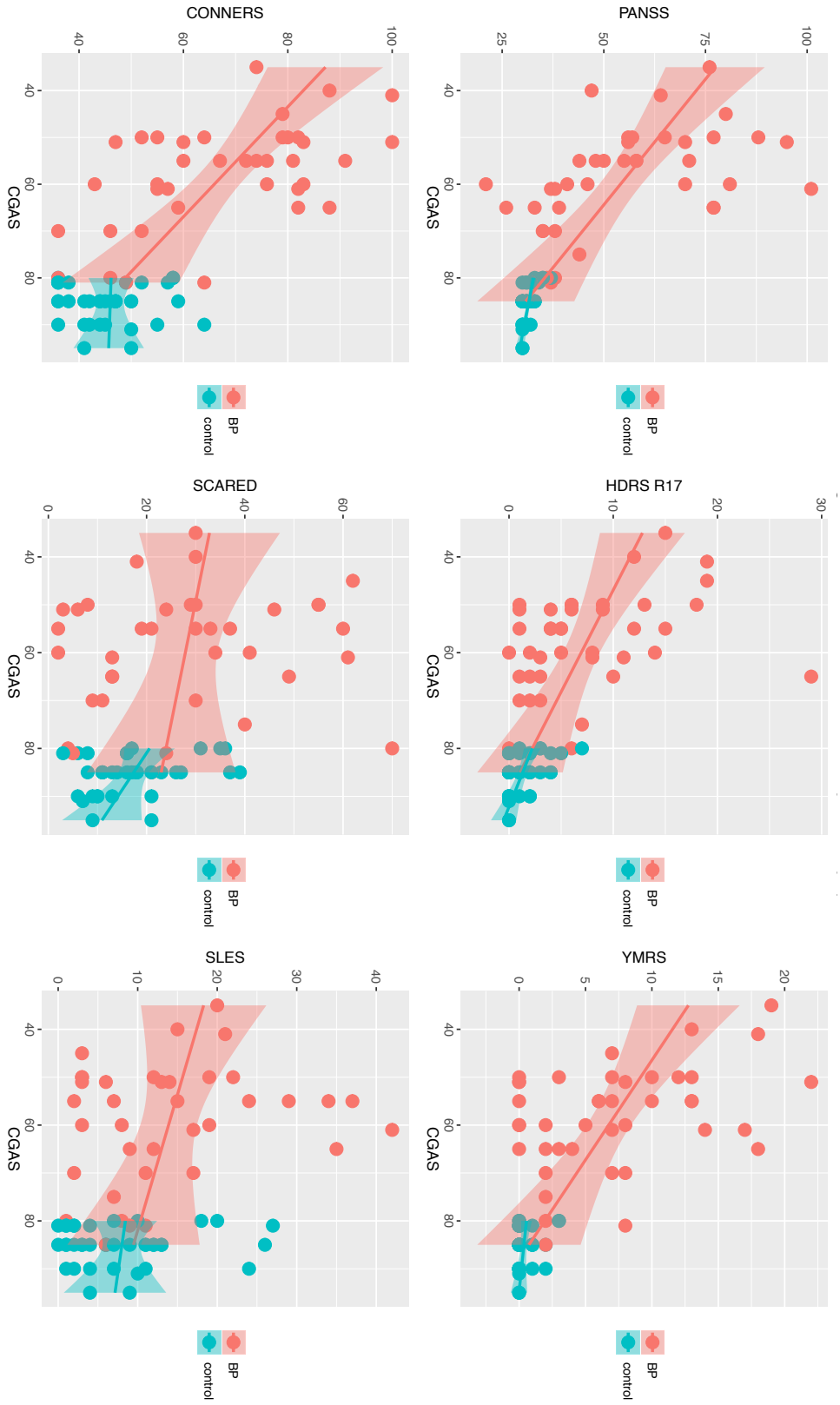


Table 28: Multivariate Analyses: CGAS, SES and other Clinical Relevant Variables.

	Multivariate Analysis OR 95% CI	p-value
5a: CGAS, socio-demographics and functionality		
SES at intake	0.92 (0.84 - 1.02)	0.1
1st degree Psychiatric Family Hx	8.88 (0.61 - 121.01)	0.1
CGAS	0.65 (0.46 - 0.93)	**0.02**
Overall performance: good	0.03 (0.01 - 0.67)	**0.03**
Akaike information criteria (AIC)	30.76	
5c: CGAS, socio-demographics and symptoms		
SES at intake	0.92 (0.84 - 1.02)	0.1
CGAS	0.7 (0.53 - 0.94)	**0.02**
HDRS-17	1.69 (0.85 - 3.38)	0.13
PANSS	0.64 (0.29 - 1.4)	0.26
Akaike information criteria (AIC)	37.89	

	Multivariate Analysis OR 95% CI	p-value
5b: CGAS, socio-demographics and categorical DO		
SES at intake	0.93 (0.86 - 1.01)	0.09
1st degree Psychiatric Family Hx	5.24 (0.6 - 45.54)	0.17
CGAS	0.67 (0.49 - 0.92)	**0.01**
Hx Substance Abuse/Dependence DO	5.93 (0.47 - 75.18)	0.17
Akaike information criteria (AIC)	35.66	
5d*: CGAS, socio-demographics and functionality		
CGAS	0.68 (0.49, 0.94)	**0.02**
Overall performance: good	0.04 (0.01, 0.47)	**0.01**
YMRS	1.99 (0.89, 4.48)	0.09
Akaike information criteria (AIC)	29.66	

OR: odds ratio; CI: confidence interval; SES: Socioeconomic status; CGAS: children's global; assessment scale; DO: disorder; Hx: history; HDRS_17: Hamilton depression rating scale; PANSS: positive and negative symptom scale.

- ***All cases and controls matched by gender and age. In bold p-values =<0.05. *Stepwise logistic regression.***

6. SCIENTIFIC PUBLICATIONS

7. DISCUSSION

In summary, the results presented in this thesis confirmed that PLE are very prevalent in children and adolescents from the general population (14.9%), with varying levels of intensity, from subthreshold and sporadic PLE to threshold levels and persistent symptoms in those at specific risk. Contrary to previous hypotheses, offspring at genetic high risk for BD did not report a higher number of PLE than offspring from the community, neither at intake nor during eight years of follow-up. Other known environmental risk factors for psychosis, such as perinatal complications, IQ or past medical history, did not increase the risk for PLE in this study. Only three factors were found to be significant predictors of the onset of PLE over time: 1) the presence of any psychiatric disorder; 2) a decline in general functioning, independently of the previous; 3) a previous history of sexual or physical abuse. If is interest to note that, in an exploratory survival analysis focused only on those offspring who did not develop any psychotic disorder at all, a combination of genetic risk factors for BD and the presence of any psychiatric disorder was the most significant predictor of risk for PLE, followed by offspring from the community with a psychiatric diagnosis. Over time, the presence of PLE was associated with a higher prevalence of any psychiatric disorder, and more specifically affective and nonaffective psychosis. The association was even stronger when we used PLE at a threshold level as opposed to PLE at a subthreshold level. Different measures of PLE are available and can be used for stratification of risk, although we found a low level of agreement between the measures we selected.

At baseline, psychosis was found to be a very rare phenomenon, with only 2.8% of both groups reporting PLE and 0.5% a psychotic disorder. On the other hand, psychosis was found to be quite prevalent in the course of BD. 40% of BD adults

reported psychosis at some point of their illness, and as high as 74.5% of adolescents, 47% at threshold level. The presence of psychotic disorders was mainly associated with BD type I phenotype in both groups, and higher morbidity. Functionality was clearly more affected in adults with BD_psy+ compared to BD_psy-, but not in the adolescent BD sample, where no differences were found between BD_psy+ vs. BD_psy-. Compared with HC from the same age and gender, BD adolescents showed a lower socio-economic status, greater past history of medical hospitalizations, and more family history of psychiatric disorders, mainly affective disorders. Even though euthymia was a requirement for inclusion in the study, most BD adolescents continued to report subthreshold symptoms and drug dependence, although drug abuse was highly prevalent in the HC as well. BD more stressful-life events and more severe compared with HC. As expected, being from the BD group and not from the HC group was clearly associated with a lower level of general functioning and academic performance. Furthermore, functionality was found to be clearly related with persistence of sub-syndromical symptoms, with psychotic symptoms showing the strongest correlation. The BD adolescent group continued to be associated with higher impairment even after controlling for the presence of symptoms, socio-demographic, family history, and stressful-life events in the multivariate analyses.

The high prevalence of PLE in BIOS, 14.9% in both BD offspring and healthy control (HC) offspring (5.8% at intake and 9.1% during follow-up), was expected in light of previous studies with children and adolescents. In a large literature review including community and clinical samples (ages 7-18 years old) with a longitudinal design, Rubio and colleagues[133] reported a baseline-prevalence between 4.9%-9%. Kelleher and colleagues also reported prevalence between 7.5%-17%, with higher rates for children ages 9 to 12 than ages 13 to18 years old[2]. The latest meta-analysis

available confirmed a PLE prevalence rate of 9%[134]. Studies with self-reported PLE have shown prevalence rates as high as 21%-50%[127–132]. I would like to highlight that the prevalence rate of self-reported psychotic symptoms was 29% in a preliminary analysis in the BIOS study. A quarter of PLE were persistent over time, with a conversion rate to psychotic disorders of 0.99% per year, similar to previous studies in children and adolescents (0.6%-1.3% on average)[133]. 2.5% of offspring developed a full psychotic disorder, in line with the Nemesis Study[115] and Health 2000 Study[144] in adults. According to the available literature, it is likely that persistence of PLE and conversions to psychotic disorders in BIOS will increase during future follow-ups[138].

As we have already discussed in the introduction section, if there is a continuum of psychosis from PLE to UHR and finally a full psychotic disorder, at least some of the genetic and non-genetic causes contributing to psychosis should be present all over the spectrum (the psychosis proneness-persistence-impairment model) (Van Os, 2009)[1]. Today it is well documented that psychosis runs in families with heritability rates ranging from 40%-70%[50,238,279,283,348], lower for BD than for SQZ. The evidence regarding the genetic risk of PLE in GHR is weak. Van Os and colleagues[325] were the first to identify the association between first degree family history of a broad range of psychoses (including PLE, mania and depression among others) and the presence of PLE in the general population. Other longitudinal population-based studies have confirmed this correlation as well[123], although more closely related with the subset of PLE persistent over time[191]. In contrast, in the Avon Longitudinal Study of Parents and Children (ALSPAC)[349,350] only parental depression and not SQZ was found to be a significant predictor of PLE. Other twin-studies have observed a higher contribution of environmental rather than genetic risk factors for the onset of PLE (49%-67% vs. 15%-59%)[326,327], in line with our results. More

recently, one study has found a higher genetic risk for PLE during adulthood than during adolescence[351]. It is interesting to note that Duffy et al.[352] in the Canadian Offspring Bipolar Study have reported a higher incidence of PLE and Psychotic Disorders in the offspring of those BD parents who responded to lithium compared with those BD parents who did not.

Exposure to early neurodevelopmental insults, such us brain injuries, perinatal complications, or exposure to cannabis or infections at early age are also associated with the increased risk to develop overt psychosis[275,278,290,353–355]. Three studies confirmed an association between perinatal complications and PLE[1,322,323,326], however these findings were not statistically significant in our offspring sample. Some studies have reported an association between low IQ during childhood and increased risk for PLE during follow-up in community samples[326,356]. More recently, lower IQ has been observed in offspring of schizophrenic parents but not in BD offspring or control offspring[357]. In line with existing evidence, it seems that low IQ is only a predictor of PLE in individuals at risk for SQZ but not affective disorders.

When we analyzed other non-genetic candidates of risk, we found a positive association between any psychiatric disorder and the later development of PLE, with almost all psychiatric disorders associated with increased risk of PLE either at intake or follow-up. Moreover, this association was stronger for BP offspring than for control offspring. Scott et al.[196] were the first to observe a positive relation between the presence of psychopathology from ages 5 to14 years old and PLE at age 21. A correlation was confirmed in the Avalon study as well. Moreover, when we split the sample into four at-risk groups (BD vs. controls, with or without psychopathology), a significant increase in risk was found by adding BD and psychopathology. Axelson and colleagues[358] have previously reported more psychiatric disorders among BP

offspring in this sample, with an increased risk for BP during the follow-up. Based in this new evidence, BP offspring also differed in the quality of the psychiatric disorders, with a higher morbidity with PLE over time. In fact, in the NEMESIS Study, they have reported an additive effect between being at genetic high-risk for affective disorders, including BD, and the presence of psychopathology with the risk of PLE during a three-year follow-up[359].

Another variable associated with the risk of PLE was low psychosocial functioning, even after controlling for the impact of psychopathology. Kelleher and colleagues[188] also found that adolescents with psychiatric disorders who reported PLE scored more than 10 points lower on the GAF than those with psychiatric disorders who did not report PLE. In fact, a decline in functioning and social isolation is considered as part of a general negative core of symptoms in the earliest stage of psychosis, prior to the onset of subthreshold psychotic symptoms and a subsequent psychotic disorder.[60,67,69]

The last variable associated with PLE was trauma. The existing literature has consistently shown a relationship between exposure to trauma and increased risk of developing psychotic disorders[275,278,290,312,360,361]. More recently, several studies have shown that early exposure to any type of maltreatment (bullying, neglect, physical or sexual abuse) that is perceived as a threat also increases the risk of PLE[326,362–369] with a dose-response relationship in terms of intensity and cumulative exposure over time[181,324]. Moreover, the relation between child abuse and PLE it seems independently of family history of PLE or psychotic disorders.[324] In our study the relation between continuous exposure to abuse and PLE was confirmed, but only in the BP offspring, even after controlling for axis I disorders. We knew from a previous analysis in BIOS[370] that, at least at intake, BP offspring and control offspring differed

in the number of previous exposures to severe life events, including sexual and physical abuse, which could explain this difference.

Conversion rates from PLE to a full psychotic disorder were found to be low, 7.9% at an average of 8 years of follow-up, compared to 15-35% conversion rates in UHR samples[71,92,94,200]. In a recent longitudinal study with a population sample of 6,000 students, Zhang et al.[371] reported an overall conversion rate to any psychiatric disorder of 3% in a three-year period, although they used self-reported PLE measures rather than face-to-face. Self-reported PLE were very prevalent in our BIOS study. Almost one third of the offspring self-reported PLE at least once. Similar to PLE reported in face-to-face interviews, they appeared almost always in the context of a psychiatric disorder, mainly affective and non-affective psychotic disorders. Whether they are measuring the same phenomena is controversial[75,96,372]. Their predictive validity for the presence of PLE was not confirmed in our study. However, in an exploratory analysis, self-reported PLE increased the risk of onset of any psychotic disorder "de novo" during the follow-up. Therefore, it can be inferred that the use of self-screening tools in daily practice could be helpful as a first-step approach in screening campaigns but cannot replace face-to-face interviews.

The UHR criteria include the category of GHR plus a decline in functioning as one of the three prodromic stages previous to the onset of a psychotic disorder. We tested this theory in our sample of BD offspring. We did not find any significant difference between offspring of parents with BD_psy+ vs. parents with BD_psy-. We observed normal to mild impairment in both groups, although it was self-perceived as very good to good in most areas of daily life. The only exception was in the area of relationships, considered good to fair by the majority but, unexpectedly, significantly worse in the offspring of BD_psy-. Studies of high-risk subjects have shown a decline

in social functioning associated with increased vulnerability for SQZ[373–375], but it is still unclear if this would be the case for BD[376–379]. Although some authors have found problems in social adjustment and isolation in offspring or clinically at-risk BD samples[352,380–383], others found no differences with control samples[384,385]. Based on our results, we could argue that the risk is more closely related with BD severity[352,386,387] than with the specific BD subtype.

Our third approach to the spectrum of psychosis was to analyze the phenomenon of psychotic symptoms in BD patients in two different samples: BD parents from BIOS, and BD adolescents from study 2. 40% of BD adults reported psychotic symptoms at some point during their illness. Prevalence rates were found to be as high as 74.5% in adolescents, 47% of which were at threshold level. The prevalence rate of BD parents was slightly lower than expected, which according to the literature should be between 50% and 90%, where the higher rates correspond to early-onset cases[46,163,167,240,388,389]. However, we did not include any specific questionnaires in the adults' assessment package referring to psychosis and psychosis was not the main target of the interviews, which could skew our results by lowering the prevalence of psychotic symptoms. In line with previous studies, in both BD parents and BD adolescents, psychotic symptoms appeared to be mostly associated with a manic episode and BD subtype I. They were a marker of severity in terms of higher comorbidity in BD adults, and higher psychiatric hospitalization rates and number of treatments in the BD adolescents' sample[8,9,164,265,390–393]. In a recent study based on an adolescent inpatient unit, Shapiro et all.[394] reported higher suicidality rates in adolescents with BD-psy+ compared with BD-psy-. However, both BD phenotypes showed similar risk for suicide in a 4 year longitudinal study with adults[265], with no information at all in most studies[9,169,246,392,395]. Suicidal ideation or

attempts were not more prevalent in our adolescents with BD-psy+ when compared with BD-psy, with no information at our adult sample. As expected, functionality was clearly more affected in adults with BD_psy+ compared to BD_psy- either in the past or present, although both groups had high levels of unemployment and family difficulties. Curiously, most BD parents self-rated their level of functioning as good or only slightly impaired. On the contrary, when functionality was compared in the adolescent BD sample, no differences were found between BD_psy+ vs. BD_psy. The fact that only half of BD parents were employed or married is consistent with previous functional recovery rates, with studies showing recovery lower than 50% regardless of the BD subtype[8,171,386,387,396,397]. The impact of psychosis on functioning is still unclear. While most studies have found significant impairment in BD with psychosis compared to BD without psychosis, both in early and late onset[9,163,167,388,390,392], there is no agreement on whether it is 1) associated with the episode[390,398–400], 2) persistent during euthymia[262,265,401,402], or 3) not different from BD without psychosis at all[253,398].

Finally, we performed a series of analyses comparing the BD adolescent sample with the HC sample, matched 1:1. Consistent with the literature, a family history of psychiatric disorders was found to be significantly associated with the BD adolescent group. More important, the association was specifically related with a family history of affective disorders. As has already been mentioned in the introduction section and in this discussion, high levels of heritability in BD had been documented, up to 60% depending on the study, with some evidence of a higher risk for the early-onset BD-phenotype[352,403–406]. Furthermore, the BD sample was statistically significantly more associated with a lower socio-economic status than the HC sample. The economic burden associated with mental disease is well documented in studies with adult

samples[407]. More recently, a large longitudinal study has also confirmed the impact of continuous exposure to poverty during childhood and the risk for psychiatric disorders in adolescence and, interestingly, even after controlling for the presence of mental disorders in first-degree relatives[408].

When we analyzed the past medical history on both samples, we did not find any association of puberty status or any previous medical condition with the BD adolescent group, but they showed a greater frequency of non-psychiatric hospitalization rates. Some studies have found a relation between migraines, circulatory and other medical conditions and BD subjects, although it is not clear which is the cause, and which is the consequence. Early exposure to BD medications may also be an important factor in this equation due to the metabolic syndrome[409–411].

Regarding the psychiatric history, as expected due the design of the study, none of HC has a previous or current history of major psychiatric disorders, whereas most BD adolescents full fill criteria for 2.3 concurrent comorbid disorders. Both BD adolescents and HC reported a high prevalence of drug use (72.7%), mainly alcohol, but this was expected due to the high prevalence of risk behaviors in youth in most modern societies[412]. However, drug dependence was significantly less prevalent, and was specifically associated with the BD group. Previous studies have signaled a significantly increased risk for early drug abuse and dependence when BD onset occurs during childhood or adolescence[230,391,413,414]. From a dimensional perspective, even though some HC reported anxiety and attentional problems, none achieve clinical significance. On the contrary, whereas BD adolescents must be euthymic at the time of inclusion, most continued to report persistent symptoms at a subthreshold level. Over the last decade, in the COBY study, the largest ongoing cohort of pediatric

BD, it has been confirmed that near 60% of the follow-up time, subjects continue to have syndromal or subsyndromal symptoms with numerous changes in symptoms and shifts of polarity[404,415–418]. Although, syndromic recovery can be achieved in 70% of cases, similar to the recovery in adults with BD[8,395,419,420].

In addition, both BD adolescents and HC recalled many stressful-life events in their past, although they were significantly more frequent and more severe in the BD group. The association between stressors and BD in pediatric[311,421–423] and adult samples is well documented[424,425]. Most studies have found a correlation between stressful-life events and socio-economic status, although the direction of causality is unclear. More recently, longitudinal studies have confirmed a relation between stressful-live events and increased risk for persistent symptoms over time, as well as relapses of psychotic episodes[423,426,427]. As expected, being from the BD group and not from the HC group was clearly associated with a lower level of general functioning and academic performance. Furthermore, functionality was found to be clearly related with persistence of sub-syndromic symptoms, with psychotic symptoms showing the strongest correlation. The relation between psychotic symptoms and functionality has been extensively discussed throughout this dissertation. It should be noted that the BD adolescent group continued to be associated with higher impairment even after controlling for sociodemographic, family history, and the presence of symptoms. Low levels of functioning have been systematically reported in pediatric BD [428–431], with an specific impact in the areas of family and peer relationships and academic performance[159,428,432,433]. Moreover, functional impairment may be greater among adolescents with BD than pre-adolescents with BD, regardless of whether onset was in childhood or adolescence[428,434]. Interestingly, whereas lower levels of functioning have been

reported in BD adults than in HC[397,424], the majority of studies found no differences regarding the level of academic attainment[435,436].

7.1.Limitation of the project.

7.1.1. Study 1:

Offspring were recruited across a broad age range (6-18 years old), which may have influenced the results because of the developmental differences regarding perception and the nature of PLE. However, age was controlled in the final analyses. In addition, most of the sample has not reached yet the period of highest risk to develop psychosis[69] (mean age at last follow-up: 19.9 years old); information regarding the symptoms and PLE was collected retrospectively at intake and for the interval between follow-ups, on average every 2.5 years; existing prodromal scales to ascertain PLE were not available at the time that this study started; and finally, most of the information about the psychopathology of biological co-parents was obtained indirectly. Lastly, the results pertain to offspring of parents with BP and may not be generalizable to other populations.

7.1.2. Study 2:

It cannot be rule out the possibility of a selection bias, taking into account the differences in socio-economic status. Information about mental health history and the appearance of the first symptoms was recalled retrospectively during the first assessments, as were medical history and obstetric complications. History of drug use was based on direct reporting without relying on a urine sample. Although recruitment involved a variety of mental health settings, most BD patients arrived from the inpatient unit and may have suffered from a more severe form of the disease. Moreover, some healthy controls had previous contact with mental health services,

although they did not have any major mental disorder at the time of the study. Finally, the sample was relatively small, which limits the power to detect differences between HC and the two BD subtypes.

7.1.3. Overall limitations.

The main limitation of this PhD Project is the high heterogeneity of the two main studies included. The first one with a longitudinal approach and based on a US sample, and the second, with a transversal design, and based on a small clinical sample from Spain. Finally, the fact that most results have not been published jet, what undoubtedly reduce the impact of the project at present, although it opens a frame of possibilities for the future.

8. CONCLUSIONS AND IMPLICATIONS FOR THE FUTURE

This thesis aimed to study the risk factors associated with the development of PLE and psychotic symptoms in the course of bipolar disorders following two different perspectives: 1) botton-up: offspring of bipolar disorders and offspring of control healthy parents; 2) top-down: adults with bipolar disorders with and without psychotic features and their offspring; and adolescents with bipolar disorders with and without psychotic features compared with healthy controls and first-degree realtives. The main conclusions of the thesis, derived from Study I (1-10) and Study II (11-12), as well as the significance of the results (13-14) and futures lines of research that could be pursued (15), can be summarized as follows:

1. PLE were not found statistically significant associated with genetic risk factors in our sample. (In contrast to the main hypothesis).
2. PLE were not found statistically significant associated with other known environmental risk factors for psychosis such us: obstetric and perinatal complications; early drug exposure; cranio-encephalic trauma; history of infections or other medical complications; or low intellectual level. (In contrast to the main hypothesis).
3. PLE were found statistically significant associated with a previous history of exposure to physical or sexual abuse. (In line with the main hypothesis).
4. PLE were found statistically significant associated with a previous diagnosis of a psychiatric disorder. (In line with the main hypothesis).
5. PLE were found statistically significant associated with a wide range of psychopathologies, with the strongest assotiation for BD and SQZ-like disorders. (In line with the secondary hypothesis 1).

6. PLE were associated with a low level of global functioning. (In line with the secondary hypothesis 1).
7. All offspring who developed a psychotic disorder reported a previous history of PLE. (In line with the secondary hypothesis 2).
8. Self-reported PLE and face-to-face PLE was evaluated as "fair agreement" for threshold scores, but not confirmed when threshold and subthreshold scores were compared separately. (In contrat with secondary hypothesis 3).
9. In the adult BD sample, the BD psychotic phenotype significantly differed from BD without psychosis in a higher prevalence of BD type I, considered more severe than BD type II, and number of comorbidities. (In line with the secondary hypothesis 4).
10. In the adolescent BD sample, the BD psychotic phenotype did not differed from the BD without psychosis sample in terms of severity, other than longer duration of hospitalitations, comorbidity or functionality. (In contrast to secondary hypothesis 4).
11. In the adolescent BD sample, when psychsosis was measured from a dimensional approach, its impact on functionality was confirmed. (In line with the secondary hypothesis 4).
12. Based on our findings and the existing literature, more attention must be given to the presence of PLE as marker of morbidity.
13. Once confirmed, both PLE and full psychosis must be specifically addressed in the design of individualized treatment plans to ensure full recovery.

14. More studies with longer follow-ups are needed to better understand the risk between PLE, functional decline and development of psychiatric disorders.

9. REFERENCES

1. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological Medicine*. 2009;39:179-195. doi:10.1017/S0033291708003814
2. Kelleher I, Connor D, Clarke MC, Devlin N, Harley M, Cannon M. Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychological Medicine*. 2012;42:1857-1863. doi:10.1017/S0033291711002960
3. Poulton R, Caspi a, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Archives of general psychiatry*. 2000;57(11):1053-1058. doi:10.1001/archpsyc.57.11.1053
4. Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia Research*. 2003;60(1):21-32. doi:10.1016/S0920-9964(02)00167-6
5. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophrenia research*. 2008;102(1-3):1-18. doi:10.1016/j.schres.2008.04.011
6. Goodwin FK; JKR. *Manic-Depressive Illness. Bipolar Disorders and Recurrent Depression.* Second. (Goodwin FK; JKR, ed.). Oxford University Press; 2007.
7. Binbay T, Drukker M, Elbi H, et al. Testing the psychosis continuum: Differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophrenia Bulletin*. 2012;38(5):992-1002. doi:10.1093/schbul/sbr003
8. Tohen M, Zarate CA, Hennen J, et al. The McLean-Harvard first-episode mania study: Prediction of recovery and first recurrence. *American Journal of Psychiatry*. 2003;160(12):2099-2107. doi:10.1176/appi.ajp.160.12.2099
9. Hua LL, Wilens TE, Martelon M, Wong P, Wozniak J, Biederman J. Psychosocial functioning, familiality, and psychiatric comorbidity in bipolar youth with and without psychotic features. *Journal of Clinical Psychiatry*. 2011;72(3):397-405. doi:10.4088/JCP.10m06025yel
10. Weinberg D.R.; Harrison PJ. *Schizophrenia*. 3rd Ed. (Weinberg D.R.; Harrison PJ, ed.). Blackwell Publishing Ltd.; 2011.
11. Vallejo Ruiloba, J.; Leal Cercós C. *Tratado de Psiquiatría*. (Vallejo Ruiloba, J.; Leal Cercós C, ed.). Marbán Libros; 2012.
12. APA: American Psychiatric Association. *DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th Ed.).* 5th ed. (American Psychiatric Publishing., ed.).; 2013.
13. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophrenia bulletin*. 2009;35(3):549-562. doi:10.1093/schbul/sbp006
14. Smoller JW, Kendler K, Craddock N, et al. Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *The Lancet*. 2013;381(9875):1371-1379. doi:10.1016/S0140-6736(12)62129-1

15. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. Diagnostic Stability of ICD/DSM First Episode Psychosis Diagnoses: Meta-analysis. *Schizophrenia Bulletin*. 2016;42(6):1395-1406. doi:10.1093/schbul/sbw020
16. Castro-Fornieles J, Baeza I, De La Serna E, et al. Two-year diagnostic stability in early-onset first-episode psychosis. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2011;52(10):1089-1098. doi:10.1111/j.1469-7610.2011.02443.x
17. Sharma, T.; Harvey PD. *The Early Course of Schizophrenia*. (Oxford University Press, ed.).; 2006.
18. Van Os J, Linscott RJ. Introduction: The extended psychosis phenotype - Relationship with schizophrenia and with ultrahigh risk status for psychosis. *Schizophrenia Bulletin*. 2012;38(2):227-230. doi:10.1093/schbul/sbr188
19. Kaymaz, N., Drukker, M., R. Lieb , H.-U. Wittchen, N. Werbeloff, M. Weiser TL, Os and J van, *. Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results N. *Psychological Medicine*. 2012;42:2239-2253. doi:10.1017/S0033291711002911
20. Häfner H, Maurer K. Early detection of schizophrenia: current evidence and future perspectives. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2006;5(3):130-138.
21. Klosterkötter J, Schultze-Lutter F, Ruhrmann S. Kraepelin and psychotic prodromal conditions. *European Archives of Psychiatry and Clinical Neuroscience*. 2008;258(SUPPL. 2):74-84. doi:10.1007/s00406-008-2010-5
22. Rzesnitzek L. "Early psychosis" as a mirror of biologist controversies in post-war german, anglo-saxon, and soviet psychiatry. *Frontiers in Psychology*. 2013;4(JUL):1-9. doi:10.3389/fpsyg.2013.00481
23. McGorry PD, Killackey E, Yung A. Early intervention in psychosis: concepts, evidence and future directions. *World Psychiatry*. 2008;7(3):148-156. doi:10.1002/j.2051-5545.2008.tb00182.x
24. McGlashan TH. Early detection and intervention of schizophrenia: rationale and research. *The British journal of psychiatrySupplement*. 1998;172(33):3-6.
25. Stone, W.S.; Faraone, S.V.; Tsuang MT. *Early Clinical Intervention and Prevention in Schizophrenia*. (William S. Stone, Stephen V. Faraone MTT, ed.). Springer Science & Business; 2003.
26. Cameron DE. Early Schizophrenia. *Am J Psychiatry*. 1938;95(3):567-582.
27. Häfner H. The concept of schizophrenia : from unity to diversity. *Advances in Psychiatry*. 2014;2014:1-109. doi:http://dx.doi.org/10.1155/2014/929434
28. Conrad K. *La Esquizofrenia Incipiente*. 1ª. (Fundación Archivos de Neurología. Editorial VV.AA. Triacastela, ed.).; 1996.
29. Mishara AL. Klaus Conrad (1905-1961): delusional mood, psychosis, and beginning schizophrenia. *Schizophrenia bulletin*. 2010;36(1):9-13. doi:10.1093/schbul/sbp144
30. Hafner H, Maurer K, Ruhrmann S, et al. Early detection and secondary prevention of psychosis: Facts and visions. *European Archives of Psychiatry and Clinical Neuroscience*. 2004;254(2):117-128. doi:10.1007/s00406-004-0508-z
31. McGlashan TH. A selective review of recent North American long-term followup studies of schizophrenia. *Schizophrenia bulletin*. 1988;14(4):515-542.

32. McGlashan TH, Johannessen JO. Early Detection and Intervention With Schizophrenia: Rationale. *Schizophrenia Bulletin*. 1996;22(2):201-222.
33. TH M, WS F. The positive-negative distinction in schizophrenia: Review of natural history validators. *Archives of General Psychiatry*. 1992;49(1):63-72.
34. Birchwood M, Smith J, Macmillan F, et al. Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers, a preliminary investigation. *Psychological medicine*. 1989;19(3):649-656.
35. Maurer K Schmidt M, Trendler G, Hafner H. HF. The early recognition inventory: structure, reliability and initial results. Schizophr Res2004; 67 (suppl): 34 . *Schizophr Res*. 2004;67((suppl)):34.
36. Hafner H, Maurer K, Loffler W, An Der Heiden W, Hambrecht M, Schultze-Lutter F. Modeling the early course of Schizophrenia. *Schizophrenia Bulletin*. 2003;29(2):325-340. doi:10.1007/s00406-005-0584-8
37. Hafner H, Maurer K, Ruhrmann S, et al. Early detection and secondary prevention of psychosis: Facts and visions. *European archives of psychiatry and clinical neuroscience*. 2004;254(2):117-128. doi:10.1007/s00406-004-0508-z
38. Perkins DO, Gu H, Boteva K, Lieberman J a. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: A critical review and meta-analysis. *American Journal of Psychiatry*. 2005;162(10):1785-1804. doi:10.1176/appi.ajp.162.10.1785
39. Singh SP. Outcome measures in early psychosis: Relevance of duration of untreated psychosis. *The British Journal of Psychiatry*. 2007;191(50):s58-63. doi:10.1192/bjp.191.50.s58
40. Crow TJ, MacMillan JF, Johnson AL JEC. A randomised controlled trial of prophylactic neuroleptic treatment. *Br J Psychiatry*. 1986;148:120-127e.
41. LoebeL A.D.; Lieberman, J.A.; Al- vir, J.M.J.; Mayerhoff, D.I.; Geisler, S.H.; and Szymanski SR. Duration of psychosis and outcome in first- episode schizophrenia. *Am J Psychiatry*. 1992;149(9):1183-1992.
42. Rabiner CJ, Wegner JT KJM. Outcome study of first-episode psychosis, I: relapse rates after 1 year. Am J Psychiatry 1986; 143:1155–1158. *Am J Psychiatry*. 1986;143:1155-1158.
43. Fennig S, Kovasznay B, Rich C, et al. Six-month stability of psychiatric diagnoses in first-admission patients with psychosis. *The American journal of psychiatry*. 1994;151(8):1200-1208. doi:10.1176/ajp.151.8.1200
44. Okasha A, el Dawla AS, Khalil AH, Saad A. Presentation of acute psychosis in an Egyptian sample: a transcultural comparison. *Comprehensive psychiatry*. 1993;34(1):4-9.
45. Jorgensen P. Comparative outcome of first-admission patients with delusional beliefs. *European psychiatry : the journal of the Association of European Psychiatrists*. 1995;10(6):276-281. doi:10.1016/0924-9338(96)80308-7
46. Gonzalez-Pinto A, Gutierrez M, Mosquera F, et al. First episode in bipolar disorder: Misdiagnosis and psychotic symptoms. *Journal of Affective Disorders*. 1998;50(1):41-44. doi:10.1016/S0165-0327(98)00032-9
47. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;344(8934):1398-1402. doi:Doi 10.1016/S0140-6736(94)90569-X

48. van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. *Archives of general psychiatry*. 1997;54(7):625-631.
49. Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *American Journal of Psychiatry*. 1999;156(9):1328-1335. doi:10.1176/ajp.156.9.1328
50. Erlenmeyer-Kimling L, Adamo UH, Rock D, et al. The New York High-Risk Project. Prevalence and comorbidity of axis I disorders in offspring of schizophrenic parents at 25-year follow-up. *Archives of General Psychiatry*. 1997;54(12):1096-1102.
51. Kendler KS, Karkowski LM, Walsh D. The structure of psychosis: latent class analysis of probands from the Roscommon Family Study. *Archives of general psychiatry*. 1998;55:492-499. doi:10.1001/archpsyc.55.6.492
52. Asarnow JR. Children at Risk for Schizophrenia: Converging Lines of Evidence. *Schizophr Bull*. 1988;14(4):613-631.
53. Erlenmeyer-Kimling L, Cornblatt BA. A summary of attentional findings in the New York High-Risk Project. *Journal of psychiatric research*. 1992;26(4):405-426.
54. Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo UH, et al. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. *Archives of General Psychiatry*. 1995;52(10):857-865.
55. Fish B, Marcus J, Hans SL, Auerbach JG PS. Infants at risk for schizophrenia: Sequelae of genetic neurointegrative defect. *Arch Gen Psychiatry*. 1992;49:221-235.
56. Meehl PE. Schizotaxia, schizotypy, schizophrenia. *American Psychologist*. 1962;17(12):827-838. doi:10.1037/h0041029
57. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson JJ. EPPIC: An envolving system of early detection and optimal management. *Schizophrenia Bulletin*. 1996;22(2):305-326.
58. Falloon IR, Kydd RR, Coverdale JH, Laidlaw TM. Early detection and intervention for initial episodes of schizophrenia. *Schizophrenia bulletin*. 1996;22(2):271-282.
59. McGorry PD. Issues for DSM-V: Clinical staging: A heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. *American Journal of Psychiatry*. 2007;164(6):859-860. doi:10.1176/ajp.2007.164.6.859
60. McGorry PD, Yung AR, Phillips LJ. The “close-in” or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophrenia bulletin*. 2003;29(4):771-790. doi:10.1093/oxfordjournals.schbul.a007046
61. McGorry PD, Edwards J. *Implementing Early Intervention in Psychosis. A Guide to Establishing Early Intervention Services.* Martin Dunitz Ltd; 2002.
62. Klosterkötter J, Ruhrmann S, Schultze-Lutter F, et al. The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. Published online 2005.

63. Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Archives of general psychiatry*. 2001;58(2):158-164. doi:10.1016/S0924-9338(99)80046-7
64. Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, et al. EPA guidance on the early intervention in clinical high risk states of psychoses. *European Psychiatry*. 2015;30(3):388-404. doi:10.1016/j.eurpsy.2015.01.013
65. Melle I, Larsen TK, Haahr U, et al. Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. *Archives of general psychiatry*. 2008;65(6):634-640. doi:10.1001/archpsyc.65.6.634
66. McGlashan TH, Addington J, Cannon T, et al. Recruitment and treatment practices for help-seeking "prodromal" patients. *Schizophrenia Bulletin*. 2007;33(3):715-726. doi:10.1093/schbul/sbm025
67. Cannon TD, Cadenhead K, Cornblatt B, et al. Prediction of Psychosis in Youth at High Clinical Risk A Multisite Longitudinal Study in North America. *Archives of General Psychiatry*. 2008;65(1):28-37.
68. Woods SW, Addington J, Cadenhead KS, et al. Validity of the prodromal risk syndrome for first psychosis: Findings from the north american prodrome longitudinal study. *Schizophrenia Bulletin*. 2009;35(5):894-908. doi:10.1093/schbul/sbp027
69. Cornblatt B a, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophrenia bulletin*. 2003;29(4):633-651. doi:10.1093/oxfordjournals.schbul.a007036
70. Marshall M, Rathbone J. Early intervention for psychosis (Cochrane Review). *Cochrane database of systematic reviews*. 2011;(6):1-166. doi:10.1002/14651858.CD004718.pub2
71. Yung AR, Stanford C, Cosgrave E, et al. Testing the Ultra High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophrenia Research*. 2006;84(1):57-66. doi:10.1016/j.schres.2006.03.014
72. Fusar-Poli P, Yung AR, McGorry P, van Os J. Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. *Psychological medicine*. 2014;44(1):17-24. doi:10.1017/S0033291713000184
73. Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: Impact on psychopathology and transition to psychosis. *Schizophrenia Bulletin*. 2014;40(1):120-131. doi:10.1093/schbul/sbs136
74. Lee K-W, Chan K-W, Chang W-C, et al. A systematic review on definitions and assessments of psychotic-like experiences. *Early intervention in psychiatry*. Published online 2015:1-14. doi:10.1111/eip.12228
75. Kelleher I, Harley M, Murtagh A, Cannon M. Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophrenia bulletin*. 2011;37(2):362-369. doi:10.1093/schbul/sbp057
76. Cannon TD, Cornblatt B, McGorry P. Editor's introduction: The empirical status of the ultra high-risk (prodromal) research paradigm. *Schizophrenia Bulletin*. 2007;33(3):661-664. doi:10.1093/schbul/sbm031

77. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis at risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70(1):107-120. doi:10.1001/jamapsychiatry.2013.269.The
78. Correll C, Hauser M, Auther A, Cornblatt B. Research in People with the Psychosis Risk Syndrome: A Review of the Current Evidence and Future Directions. *J Child Psychol Psychiatry*. 2011;51(4):390-431. doi:10.1111/j.1469-7610.2010.02235.x.Research
79. Carpenter WT. Anticipating DSM-V: Should psychosis risk become a diagnostic class? *Schizophrenia Bulletin*. 2009;35(5):841-843. doi:10.1093/schbul/sbp071
80. Arango C. Attenuated psychotic symptoms syndrome: How it may affect child and adolescent psychiatry. *European Child and Adolescent Psychiatry*. 2011;20(2):67-70. doi:10.1007/s00787-010-0144-2
81. van Os J, Guloksuz S. A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry*. 2017;16(2):200-206. doi:10.1002/wps.20423
82. Gross G, Huber G. The history of the basic symptom concept. *Acta Clinica Croatica*. 2010;49(2):47-59.
83. Schultze-Lutter F, Ruhrmann S, Berning J, Maier W, Klosterkötter J. Basic symptoms and ultrahigh risk criteria: Symptom development in the initial prodromal state. *Schizophrenia Bulletin*. 2010;36(1):182-191. doi:10.1093/schbul/sbn072
84. Frauke Schultze-Lutter, Joachim Klosterkötter, Heinz Picker, Eckhard-Michael Steinmeyer SR. Predicting first episode of psychosis by basic symptoms criteria. *Clinical Neuropsychyatry*. 2007;4(1):11-22.
85. Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. *Schizophrenia Research*. 2014;154(1-3):100-106. doi:10.1016/j.schres.2014.02.010
86. Koutsouleris N, Schmitt GJE, Gaser C, et al. Neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes. *British Journal of Psychiatry*. 2009;195(3):218-226. doi:10.1192/bjp.bp.108.052068
87. Ruhrmann S, Schultze-Lutter F, Salokangas RKR, et al. Prediction of Psychosis in Adolescents and Young Adults at High Risk. *Archives of General Psychiatry*. 2010;67(3):241. doi:10.1001/archgenpsychiatry.2009.206
88. Ziermans TB, Schothorst PF, Sprong M, van Engeland H. Transition and remission in adolescents at ultra-high risk for psychosis. *Schizophrenia Research*. 2011;126(1-3):58-64. doi:10.1016/j.schres.2010.10.022
89. Cannon TD, Cadenhead K, Cornblatt B, Woods SW. Prediction of Psychosis in Youth at High Clinical Risk. A Multisite Longitudinal Study in North America. *Arch Gen Psychiatry*. 2008;65(1):28-37.
90. Yung AR, Stanford C, Cosgrave E, et al. Testing the Ultra High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophrenia Research*. 2006;84(1):57-66. doi:10.1016/j.schres.2006.03.014
91. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *The Australian and New Zealand Journal of Psychiatry*. 2005;39(11-12):964-971. doi:10.1111/j.1440-1614.2005.01714.x

92. Fusar-Poli P, De Micheli A, Cappucciati M, et al. Diagnostic and Prognostic Significance of DSM-5 Attenuated Psychosis Syndrome in Services for Individuals at Ultra High Risk for Psychosis. *Schizophrenia bulletin*. 2018;44(2):264-275. doi:10.1093/schbul/sbx055
93. Fusar-Poli P, Bechdolf A, Taylor MJ, et al. At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophrenia Bulletin*. 2013;39(4):923-932. doi:10.1093/schbul/sbs060
94. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: Meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry*. 2012;69(3):220-229. doi:10.1001/archgenpsychiatry.2011.1472
95. Armando M, Pontillo M, De Crescenzo F, et al. Twelve-month psychosis-predictive value of the ultra-high risk criteria in children and adolescents. *Schizophrenia research*. 2015;169(1-3):186-192. doi:10.1016/j.schres.2015.10.033
96. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. *World Psychiatry*. 2015;14(3):322-332. doi:10.1002/wps.20250
97. Drake RJ, Husain N, Marshall M, et al. Effect of delaying treatment of first-episode psychosis on symptoms and social outcomes: a longitudinal analysis and modelling study. *The lancet Psychiatry*. 2020;7(7):602-610. doi:10.1016/S2215-0366(20)30147-4
98. Correll CU, Galling B, Pawar A, et al. Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA psychiatry*. 2018;75(6):555-565. doi:10.1001/jamapsychiatry.2018.0623
99. Davies C, Cipriani A, Ioannidis JPA, et al. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. *World Psychiatry*. 2018;17(2):196-209. doi:10.1002/wps.20526
100. Bosnjak Kuharic D, Kekin I, Hew J, Rojnic Kuzman M, Puljak L. Interventions for prodromal stage of psychosis. *The Cochrane database of systematic reviews*. 2019;2019(11). doi:10.1002/14651858.CD012236.pub2
101. Raballo A, Poletti M. Overlooking the transition elephant in the ultra-high-risk room: are we missing functional equivalents of transition to psychosis? *Psychological Medicine*. Published online 2019:1-4. doi:10.1017/s0033291719003337
102. Ajnakina O, David AS, Murray RM. "At risk mental state" clinics for psychosis - an idea whose time has come - and gone! *Psychological medicine*. Published online December 2018:1-6. doi:10.1017/S0033291718003859
103. Lee TY, Lee J, Kim M, Choe E, Kwon JS. Can we predict psychosis outside the clinical high-risk state? A systematic review of non-psychotic risk syndromes for mental disorders. *Schizophrenia Bulletin*. 2018;44(2):276-285. doi:10.1093/schbul/sbx173
104. Ajnakina O, Morgan C, Gayer-Anderson C, et al. Only a small proportion of patients with first episode psychosis come via prodromal services: A retrospective survey of a large UK mental health programme. *BMC Psychiatry*. 2017;17(1):1-9. doi:10.1186/s12888-017-1468-y

105. Addington J, Cornblatt BA, Cadenhead KS, et al. At clinical high risk for psychosis: Outcome for nonconverters. *American Journal of Psychiatry*. 2011;168(8):800-805. doi:10.1176/appi.ajp.2011.10081191
106. Gronholm PC, Thornicroft G, Laurens KR, Evans-Lacko S. Mental health-related stigma and pathways to care for people at risk of psychotic disorders or experiencing first-episode psychosis: a systematic review. *Psychological Medicine*. 2017;47(11):1867-1879. doi:DOI: 10.1017/S0033291717000344
107. Moritz S, Gawęda Ł, Heinz A, Gallinat J. Four reasons why early detection centers for psychosis should be renamed and their treatment targets reconsidered: we should not catastrophize a future we can neither reliably predict nor change. *Psychological Medicine*. 2019;49(13):2134-2140. doi:DOI: 10.1017/S0033291719001740
108. Ajnakina O, David AS, Murray RM. "At risk mental state" clinics for psychosis - An idea whose time has come - And gone! *Psychological Medicine*. 2019;49(4):529-534. doi:10.1017/S0033291718003859
109. Guloksuz S, van Os J. Need for evidence-based early intervention programmes: a public health perspective. *Evidence-based mental health*. 2018;21(4):128-130. doi:10.1136/ebmental-2018-300030
110. van Os J, Guloksuz S. A critique of the "ultra-high risk" and "transition" paradigm. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2017;16(2):200-206. doi:10.1002/wps.20423
111. Hartmann JA, Nelson B, Ratheesh A, Treen D, McGorry PD. At-risk studies and clinical antecedents of psychosis, bipolar disorder and depression: a scoping review in the context of clinical staging. *Psychological medicine*. 2019;49(2):177-189. doi:10.1017/S0033291718001435
112. Tien AY. Distributions of hallucinations in the population. *Social psychiatry and psychiatric epidemiology*. 1991;26(6):287-292.
113. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry*. 1994;51(1):8-19. doi:10.1001/archpsyc.51.1.8
114. Kessler RC, Birnbaum H, Demler O, et al. The prevalence and correlates of non-affective psychosis in the National Comorbidity Survey Replication (NCS-R). *Biological psychiatry*. 2005;58(8):668-676. doi:10.1016/j.biopsych.2005.04.034.The
115. van Os J, Hanssen M, Bijl R v, Vollebergh W. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. *Archives of general psychiatry*. 2001;58(7):663-668. doi:10.1001/archpsyc.58.7.663
116. Johns LC, Cannon M, Singleton N, et al. Prevalence and correlates of self-reported psychotic symptoms in the British population Prevalence and correlates of self-reported psychotic symptoms in the British population. *British Journal of Psychiatry*. 2004;185:298-305. doi:10.1192/bjp.185.4.298
117. Schultze-Lutter F, Michel C, Ruhrmann S, Schimmelmann BG. Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychological Medicine*. Published online 2017:1-15. doi:10.1017/S0033291717002586

118. Rössler W, Riecher-Rössler A, Angst J, et al. Psychotic experiences in the general population: A twenty-year prospective community study. *Schizophrenia Research*. 2007;92(1-3):1-14. doi:10.1016/j.schres.2007.01.002
119. Werbeloff N. Self-reported Attenuated Psychotic Symptoms as Forerunners of Severe Mental Disorders Later in Life. *Archives of General Psychiatry*. 2012;69(5):467. doi:10.1001/archgenpsychiatry.2011.1580
120. McGrath JJ, Saha S, Al-Hamzawi A, et al. Psychotic experiences in the general population: A cross-national analysis based on 31 261 respondents from 18 countries. *JAMA Psychiatry*. 2015;72(7):697-705. doi:10.1001/jamapsychiatry.2015.0575
121. Dhossche D, Ferdinand R, Van der Ende J, Hofstra MB, Verhulst F. Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychological medicine*. 2002;32(4):619-627. doi:10.1017/S003329170200555X
122. Scott J, Martin G, Bor W, Sawyer M, Clark J, McGrath J. The prevalence and correlates of hallucinations in Australian adolescents: Results from a national survey. *Schizophrenia Research*. 2009;107(2-3):179-185. doi:10.1016/j.schres.2008.11.002
123. Jeppesen P, Larsen JT, Clemmensen L, et al. The CCC2000 birth cohort study of register-based family history of mental disorders and psychotic experiences in offspring. *Schizophrenia Bulletin*. 2015;41(5):1084-1094. doi:10.1093/schbul/sbu167
124. Bartels-Velthuis AA, Van De Willige G, Jenner JA, Van Os J, Wiersma D. Course of auditory vocal hallucinations in childhood: 5-Year follow-up study. *British Journal of Psychiatry*. 2011;199(4):296-302. doi:10.1192/bjp.bp.110.086918
125. Bartels-Velthuis AA, van de Willige G, Jenner JA, Wiersma D, van Os J. Auditory hallucinations in childhood: associations with adversity and delusional ideation. *Psychological Medicine*. 2012;42(03):583-593. doi:10.1017/S0033291711001590
126. Welham, J. Scott, G. Williams, J. Najman, W. Bor MO and JMcGrath, Welham J, Scott J, et al. Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21-year birth cohort study. *Psychological medicine*. 2009;39(4):625-634. doi:10.1017/S0033291708003760
127. Nehemiah N, Turnip SS. The prevalence and psychosocial risk factors for psychotic-like experiences (PLE) among high school students in Jakarta. *Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists*. 2018;10(4):e12337. doi:10.1111/appy.12337
128. Laurens KR, Hobbs MJ, Sunderland M, Green MJ, Mould GL. Psychotic-like experiences in a community sample of 8000 children aged 9 to 11 years: an item response theory analysis. *Psychological Medicine*. 2012;42:1495-1506. doi:10.1017/S0033291711002108
129. Barragan M, Laurens KR, Navarro JB, Obiols JE. Psychotic-like experiences and depressive symptoms in a community sample of adolescents. *European Psychiatry*. 2011;26(6):396-401. doi:10.1016/j.eurpsy.2010.12.007
130. Yung AR, Nelson B, Baker K, Buckby JA, Bakshee G, Cosgra EM. Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia Alison.

Australian and New Zealand Journal of Psychiatry. 2009;43:118-128. doi:10.1038/npp.2008.223.Reduced
131. Armando M, Nelson B, Yung AR, et al. Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. *Schizophrenia Research*. 2010;119(1-3):258-265. doi:10.1016/j.schres.2010.03.001
132. Yoshizumi T, Murase S, Honjo S, Kaneko H, Murakami T. Hallucinatory experiences in a community sample of Japanese children. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004;43(8):1030-1036. doi:10.1097/01.chi.0000126937.44875.6b
133. Rubio JM, Sanjuán J, Flórez-Salamanca L, Cuesta MJ. Examining the course of hallucinatory experiences in children and adolescents: A systematic review. *Schizophrenia Research*. 2012;138(2-3):248-254. doi:10.1016/j.schres.2012.03.012
134. Healy C, Brannigan R, Dooley N, et al. Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. *Psychological medicine*. 2019;49(10):1589-1599. doi:10.1017/S0033291719000485
135. Dominguez MDG, Wichers M, Lieb R, Wittchen HU, Van Os J. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: An 8-year cohort study. *Schizophrenia Bulletin*. 2011;37(1):84-93. doi:10.1093/schbul/sbp022
136. De Loore E, Gunther N, Drukker M, et al. Persistence and outcome of auditory hallucinations in adolescence: A longitudinal general population study of 1800 individuals. *Schizophrenia Research*. 2011;127(1-3):252-256. doi:10.1016/j.schres.2011.01.015
137. Zammit S, Kounali D, Cannon M, et al. Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry*. 2013;170(7):742-750. doi:10.1176/appi.ajp.2013.12060768
138. MacKie CJ, Castellanos-Ryan N, Conrod PJ. Developmental trajectories of psychotic-like experiences across adolescence: Impact of victimization and substance use. *Psychological Medicine*. 2011;41(1):47-58. doi:10.1017/S0033291710000449
139. Kelleher I, Murtagh A, Molloy C, et al. Identification and characterization of prodromal risk syndromes in young adolescents in the community: a population-based clinical interview study. *Schizophrenia bulletin*. 2012;38(2):239-246. doi:10.1093/schbul/sbr164
140. Gaudiano BA, Zimmerman M. Prevalence of attenuated psychotic symptoms and their relationship with DSM-IV diagnoses in a general psychiatric outpatient clinic. *The Journal of clinical psychiatry*. 2013;74(2):149-155. doi:10.4088/JCP.12m07788
141. Wigman JTW, Devlin N, Kelleher I, et al. Psychotic symptoms, functioning and coping in adolescents with mental illness. *BMC psychiatry*. 2014;14:97. doi:10.1186/1471-244X-14-97
142. Kelleher I, Devlin N, Wigman JTW, et al. Psychotic experiences in a mental health clinic sample: Implications for suicidality, multimorbidity and functioning. *Psychological Medicine*. 2014;44(8):1615-1624. doi:10.1017/S0033291713002122

143. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *Journal of affective disorders*. 2003;73(1-2):123-131. doi:10.1016/S0165-0327(02)00332-4
144. Perälä J, Suvisaari J, Saarni SI, et al. Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population. *Arch Gen Psychiatry*. 2015;37(1):19-28. doi:10.1001/archpsyc.64.1.19
145. Chang WC, Wong CSM, Chen EYH, et al. Lifetime Prevalence and Correlates of Schizophrenia-Spectrum, Affective, and Other Non-affective Psychotic Disorders in the Chinese Adult Population. *Schizophrenia Bulletin*. 2017;43(6):1280-1290. doi:10.1093/schbul/sbx056
146. Jääskeläinen E, Juola T, Korpela H, et al. Epidemiology of psychotic depression - systematic review and meta-analysis. *Psychological medicine*. 2018;48(6):905-918. doi:10.1017/S0033291717002501
147. Post RM, Luckenbaugh DA, Leverich GS, et al. Incidence of childhood-onset bipolar illness in the USA and Europe. *British Journal of Psychiatry*. 2008;192(2):150-151. doi:10.1192/bjp.bp.107.037820
148. Costello E, Angold A, Burns B, et al. The Great Smoky Mountains Study of Youth: Goals, Design, Methods, and the Prevalence of DSM-III-R Disorders. *Archives of General Psychiatry*. 1996;53:1129-1136.
149. Canino G et al. The DSM-IV Rates of Child and Adolescent Disorders in Puerto Rico. *Arch Gen Psychiatry*. 2004;61:85-93.
150. Verhulst F, Van der Ende J, Ferdinand R, Kasius M. The Prevalence of DSM-III-R Diagnoses in a National Sample of Dutch Adolescents. *Archives of General Psychiatry*. 1997;54(4):329-336.
151. Polanczyk G V., Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2015;56(3):345-365. doi:10.1111/jcpp.12381
152. Ford T, Goodman R, Meltzer H. The British Child and Adolescent Mental Health Survey 1999: The Prevalence of DSM-IV Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2003;42(10):1203-1211.
153. Burd L, Kerbeshian J. A North Dakota prevalence study of schizophrenia presenting in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1987;26(3):347-350. doi:10.1097/00004583-198705000-00012
154. Wiener JM, Dulcan MK. *Tratado de Psiquiatría de a Infancia y La Adolescencia*. Masson, S.A.; 2006.
155. Gillberg C, Wahlstrom J, Forsman A, Hellgren L, Gillberg IC. Teenage psychoses--epidemiology, classification and reduced optimality in the pre-, peri- and neonatal periods. *Journal of child psychology and psychiatry, and allied disciplines*. 1986;27(1):87-98.
156. Taylor E, Rutter M. *Child and Adolescent Psychiatry. 4th Edition.* Blackwell Publishing; 2002.
157. Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: Results from the national comorbidity survey replication-adolescent supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010;49(10):980-989. doi:10.1016/j.jaac.2010.05.017

158. Kessler RC, Avenevoli S, Costello EJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Archives of General Psychiatry*. 2012;69(4):372-380. doi:10.1001/archgenpsychiatry.2011.160
159. Lewinsohn PM, Klein DN, Seeley JR, Pm L, Dn K, Seeley. Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar disorders*. 2000;2(3):281-293.
160. Van Meter AR, Moreira ALR, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *The Journal of clinical psychiatry*. Published online May 31, 2011. doi:10.4088/JCP.10m06290
161. Post RM, Altshuler LL, Kupka R, et al. More childhood onset bipolar disorder in the United States than Canada or Europe: Implications for treatment and prevention. *Neuroscience & Biobehavioral Reviews*. 2017;74:204-213. doi:10.1016/j.neubiorev.2017.01.022
162. James A, Hoang U, Seagroatt V, Clacey J, Goldacre M, Leibenluft E. A comparison of American and English hospital discharge rates for pediatric bipolar disorder, 2000 to 2010. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2014;53(6):614-624. doi:10.1016/j.jaac.2014.02.008
163. Canuso CM, Bossie CA, Zhu Y, Youssef E, Dunner DL. Psychotic symptoms in patients with bipolar mania. *Journal of affective disorders*. 2008;111(2-3):164-169. doi:10.1016/j.jad.2008.02.014
164. Keck PE, Mcelroy SL, Havens JR, et al. Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. *Comprehensive psychiatry*. 2003;44(4):263-269. doi:10.1016/S0010-440X(03)00089-0
165. Méndez I, Birmaher B. Pediatric Bipolar Disorder: Do we know how to detect it? *Actas espanolas de psiquiatria*. 2010;38(3):170-182.
166. Mendez, I; Birmaher B. 14. El Trastorno Bipolar Pediátrico. In: Palacio JD, ed. *Aspecto Claves: Psiquiatría Infantil*. 1a.ed. Fondo Editorial CIB; 2014.
167. Pavuluri MN, Herbener ES, Sweeney JA. Psychotic symptoms in pediatric bipolar disorder. *Journal of Affective Disorders*. 2004;80(1):19-28. doi:10.1016/S0165-0327(03)00053-3
168. McGlashan TH. Adolescent versus adult onset of mania. *The American journal of psychiatry*. 1988;145(2):221-223. doi:10.1176/ajp.145.2.221
169. McElroy SL, Strakowski SM, West SA, Keck PE, Mcconville BJ. Phenomenology of adolescent and adult mania in hospitalized patients with bipolar disorder. *American Journal of Psychiatry*. 1997;154(1):44-49. doi:10.1176/ajp.154.1.44
170. Carlson GA, Bromet EJ, Sievers S. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *American Journal of Psychiatry*. 2000;157(2):213-219. doi:10.1176/appi.ajp.157.2.213
171. Strakowski SM, Keck PE, McElroy SL, et al. Twelve-Month Outcome After a First Hospitalization for Affective Psychosis. *Archives of General Psychiatry*. 1998;55(1):49-55. doi:10.1001/archpsyc.55.1.49
172. Amminger GP, Harris MG, Conus P, et al. Treated incidence of first-episode psychosis in the catchment area of EPPIC between 1997 and 2000. *Acta Psychiatrica Scandinavica*. 2006;114(5):337-345. doi:10.1111/j.1600-0447.2006.00790.x
173. Nesvåg R, Bramness JG, Handal M, Hartz I, Hjellvik V, Skurtveit S. The incidence, psychiatric co-morbidity and pharmacological treatment of severe

mental disorders in children and adolescents. *European Psychiatry*. 2018;49:16-22. doi:10.1016/j.eurpsy.2017.12.009
174. Garralda M. Hallucinations in children with conduct and emotional disorders: II. The follow-up study. *Psychological Medicine*. 1984;14(3):597-603.
175. Jardri R, Bartels-Velthuis AA, Debban M, et al. From phenomenology to neurophysiological understanding of hallucinations in children and adolescents. *Schizophrenia Bulletin*. 2014;40(SUPPL. 4):221-232. doi:10.1093/schbul/sbu029
176. Walker E, Bollini AM. Pubertal neurodevelopment and the emergence of psychotic symptoms. *Schizophrenia Research*. 2002;54(1-2):17-23. doi:10.1016/S0920-9964(01)00347-4
177. Kelleher I, Keeley H, Corcoran P, et al. Clinicopathological significance of psychotic experiences in non-psychotic young people: Evidence from four population-based studies. *British Journal of Psychiatry*. 2012;201(1):26-32. doi:10.1192/bjp.bp.111.101543
178. Laurens KR, Hodgins S, Maughan B, Murray RM, Rutter ML, Taylor EA. Community screening for psychotic-like experiences and other putative antecedents of schizophrenia in children aged 9-12 years. *Schizophrenia Research*. 2007;90(1-3):130-146. doi:10.1016/j.schres.2006.11.006
179. Connell M, Betts K, McGrath JJ, et al. Hallucinations in adolescents and risk for mental disorders and suicidal behaviour in adulthood: Prospective evidence from the MUSP birth cohort study. *Schizophrenia research*. 2016;176(2-3):546-551. doi:10.1016/j.schres.2016.06.009
180. Degenhardt L, Saha S, Lim CCW, et al. The associations between psychotic experiences and substance use and substance use disorders: findings from the World Health Organization World Mental Health surveys. *Addiction (Abingdon, England)*. 2018;113(5):924-934. doi:10.1111/add.14145
181. Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen H-U, van Os J. Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. *Psychological Medicine*. 2015;FirstView:1-13.
182. Downs JM, Cullen AE, Barragan M, Laurens KR. Persisting psychotic-like experiences are associated with both externalising and internalising psychopathology in a longitudinal general population child cohort. *Schizophrenia Research*. 2013;144(1-3):99-104. doi:10.1016/j.schres.2012.12.009
183. Bartels-Velthuis A a., Jenner J a., Van De Willige G, Van Os J, Wiersma D. Prevalence and correlates of auditory vocal hallucinations in middle childhood. *British Journal of Psychiatry*. 2010;196(1):41-46. doi:10.1192/bjp.bp.109.065953
184. Nishida A, Sasaki T, Nishimura Y, et al. Psychotic-like experiences are associated with suicidal feelings and deliberate self-harm behaviors in adolescents aged 12-15 years. *Acta Psychiatrica Scandinavica*. 2010;121(4):301-307. doi:10.1111/j.1600-0447.2009.01439.x
185. Kelleher I, Lynch F, Harley M, et al. Psychotic Symptoms in Adolescence Index Risk for Suicidal Behavior. *Archives of General Psychiatry*. 2012;69(12):1277. doi:10.1001/archgenpsychiatry.2012.164
186. Kelleher I, Cederlöf M, Lichtenstein P. Psychotic experiences as a predictor of the natural course of suicidal ideation: a Swedish cohort study. *World*

psychiatry : official journal of the World Psychiatric Association (WPA). 2014;13(2):184-188. doi:10.1002/wps.20131

187. Bromet EJ, Nock MK, Saha S, et al. Association Between Psychotic Experiences and Subsequent Suicidal Thoughts and Behaviors: A Cross-National Analysis From the World Health Organization World Mental Health Surveys. *JAMA psychiatry*. 2017;74(11):1136-1144. doi:10.1001/jamapsychiatry.2017.2647
188. Kelleher I, Wigman JTW, Harley M, et al. Psychotic experiences in the population: Association with functioning and mental distress. *Schizophrenia Research*. 2015;165:9-14. doi:10.1016/j.schres.2015.03.020
189. Alonso J, Saha S, Lim CCW, et al. The association between psychotic experiences and health-related quality of life: a cross-national analysis based on World Mental Health Surveys. *Schizophrenia research*. Published online May 2018. doi:10.1016/j.schres.2018.04.044
190. Navarro-Mateu F, Alonso J, Lim CCW, et al. The association between psychotic experiences and disability: results from the WHO World Mental Health Surveys. *Acta psychiatrica Scandinavica*. 2017;136(1):74-84. doi:10.1111/acps.12749
191. Janssens M, Boyette L Lou, Heering HD, et al. Developmental course of subclinical positive and negative psychotic symptoms and their associations with genetic risk status and impairment. *Schizophrenia Research*. 2016;174(1-3):177-182. doi:10.1016/j.schres.2016.03.028
192. Mollon J, David AS, Morgan C, et al. Psychotic Experiences and Neuropsychological Functioning in a Population-based Sample. *JAMA Psychiatry*. Published online 2015:1. doi:10.1001/jamapsychiatry.2015.2551
193. Koike S, Barnett J, Jones PB, Richards M. Cognitive profiles in childhood and adolescence differ between adult psychotic and affective symptoms: A prospective birth cohort study. *Psychological Medicine*. 2018;48(1):11-22. doi:10.1017/S0033291717000393
194. Escher S, Romme M, Buiks A, Delespaul P, Os JIMV a N. Independent course of childhood auditory hallucinations: a sequential 3-year follow-up study. *The British Journal of Psychiatry*. 2002;181(suppl. 43):s10-s18. doi:10.1192/bjp.181.43.s10
195. Bak M, Myin-Germeys I, Hanssen M, et al. When does experience of psychosis result in a need for care? A prospective general population study. *Schizophr Bull*. 2003;29(2):349-352.
196. Scott J, Martin G, Welham J, et al. Psychopathology during childhood and adolescence predicts delusional-like experiences in adults: A 21-year birth cohort study. *American Journal of Psychiatry*. 2009;166(5):567-574. doi:10.1176/appi.ajp.2008.08081182
197. Bak M, Delespaul P, Hanssen M, De Graaf R, Vollebergh W, Van Os J. How false are "false" positive psychotic symptoms? [2]. *Schizophrenia Research*. 2003;62(1-2):187-189. doi:10.1016/S0920-9964(02)00336-5
198. Schultze-Lutter F, Hubl D, Schimmelmann BG, Michel C. Age effect on prevalence of ultra-high risk for psychosis symptoms: replication in a clinical sample of an early detection of psychosis service. *European Child and Adolescent Psychiatry*. 2017;26(11):1401-1405. doi:10.1007/s00787-017-0994-y

199. Tor J, Dolz M, Sintes A, et al. Clinical high risk for psychosis in children and adolescents: a systematic review. *European Child & Adolescent Psychiatry*. 2017;27(6):683-700. doi:10.1007/s00787-017-1046-3
200. Miller TJ, McGlashan TH, Rosen JL, et al. 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*. 2002;159(5):863-865. doi:10.1176/appi.ajp.159.5.863
201. Nelson B, Yuen HP, Wood SJ, et al. Long-term follow-up of a group at ultra high risk ("Prodromal") for psychosis the PACE 400 study. *JAMA Psychiatry*. 2013;70(8):793-802. doi:10.1001/jamapsychiatry.2013.1270
202. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature genetics*. 2018;50(5):668-681. doi:10.1038/s41588-018-0090-3
203. Fusar-Poli P, Cappucciati M, Borgwardt S, et al. Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk. *JAMA Psychiatry*. Published online 2015:1. doi:10.1001/jamapsychiatry.2015.2324
204. Fusar-Poli P, Salazar de Pablo G, Correll CU, et al. Prevention of Psychosis: Advances in Detection, Prognosis, and Intervention. *JAMA psychiatry*. 2020;77(7):755-765. doi:10.1001/jamapsychiatry.2019.4779
205. Schultze-Lutter F, Schimmelmann BG, Klosterkötter J, Ruhrmann S. Comparing the prodrome of schizophrenia-spectrum psychoses and affective disorders with and without psychotic features. *Schizophrenia Research*. 2012;138(2-3):218-222. doi:10.1016/j.schres.2012.04.001
206. Correll CU, Smith CW, Auther AM, et al. Predictors of remission, schizophrenia, and bipolar disorder in adolescents with brief psychotic disorder or psychotic disorder not otherwise specified considered at very high risk for schizophrenia. *Journal of child and adolescent psychopharmacology*. 2008;18(5):475-490. doi:10.1089/cap.2007.110
207. Beck K, Andreou C, Studerus E, et al. Clinical and functional long-term outcome of patients at clinical high risk (CHR) for psychosis without transition to psychosis: A systematic review. *Schizophrenia research*. 2019;210:39-47. doi:10.1016/j.schres.2018.12.047
208. Schultze-Lutter F, Schimmelmann BG, Flückiger R, Michel C. Effects of age and sex on clinical high-risk for psychosis in the community. *World Journal of Psychiatry*. 2020;10(5):101-124. doi:10.5498/wjp.v10.i5.101
209. Schimmelmann BG, Michel C, Martz-Irngartinger A, Linder C, Schultze-Lutter F. Age matters in the prevalence and clinical significance of ultra-high-risk for psychosis symptoms and criteria in the general population: Findings from the BEAR and BEARS-kid studies. *World Psychiatry*. 2015;14(2):189-197. doi:10.1002/wps.20216
210. Schultze-Lutter F, Hubl D, Schimmelmann BG, Michel C. Age effect on prevalence of ultra-high risk for psychosis symptoms: replication in a clinical sample of an early detection of psychosis service. *European Child and Adolescent Psychiatry*. 2017;26(11):1401-1405. doi:10.1007/s00787-017-0994-y
211. Lo Cascio N, Saba R, Hauser M, et al. Attenuated psychotic and basic symptom characteristics in adolescents with ultra-high risk criteria for

psychosis, other non-psychotic psychiatric disorders and early-onset psychosis. *European Child and Adolescent Psychiatry*. 2016;25(10):1091-1102. doi:10.1007/s00787-016-0832-7

212. Ribolsi M, Lin A, Wardenaar KJ, et al. Clinical presentation of Attenuated Psychosis Syndrome in children and adolescents: Is there an age effect? *Psychiatry research*. 2017;252:169-174. doi:10.1016/j.psychres.2017.02.050
213. Allswede DM, Addington J, Bearden CE, et al. Characterizing Covariant Trajectories of Individuals at Clinical High Risk for Psychosis Across Symptomatic and Functional Domains. *The American journal of psychiatry*. 2020;177(2):164-171. doi:10.1176/appi.ajp.2019.18111290
214. Lo Cascio N, Curto M, Pasqualetti P, et al. Impairment in Social Functioning differentiates youth meeting Ultra-High Risk for psychosis criteria from other mental health help-seekers: A validation of the Italian version of the Global Functioning: Social and Global Functioning: Role scales. *Psychiatry Research*. 2017;253(September 2016):296-302. doi:10.1016/j.psychres.2017.04.008
215. Polari A, Yuen HP, Amminger P, et al. Prediction of clinical outcomes beyond psychosis in the ultra-high risk for psychosis population. *Early intervention in psychiatry*. Published online June 2020. doi:10.1111/eip.13002
216. Nieman DH, Ruhrmann S, Dragt S, et al. Psychosis prediction: Stratification of risk estimation with information-processing and premorbid functioning variables. *Schizophrenia Bulletin*. 2014;40(6):1482-1490. doi:10.1093/schbul/sbt145
217. Carrión RE, McLaughlin D, Goldberg TE, et al. Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry*. 2013;70(11):1133-1142. doi:10.1001/jamapsychiatry.2013.1909
218. Cornblatt B a., Carrión RE, Addington J, et al. Risk factors for psychosis: Impaired social and role functioning. *Schizophrenia Bulletin*. 2012;38(6):1247-1257. doi:10.1093/schbul/sbr136
219. Dannevang AL, Randers L, Gondan M, Krakauer K, Nordholm D, Nordentoft M. Premorbid adjustment in individuals at ultra-high risk for developing psychosis: a case-control study. *Early intervention in psychiatry*. 2018;12(5):839-847. doi:10.1111/eip.12375
220. Goines KB, LoPilato AM, Addington J, et al. Sleep problems and attenuated psychotic symptoms in youth at clinical high-risk for psychosis. *Psychiatry research*. 2019;282:112492. doi:10.1016/j.psychres.2019.112492
221. Correll C, Hauser M, Auther A, Cornblatt B. Research in People with the Psychosis Risk Syndrome: A Review of the Current Evidence and Future Directions. *J Child Psychol Psychiatry*. 2011;51(4):390-431. doi:10.1111/j.1469-7610.2010.02235.x.Research
222. Bourgin J, Duchesnay E, Magaud E, Gaillard R, Kazes M, Krebs M-O. Predicting the individual risk of psychosis conversion in at-risk mental state (ARMS): a multivariate model reveals the influence of nonpsychotic prodromal symptoms. *European child & adolescent psychiatry*. Published online December 2019. doi:10.1007/s00787-019-01461-y
223. Ratheesh A, Cotton SM, Davey CG, et al. Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis. *Schizophrenia research*. 2018;192:345-350. doi:10.1016/j.schres.2017.04.036
224. Correll CU, Smith CW, Auther AM, et al. Predictors of remission, schizophrenia, and bipolar disorder in adolescents with brief psychotic disorder

or psychotic disorder not otherwise specified considered at very high risk for schizophrenia. *Journal of child and adolescent psychopharmacology*. 2008;18(5):475-490. doi:10.1089/cap.2007.110

225. Conus P, Wardb J, Hallam KT, et al. The proximal prodrome to first episode mania - A new target for early intervention. *Bipolar Disorders*. 2008;10(5):555-565. doi:10.1111/j.1399-5618.2008.00610.x
226. Duffy A, Vandeleur C, Heffer N, Preisig M. The clinical trajectory of emerging bipolar disorder among the high-risk offspring of bipolar parents: current understanding and future considerations. *International Journal of Bipolar Disorders*. 2017;5(1):37. doi:10.1186/s40345-017-0106-4
227. Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. *Journal of Affective Disorders*. 2010;121(1-2):127-135. doi:10.1016/j.jad.2009.05.022
228. Birmaher B. The Risks of Persistent Irritability. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2016;55(7):538-539. doi:10.1016/j.jaac.2016.04.015
229. Birmaher B, Goldstein BI, Axelson D, et al. Mood lability among offspring of parents with bipolar disorder and community controls. *Bipolar disorders*. 2013;15(3):253-263. doi:10.1111/bdi.12060
230. Birmaher B, Axelson D, Monk K, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. *Archives of general psychiatry*. 2009;66(3):287-296. doi:10.1001/archgenpsychiatry.2008.546
231. Hafeman DM, Merranko J, Axelson D, et al. Toward the definition of a bipolar prodrome: Dimensional predictors of bipolar spectrum disorders in at-risk youths. *American Journal of Psychiatry*. 2016;173(7):695-704. doi:10.1176/appi.ajp.2015.15040414
232. Fusar-Poli P, Rutigliano G, Stahl D, et al. Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis. *JAMA Psychiatry*. 2017;74(5):493-500. doi:10.1001/jamapsychiatry.2017.0284
233. Mechelli A, Lin A, Wood S, et al. Using clinical information to make individualized prognostic predictions in people at ultra high risk for psychosis. *Schizophrenia research*. 2017;184:32-38. doi:10.1016/j.schres.2016.11.047
234. Cannon TD, Yu C, Addington J, et al. An individualized risk calculator for research in prodromal psychosis. *American Journal of Psychiatry*. 2016;173(10):980-988. doi:10.1176/appi.ajp.2016.15070890
235. Hafeman DM, Merranko J, Goldstein TR, et al. Assessment of a Person-Level Risk Calculator to Predict New-Onset Bipolar Spectrum Disorder in Youth at Familial Risk. *JAMA Psychiatry*. 2017;74(8):841. doi:10.1001/jamapsychiatry.2017.1763
236. McGorry PD, Hartmann JA, Spooner R, Nelson B. Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry*. 2018;17(2):133-142. doi:10.1002/wps.20514
237. Mongan D, Föcking M, Healy C, et al. T21. Development of Proteomic Prediction Models for Outcomes in the Clinical High Risk State and Psychotic Experiences in Adolescence: Machine Learning Analyses in Two Nested Case-Control Studies. *Schizophrenia Bulletin*. 2020;46(Supplement_1):S238-S239. doi:10.1093/schbul/sbaa029.581

238. Yassin W, Nakatani H, Zhu Y, et al. The promise of biological markers for treatment response in first-episode psychosis: A systematic review. *Schizophrenia Bulletin*. 2020;41(2):349-360. doi:10.1001/archgenpsychiatry.2008.514
239. Sanfelici R, Dwyer DB, Antonucci LA, Koutsouleris N. Individualized Diagnostic and Prognostic Models for Patients With Psychosis Risk Syndromes: A Meta-analytic View on the State of the Art. *Biological Psychiatry*. 2020;88(4):349-360. doi:10.1016/j.biopsych.2020.02.009
240. Rosen LN, Rosenthal NE, Van Dusen PH, Dunner DL, Fieve RR. Age at onset and number of psychotic symptoms in bipolar I and schizoaffective disorder. *The American journal of psychiatry*. 1983;140(11):1523-1524. doi:10.1176/ajp.140.11.1523
241. Werry JS, McClellan JM, Chard L. Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: a clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1991;30(3):457-465. doi:10.1097/00004583-199105000-00017
242. Carlson GA, Fennig S, Bromet EJ. The confusion between bipolar disorder and schizophrenia in youth: where does it stand in the 1990s? *Journal of the American Academy of Child and Adolescent Psychiatry*. 1994;33(4):453-460. doi:10.1097/00004583-199405000-00002
243. González-Pinto A, Van Os J, Pérez de Heredia JL, et al. Age-dependence of Schneiderian psychotic symptoms in bipolar patients. *Schizophrenia Research*. 2003;61(2-3):157-162. doi:10.1016/S0920-9964(02)00320-1
244. Bromet EJ, Kotov R, Fochtmann LJ, et al. Diagnostic shifts during the decade following first admission for psychosis. *The American journal of psychiatry*. 2011;168(11):1186-1194. doi:10.1176/appi.ajp.2011.11010048
245. McClellan JM, Werry JS, Ham M. A follow-up study of early onset psychosis: comparison between outcome diagnoses of schizophrenia, mood disorders, and personality disorders. *Journal of autism and developmental disorders*. 1993;23(2):243-262.
246. Tohen M, Strakowski SM, Zarate C, et al. The McLean-Harvard First-Episode Project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. *Biological Psychiatry*. 2000;48(6):467-476. doi:10.1016/S0006-3223(00)00915-X
247. Peralta V, Gil-Berrozpe GJ, Sánchez-Torres A, Cuesta MJ. The network and dimensionality structure of affective psychoses: an exploratory graph analysis approach. *Journal of affective disorders*. 2020;277:182-191. doi:10.1016/j.jad.2020.08.008
248. Corponi F, Anmella G, Pacchiarotti I, et al. Deconstructing major depressive episodes across unipolar and bipolar depression by severity and duration: a cross-diagnostic cluster analysis on a large, international, observational study. *Translational psychiatry*. 2020;10(1):241. doi:10.1038/s41398-020-00922-2
249. Charney AW, Mullins N, Park YJ, Xu J. On the diagnostic and neurobiological origins of bipolar disorder. *Translational psychiatry*. 2020;10(1):118. doi:10.1038/s41398-020-0796-8
250. Parker G, Spoelma MJ, Tavella G, et al. The bipolar disorders: A case for their categorically distinct status based on symptom profiles. *Journal of affective disorders*. 2020;277:225-231. doi:10.1016/j.jad.2020.08.014

251. Tohen M, Waternaux CM, Tsuang MT, Hunt AT. Four-year follow-up of twenty-four first-episode manic patients. *Journal of affective disorders*. 1990;19(2):79-86.
252. Goes FS, Zandi PP, Miao K, et al. Mood-incongruent psychotic features in bipolar disorder: Familial aggregation and suggestive linkage to 2p11-q14 and 13q21-33. *American Journal of Psychiatry*. 2004;164(4):264-268. doi:10.1176/ajp.2007.164.2.236
253. Keck PE, McElroy SL, Havens JR, et al. Psychosis in bipolar disorder: Phenomenology and impact on morbidity and course of illness. *Comprehensive Psychiatry*. 2003;44(4):263-269. doi:10.1016/S0010-440X(03)00089-0
254. Tillman R, Geller B, Klages T, Corrigan M, Bolhofner K, Zimerman B. Psychotic phenomena in 257 young children and adolescents with bipolar I disorder: delusions and hallucinations (benign and pathological). *Bipolar disorders*. 2008;10(1):45-55. doi:10.1111/j.1399-5618.2008.00480.x
255. Caetano SC, Olvera RL, Hunter K, et al. Association of psychosis with suicidality in pediatric bipolar I, II and bipolar NOS patients. *Journal of Affective Disorders*. 2006;91(1):33-37. doi:10.1016/j.jad.2005.12.008
256. Goes FS, Zandi PP, Miao K, et al. Mood-incongruent psychotic features in bipolar disorder: Familial aggregation and suggestive linkage to 2p11-q14 and 13q21-33. *American Journal of Psychiatry*. 2007;164(2):236-247. doi:10.1176/appi.ajp.164.2.236
257. Tondo L, Baldessarini RJ, Barbuti M, et al. Factors associated with single versus multiple suicide attempts in depressive disorders. *Journal of affective disorders*. 2020;277:306-312. doi:10.1016/j.jad.2020.08.021
258. Gournellis R, Tournikioti K, Touloumi G, et al. Psychotic (delusional) depression and completed suicide: a systematic review and meta-analysis. *Annals of general psychiatry*. 2018;17:39. doi:10.1186/s12991-018-0207-1
259. Musliner KL, Krebs MD, Albiñana C, et al. Polygenic Risk and Progression to Bipolar or Psychotic Disorders Among Individuals Diagnosed With Unipolar Depression in Early Life. *The American journal of psychiatry*. Published online July 2020:appiajp202019111195. doi:10.1176/appi.ajp.2020.19111195
260. Nelson B, Yuen K, Yung AR. Ultra high risk (UHR) for psychosis criteria: Are there different levels of risk for transition to psychosis? *Schizophrenia Research*. 2011;125(1):62-68. doi:10.1016/j.schres.2010.10.017
261. Carlson GA, Kotov R, Chang SW, Ruggero C, Bromet EJ. Early determinants of four-year clinical outcomes in bipolar disorder with psychosis. *Bipolar Disorders*. 2012;14(1):19-30. doi:10.1111/j.1399-5618.2012.00982.x
262. Jiménez-López E, Sánchez-Morla EM, Aparicio AI, et al. Psychosocial functioning in patients with psychotic and non-psychotic bipolar I disorder. A comparative study with individuals with schizophrenia. *Journal of Affective Disorders*. 2018;229(September 2017):177-185. doi:10.1016/j.jad.2017.12.094
263. Harrow M, Grossman LS, Herbener ES, Davies EW. Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders and mood-incongruent psychotic symptoms. *The British journal of psychiatry : the journal of mental science*. 2000;177:421-426.
264. Conus P, Abdel-Baki A, Harrigan S, Lambert M, McGorry PD. Schneiderian first rank symptoms predict poor outcome within first episode manic psychosis. *Journal of Affective Disorders*. 2004;81(3):259-268. doi:10.1016/j.jad.2003.09.003

265. Coryell W, Leon AC, Turvey C, Akiskal HS, Mueller T, Endicott J. The significance of psychotic features in manic episodes: A report from the NIMH collaborative study. *Journal of Affective Disorders*. 2001;67(1-3):79-88. doi:10.1016/S0165-0327(99)00024-5
266. Doyle AE, Wilens TE, Kwon A, et al. Neuropsychological functioning in youth with bipolar disorder. *Biological Psychiatry*. 2005;58(7):540-548. doi:10.1016/j.biopsych.2005.07.019
267. Lera-Miguel S, Andrés-Perpiñá S, Fatjó-Vilas M, Fañanás L, Lázaro L. Two-year follow-up of treated adolescents with early-onset bipolar disorder: Changes in neurocognition. *Journal of Affective Disorders*. 2015;172:48-54. doi:10.1016/j.jad.2014.09.041
268. Paya B, Rodriguez-Sanchez JM, Otero S, et al. Premorbid impairments in early-onset psychosis: differences between patients with schizophrenia and bipolar disorder. *Schizophrenia research*. 2013;146(1-3):103-110. doi:10.1016/j.schres.2013.01.029
269. Del Rey-Mejias A, Fraguas D, Diaz-Caneja CM, et al. Functional deterioration from the premorbid period to 2 years after the first episode of psychosis in early-onset psychosis. *European child & adolescent psychiatry*. 2015;24(12):1447-1459. doi:10.1007/s00787-015-0693-5
270. Bombin I, Mayoral M, Castro-Fornieles J, et al. Neuropsychological evidence for abnormal neurodevelopment associated with early-onset psychoses. *Psychological medicine*. 2013;43(4):757-768. doi:10.1017/S0033291712001535
271. Zabala A, Rapado M, Arango C, et al. Neuropsychological functioning in early-onset first-episode psychosis: Comparison of diagnostic subgroups. *European Archives of Psychiatry and Clinical Neuroscience*. 2010;260(3):225-233. doi:10.1007/s00406-009-0046-9
272. Torrent C, Reinares M, Martinez-Arán A, et al. Affective versus first-episode non-affective first-episode psychoses: A longitudinal study. *Journal of Affective Disorders*. 2018;238(March):297-304. doi:10.1016/j.jad.2018.06.005
273. Brissos S, Dias V V, Kapczinski F. Cognitive performance and quality of life in bipolar disorder. *Canadian journal of psychiatryRevue canadienne de psychiatrie*. 2008;53(8):517-524.
274. Hill SK, Reilly JL, Keefe RSE, et al. Neuropsychological Impairments in Schizophrenia and Psychotic Bipolar Disorder: Findings from the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study. *The American journal of psychiatry*. 2013;(November):1-10. doi:10.1176/appi.ajp.2013.12101298
275. Arango C, Fraguas D, Parellada M. Differential Neurodevelopmental Trajectories in Patients With Early-Onset Bipolar and Schizophrenia Disorders. *Schizophrenia Bulletin*. 2013;40(Suppl 2):S138-S146. doi:10.1093/schbul/sbt198
276. Nieto RG, Castellanos FX. A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. *Journal of Clinical Child and Adolescent Psychology*. 2011;40(2):266-280. doi:10.1080/15374416.2011.546049
277. Velthorst E, Fett AKJ, Reichenberg A, et al. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders.

American Journal of Psychiatry. 2017;174(11):1075-1085. doi:10.1176/appi.ajp.2016.15111419

278. Radua J, Ramella-Cravaro V, Ioannidis JPA, et al. What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*. 2018;17(1):49-66. doi:10.1002/wps.20490
279. Cannon TD, Kaprio J, Lönnqvist J, Huttunen M, Koskenvuo M. The genetic epidemiology of schizophrenia in a Finnish twin cohort: A population-based modeling study. *Archives of General Psychiatry*. 1998;55(1):67-74. doi:10.1001/archpsyc.55.1.67
280. Parnas J, Cannon TD, Jacobsen B, Schulsinger H, Schulsinger F, Mednick SA. Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. Results from the Copenhagen High-Risk Study. *Archives of General Psychiatry*. 1993;50(9):707-714.
281. Allardyce J, Leonenko G, Hamshere M, et al. Psychosis and the level of mood incongruence in Bipolar Disorder are related to genetic liability for Schizophrenia. *DoiOrg*. Published online 2017:160119. doi:10.1101/160119
282. Potash JB, Willour VL, Chiu YF, et al. The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. *American Journal of Psychiatry*. 2001;158(8):1258-1264. doi:10.1176/appi.ajp.158.8.1258
283. Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E, Pedersen CB. Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Archives of General Psychiatry*. 2010;67(8):822-829. doi:10.1001/archgenpsychiatry.2010.86
284. Gottesman II, Laursen TM, Bertelsen A, Mortensen PB. Severe mental disorders in offspring with 2 psychiatrically ill parents. *Archives of General Psychiatry*. 2010;67(3):252-257. doi:10.1001/archgenpsychiatry.2010.1
285. Goldstein JM, Buka SL, Seidman LJ, Tsuang MT. Specificity of Familial Transmission of Schizophrenia Psychosis Spectrum and Affective Psychoses in the New England Family Study's High-Risk Design. *Archives of General Psychiatry*. 2010;67(5):458-467. doi:10.1001/archgenpsychiatry.2010.38
286. Henriksen MG, Nordgaard J, Jansson LB. Genetics of Schizophrenia: Overview of Methods, Findings and Limitations. *Frontiers in Human Neuroscience*. 2017;11(June):1-9. doi:10.3389/fnhum.2017.00322
287. Lieberman JA, Perkins D, Belger A, et al. The Early Stages of Schizophrenia : Speculations on Pathogenesis, Pathophysiology, and Therapeutic Approaches. *Biological Psychiatry*. 2001;50:884-897.
288. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468(7321):187-193. doi:10.1038/nature09552
289. Kaymaz N, Van Os J. Editorial: Murray et al. (2004) revisited: Is bipolar disorder identical to schizophrenia without developmental impairment? *Acta Psychiatrica Scandinavica*. 2009;120(4):249-252. doi:10.1111/j.1600-0447.2009.01472.x
290. Demjaha A, MacCabe JH, Murray RM. How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. *Schizophrenia Bulletin*. 2012;38(2):209-214. doi:10.1093/schbul/sbr100
291. Murray RM, Sham P, Van Os J, et al. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia research*. 2004;71(2-3):405-416. doi:10.1016/j.schres.2004.03.002

292. Parellada M, Gomez-Vallejo S, Burdeus M, Arango C. Developmental Differences between Schizophrenia and Bipolar Disorder. *Schizophrenia Bulletin*. 2017;43(6):1176-1189. doi:10.1093/schbul/sbx126
293. Arango C, Rapado-Castro M, Reig S, et al. Progressive brain changes in children and adolescents with first-episode psychosis. *Archives of general psychiatry*. 2012;69(1):16-26. doi:10.1001/archgenpsychiatry.2011.150
294. de la Serna E, Baeza I, Andres S, et al. Comparison between young siblings and offspring of subjects with schizophrenia: clinical and neuropsychological characteristics. *Schizophrenia research*. 2011;131(1-3):35-42. doi:10.1016/j.schres.2011.06.015
295. de la Serna E, Baeza I, Toro J, et al. Relationship between clinical and neuropsychological characteristics in child and adolescent first degree relatives of subjects with schizophrenia. *Schizophrenia research*. 2010;116(2-3):159-167. doi:10.1016/j.schres.2009.09.001
296. Cardenas SA, Kassem L, Brotman MA, Leibenluft E, McMahon FJ. Neurocognitive functioning in euthymic patients with bipolar disorder and unaffected relatives: A review of the literature. *Neuroscience and biobehavioral reviews*. 2016;69:193-215. doi:10.1016/j.neubiorev.2016.08.002
297. Frías Á, Palma C, Farriols N. Neurocognitive impairments among youth with pediatric bipolar disorder: A systematic review of neuropsychological research. *Journal of Affective Disorders*. 2014;166:297-306. doi:10.1016/j.jad.2014.05.025
298. Tiihonen J, Haukka J, Henriksson M, et al. Premorbid intellectual functioning in bipolar disorder and schizophrenia: Results from a cohort study of male conscripts. *American Journal of Psychiatry*. 2005;162(10):1904-1910. doi:10.1176/appi.ajp.162.10.1904
299. Zammit S, Allebeck P, David AS et al. A Longitudinal Study of Premorbid IQ Score and Risk of Developing Schizophrenia,Bipolar Disorder, Severe Depression, and Other Nonaffective Psychoses. *Archives of general psychiatry*. 2004;61(4):354-360.
300. Reichenberg A, Weiser M, Rabinowitz J, et al. A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *American Journal of Psychiatry*. 2002;159(12):2027-2035. doi:10.1176/appi.ajp.159.12.2027
301. Ullman VZ, Levine SZ, Reichenberg A, Rabinowitz J. Real-world premorbid functioning in schizophrenia and affective disorders during the early teenage years: A population-based study of school grades and teacher ratings. *Schizophrenia Research*. 2012;136(1-3):13-18. doi:10.1016/j.schres.2012.01.021
302. Seidman LJ, Giuliano AJ, Smith CW, et al. Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside Adolescent High Risk Studies. *Schizophrenia bulletin*. 2006;32(3):507-524. doi:10.1093/schbul/sbj078
303. De la Serna E, Camprodon-Boadas P, Ilzarbe D, et al. Neuropsychological development in the child and adolescent offspring of patients diagnosed with schizophrenia or bipolar disorder: A two-year follow-up comparative study.

Progress in neuro-psychopharmacology & biological psychiatry. 2020;103:109972. doi:10.1016/j.pnpbp.2020.109972
304. Woodberry K a., Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: A meta-analytic review. *American Journal of Psychiatry*. 2008;165(May):579-587. doi:10.1176/appi.ajp.2008.07081242
305. Smith DJ, Anderson J, Zammit S, Meyer TD, Pell JP, Mackay D. Childhood IQ and risk of bipolar disorder in adulthood: prospective birth cohort study. *British Journal of Psychiatry Open*. 2015;1(1):74-80. doi:10.1192/bjpo.bp.115.000455
306. MacCabe JH, Lambe MP, Cnattingius S, et al. Excellent school performance at age 16 and risk of adult bipolar disorder: National cohort study. *British Journal of Psychiatry*. 2010;196(2):109-115. doi:10.1192/bjp.bp.108.060368
307. Koenen KC, Moffitt TE, Roberts AL, et al. Childhood IQ and adult mental disorders: A test of the cognitive reserve hypothesis. *American Journal of Psychiatry*. 2009;166(1):50-57. doi:10.1176/appi.ajp.2008.08030343
308. Cornblatt B a., Carrión RE, Addington J, et al. Risk factors for psychosis: Impaired social and role functioning. *Schizophrenia Bulletin*. 2012;38(6):1247-1257. doi:10.1093/schbul/sbr136
309. Schäfer I, Fisher HL, Schafer I, Fisher HL. Childhood trauma and posttraumatic stress disorder in patients with psychosis: Clinical challenges and emerging treatments. *Curr Opin Psychiatry*. 2011;24(6):514*518. doi:10.1097/YCO.0b013e32834b56c8
310. Varese F, Smeets F, Drukker M, et al. Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies. *Schizophrenia Bulletin*. 2012;38(4):661-671. doi:10.1093/schbul/sbs050
311. Romero S, Birmaher B, Axelson D, et al. Prevalence and correlates of physical and sexual abuse in children and adolescents with bipolar disorder. *Journal of Affective Disorders*. 2009;112(1-3):144-150. doi:10.1016/j.jad.2008.04.005
312. Matheson SL, Shepherd AM, Laurens KR, Carr VJ. A systematic meta-review grading the evidence for non-genetic risk factors and putative antecedents of schizophrenia. *Schizophrenia Research*. 2011;133(1-3):133-142. doi:10.1016/j.schres.2011.09.020
313. Moreno D, Moreno-Iñiguez M, Vigil D, et al. Obstetric complications as a risk factor for first psychotic episodes in childhood and adolescence. *European Child and Adolescent Psychiatry*. 2009;18(3):180-184. doi:10.1007/s00787-008-0692-x
314. Baeza I, Graell M, Moreno D, et al. Cannabis use in children and adolescents with first episode psychosis: Influence on psychopathology and short-term outcome (CAFEPS study). *Schizophrenia Research*. 2009;113(2-3):129-137. doi:10.1016/j.schres.2009.04.005
315. Sugranyes G, Flamarique I, Parellada E, et al. Cannabis use and age of diagnosis of schizophrenia. *European psychiatry : the journal of the Association of European Psychiatrists*. 2009;24(5):282-286. doi:10.1016/j.eurpsy.2009.01.002
316. Howes OD, Murray RM. 1 Europe PMC Funders Group Schizophrenia : an integrated sociodevelopmental-cognitive model. *Lancet*. 2014;383(9929):1677-1687. doi:10.1016/S0140-6736(13)62036-X.Schizophrenia

317. Howes OD, Montgomery AJ, Asselin MC, et al. Elevated striatal dopamine function linked to prodromal signs of schizophenia. *Archives of General Psychiatry*. 2009;66(1):13-20. doi:10.1001/archgenpsychiatry.2008.514
318. Cao H, Chén OY, Chung Y, et al. Cerebello-thalamo-cortical hyperconnectivity as a state-independent functional neural signature for psychosis prediction and characterization. *Nature communications*. 2018;9(1):3836. doi:10.1038/s41467-018-06350-7
319. Sugranyes G, de la Serna E, Ilzarbe D, et al. Brain structural trajectories in youth at familial risk for schizophrenia or bipolar disorder according to development of psychosis spectrum symptoms. *Journal of child psychology and psychiatry, and allied disciplines*. Published online September 2020. doi:10.1111/jcpp.13321
320. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine Alterations in Schizophrenia: An Updated Review. *Frontiers in Psychiatry*. 2019;10(December):1-12. doi:10.3389/fpsyt.2019.00892
321. Cannon M, Caspi A, Moffitt TE, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Archives of General Psychiatry*. 2002;59(5):449-456.
322. Zammit S, Odd D, Horwood J, et al. Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort. *Psychological Medicine*. 2009;39(09):1457. doi:10.1017/S0033291708005126
323. Newbury J, Arseneault L, Caspi A, Moffitt TE, Odgers CL, Fisher HL. Why Are Children in Urban Neighborhoods at Increased Risk for Psychotic Symptoms? Findings from a UK Longitudinal Cohort Study. *Schizophrenia Bulletin*. 2016;42(6):1372-1383. doi:10.1093/schbul/sbw052
324. Arseneault L, Cannon M, Fisher HL, et al. Childhood Trauma and Children's Emerging Psychotic Symptoms: A Genetically Sensitive Longitudinal Cohort Study. *American Journal of Psychiatry*. 2011;168(1):65-72. doi:10.1176/appi.ajp.2010.10040567
325. Van Os J, Hanssen M, Bak M, Bijl R V., Vollebergh W. Do urbanicity and familial liability coparticipate in causing psychosis? *American Journal of Psychiatry*. 2003;160(3):477-482. doi:10.1176/appi.ajp.160.3.477
326. Polanczyk G, Moffitt TE, Arseneault L, et al. Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Archives of general psychiatry*. 2010;67(4):328-338. doi:10.1001/archgenpsychiatry.2010.14
327. Hur YM, Cherny SS, Sham PC. Heritability of hallucinations in adolescent twins. *Psychiatry Research*. 2012;199(2):98-101. doi:10.1016/j.psychres.2012.04.024
328. Puig-Antich J, Ryan N. *The Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS)*. Western Psychiatric Institute and Clinic; 1986.
329. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Archives of General Psychiatry*. 1978;35(7):837-844.
330. Axelson D, Birmaher BJ, Brent D, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children

mania rating scale for children and adolescents. *Journal of child and adolescent psychopharmacology*. 2003;13(4):463-470. doi:10.1089/104454603322724850
331. Achenbach TM. *Integrative Guide to the CBCL/4-18, YSR, and TRF Profiles*.; 1991.
332. Hartman DE. Wechsler Adult Intelligence Scale IV (WAIS IV): return of the gold standard. *Applied Neuropsychology*. 2009;16(1):85-87. doi:10.1080/09084280802644466
333. Shaffer D, S. Gould M, Brasic J, et al. A Children's Global Assessment Scale (CGAS). *Archives of general psychiatry*. 1983;40(11):1228-1231.
334. APA: American Psychiatric Association. DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders. Published online 1994.
335. Leon AC, Solomon DA, Mueller TI, et al. A brief assessment of psychosocial functioning of subjects with bipolar I disorder: the LIFE-RIFT. Longitudinal Interval Follow-up Evaluation-Range Impaired Functioning Tool. *The Journal of nervous and mental disease*. 2000;188(12):805-812.
336. Hollingshead AB. Index of social status. In: Mangen DJ, Peterson WA, eds. *Research Instruments in Social Gerontology. Vol. 2: Social Roles and Participation*. ; 1982.
337. Williamson DE, Birmaher B, Ryan ND, et al. The stressful life events schedule for children and adolescents: development and validation. *Psychiatry research*. 2003;119(3):225-241.
338. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia bulletin*. 1982;8(3):470-484.
339. W. G. CGI: Clinical Global Impression Scale. In: Rockville MD, ed. *ECDEU Assessment Manual for Psychopharmacology, Revised National Institute of Mental Health*. ; 1976.
340. Hamilton M. Rating depressive patients. *The Journal of clinical psychiatry*. 1980;41(12 Pt 2):21-24.
341. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *The British journal of psychiatry : the journal of mental science*. 1978;133:429-435.
342. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *Journal of personality assessment*. 1996;67(3):588-597.
343. Pavuluri MN, Henry DB, Devineni B, Carbray JA, Birmaher B. Child mania rating scale: development, reliability, and validity. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006;45(5):550-560. doi:10.1097/01.chi.0000205700.40700.50
344. Wagner KD, Hirschfeld RM, Emslie GJ, Findling RL, Gracious BL, Reed ML. Validation of the Mood Disorder Questionnaire for bipolar disorders in adolescents. *The Journal of clinical psychiatry*. 2006;67(5):827-830.
345. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin*. 1987;13(2):261-276.
346. Miller TJ, McGlashan TH, Woods SW, et al. Symptom assessment in schizophrenic prodromal states. *The Psychiatric quarterly*. 1999;70(4):273-287.

347. Therneau T, Crowson C, Atkinson E. Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model. *Mayo Clinic*. Published online 2017:1-25.
348. Allardyce J, Leonenko G, Hamshere M, et al. Association Between Schizophrenia-Related Polygenic Liability and the Occurrence and Level of Mood-Incongruent Psychotic Symptoms in Bipolar Disorder. *JAMA Psychiatry*. 2017;75(1):28-35. doi:10.1001/jamapsychiatry.2017.3485
349. Zammit S, Horwood J, Thompson A, et al. Investigating if psychosis-like symptoms (PLIKS) are associated with family history of schizophrenia or paternal age in the ALSPAC birth cohort. *Schizophrenia Research*. 2008;104(1-3):279-286. doi:10.1016/j.schres.2008.04.036
350. Srinivasan R, Pearson RM, Johnson S, Lewis G, Lewis G. Maternal perinatal depressive symptoms and offspring psychotic experiences at 18 years of age: a longitudinal study. *The lancet Psychiatry*. 2020;7(5):431-440. doi:10.1016/S2215-0366(20)30132-2
351. Barkhuizen W, Pain O, Dudbridge F, Ronald A. Genetic overlap between psychotic experiences in the community across age and with psychiatric disorders. *Translational Psychiatry*. 2020;10(1). doi:10.1038/s41398-020-0765-2
352. Duffy A, Goodday S, Keown-Stoneman C, Grof P. The emergent course of bipolar disorder: Observations over two decades from the Canadian high-risk offspring cohort. *American Journal of Psychiatry*. 2019;176(9):720-729. doi:10.1176/appi.ajp.2018.18040461
353. Davies C, Segre G, Estradé A, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *The lancet Psychiatry*. 2020;7(5):399-410. doi:10.1016/S2215-0366(20)30057-2
354. Lee YH, Cherkerzian S, Seidman LJ, et al. Maternal Bacterial Infection During Pregnancy and Offspring Risk of Psychotic Disorders: Variation by Severity of Infection and Offspring Sex. *The American journal of psychiatry*. 2020;177(1):66-75. doi:10.1176/appi.ajp.2019.18101206
355. Matheson SL, Shepherd AM, Laurens KR, Carr VJ. A systematic meta-review grading the evidence for non-genetic risk factors and putative antecedents of schizophrenia. *Schizophrenia Research*. 2011;133(1-3):133-142. doi:10.1016/j.schres.2011.09.020
356. Horwood J, Salvi G, Thomas K, et al. IQ and non-clinical psychotic symptoms in 12-year-olds: Results from the ALSPAC birth cohort. *British Journal of Psychiatry*. 2008;193(3):185-191. doi:10.1192/bjp.bp.108.051904
357. Sugranyes G, De La Serna E, Borras R, et al. Clinical, Cognitive, and Neuroimaging Evidence of a Neurodevelopmental Continuum in Offspring of Probands with Schizophrenia and Bipolar Disorder. *Schizophrenia Bulletin*. 2017;43(6):1208-1219. doi:10.1093/schbul/sbx002
358. Axelson D, Goldstein B, Goldstein T, et al. Diagnostic Precursors to Bipolar Disorder in Offspring of Parents With Bipolar Disorder: A Longitudinal Study. *American Journal of Psychiatry*. 2015;172(7):638-646. doi:10.1176/appi.ajp.2014.14010035
359. Pries L, Guloksuz S, Have M, et al. Evidence That Environmental and Familial Risks for Psychosis Additively Impact a Multidimensional Subthreshold Psychosis Syndrome. *Schizophrenia Bulletin*. 2018;44(May):710-719. doi:10.1093/schbul/sby051

360. Bendall S, Jackson HJ, Hulbert CA, McGorry PD. Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. *Schizophrenia bulletin*. 2008;34(3):568-579. doi:10.1093/schbul/sbm121
361. Yung AR, Cotter J, Wood SJ, et al. Childhood maltreatment and transition to psychotic disorder independently predict long-term functioning in young people at ultra-high risk for psychosis. *Psychological Medicine*. 2015;45(16):3453-3465. doi:10.1017/S003329171500135X
362. Mcgrath JJ, Mclaughlin KA, Saha S, et al. The association between childhood adversities and subsequent first onset of psychotic experiences: a cross-national analysis of 23,998 respondents from 17 countries. *Psychological Medicine*. 2017;47(7):1230-1245. doi:10.1017/S0033291716003263.The
363. van Dam DS, van der Ven E, Velthorst E, Selten JP, Morgan C, de Haan L. Childhood bullying and the association with psychosis in non-clinical and clinical samples: a review and meta-analysis. *Psychological Medicine*. 2012;42(12):2463-2474. doi:10.1017/S0033291712000360
364. Kelleher I, Harley M, Lynch F, Arseneault L, Fitzpatrick C, Cannon M. Associations between childhood trauma, bullying and psychotic symptoms among a school-based adolescent sample. *The British journal of psychiatry : the journal of mental science*. 2008;193(5):378-382. doi:10.1192/bjp.bp.108.049536
365. Kelleher I, Keeley H, Corcoran P, et al. Childhood trauma and psychosis in a prospective cohort study: Cause, effect, and directionality. *American Journal of Psychiatry*. 2013;170(7):734-741. doi:10.1176/appi.ajp.2012.12091169
366. Fisher HL, Schreier A, Zammit S, et al. Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. *Schizophrenia bulletin*. 2013;39(5):1045-1055. doi:10.1093/schbul/sbs088
367. Zavos H, Freeman D, Haworth CM a, et al. Consistent etiology of severe, frequent psychotic experiences and milder, less frequent manifestations: a twin study of specific psychotic experiences in adolescence. *JAMA psychiatry*. 2014;71(9):1049-1057. doi:10.1001/jamapsychiatry.2014.994
368. Saha S, Varghese D, Slade T, et al. The association between trauma and delusional-like experiences. *Psychiatry Research*. 2011;189(2):259-264. doi:10.1016/j.psychres.2011.03.019
369. Schreier A, Wolke D, Thomas K, et al. Prospective study of peer victimization in childhood and psychotic symptoms in a nonclinical population at age 12 years. *Archives of General Psychiatry*. 2009;66(5):527-536. doi:10.1001/archgenpsychiatry.2009.23
370. Pan LA, Goldstein TR, Rooks BT, et al. The Relationship Between Stressful Life Events and Axis I Diagnoses Among Adolescent Offspring of Probands With Bipolar and Non-Bipolar Psychiatric Disorders and Healthy Controls: The Pittsburgh Bipolar Offspring Study (BIOS). *The Journal of clinical psychiatry*. 2017;78(3):e234-e243. doi:10.4088/JCP.15m09815
371. Zhang W, Zhu Y, Sun M, et al. Longitudinal Trajectories of Psychotic-Like Experiences and Their Relationship to Emergent Mental Disorders Among Adolescents: A 3-Year Cohort Study. *The Journal of clinical psychiatry*. 2019;80(4). doi:10.4088/JCP.18m12437
372. Welham J, Scott J, Williams G, et al. Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21-year birth

cohort study. *Psychological Medicine*. 2009;39(4):625-634. doi:DOI: 10.1017/S0033291708003760
373. Addington J, Penn D, Woods SW, Addington D, Perkins DO. Social functioning in individuals at clinical high risk for psychosis. *Schizophrenia research*. 2008;99(1-3):119-124. doi:10.1016/j.schres.2007.10.001
374. Tarbox SI, Pogue-Geile MF. Development of social functioning in preschizophrenia children and adolescents: a systematic review. *Psychological bulletin*. 2008;134(4):561-583. doi:10.1037/0033-2909.34.4.561
375. Gibson CM, Penn DL, Prinstein MJ, Perkins DO, Belger A. Social skill and social cognition in adolescents at genetic risk for psychosis. *Schizophrenia research*. 2010;122(1-3):179-184. doi:10.1016/j.schres.2010.04.018
376. Correll CU, Penzner JB, Lencz T, et al. Early identification and high-risk strategies for bipolar disorder. *Bipolar Disord*. 2007;9(4):324-338. doi:10.1111/j.1399-5618.2007.00487.x
377. Conusa P, Wardb J, Hallam KTK, et al. The proximal prodrome to first episode mania--a new target for early intervention. *Bipolar Disorders*. 2008;10(5):555-565. doi:10.1111/j.1399-5618.2008.00610.x
378. Bechdolf A, Nelson B, Cotton SM, et al. A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults. *Journal of affective disorders*. Published online July 7, 2010. doi:10.1016/j.jad.2010.06.016
379. Scott J, Marwaha S, Ratheesh A, et al. Bipolar At-Risk Criteria: An Examination of Which Clinical Features Have Optimal Utility for Identifying Youth at Risk of Early Transition from Depression to Bipolar Disorders. *Schizophrenia Bulletin*. 2017;43(4):737-744. doi:10.1093/schbul/sbw154
380. Findling RL, Youngstrom EA, McNamara NK, et al. Early symptoms of mania and the role of parental risk. *Bipolar Disorders*. 2005;7(6):623-634. doi:10.1111/j.1399-5618.2005.00260.x
381. Cannon M, Jones P, Gilvarry C, et al. Premorbid social functioning in schizophrenia and bipolar disorder: similarities and differences. *The American journal of psychiatry*. 1997;154(11):1544-1550. doi:10.1176/ajp.154.11.1544
382. Petti T, Reich W, Todd RD, et al. Psychosocial variables in children and teens of extended families identified through bipolar affective disorder probands. *Bipolar disorders*. 2004;6(2):106-114.
383. De la Serna E, Ilzarbe D, Sugranyes G, et al. Lifetime psychopathology in child and adolescent offspring of parents diagnosed with schizophrenia or bipolar disorder: a 2-year follow-up study. *European Child and Adolescent Psychiatry*. Published online 2020. doi:10.1007/s00787-020-01500-z
384. Linnen AM, aan het Rot M, Ellenbogen MA, et al. Interpersonal functioning in adolescent offspring of parents with bipolar disorder. *Journal of affective disorders*. 2009;114(1-3):122-130. doi:10.1016/j.jad.2008.06.016
385. Reichart CG, van der Ende J, Wals M, et al. Social functioning of bipolar offspring. *Journal of Affective Disorders*. 2007;98(3):207-213. doi:10.1016/j.jad.2006.07.018
386. Gyulai L, Bauer MS, Marangell LB, et al. Correlates of functioning in bipolar disorder. *Psychopharmacology bulletin*. 2008;41(4):51-64.
387. Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E. Functional impairment in the remission phase of bipolar disorder. *Bipolar disorders*. 2005;7(3):281-285. doi:10.1111/j.1399-5618.2005.00207.x

388. Tillman R, Geller B, Klages T, Corrigan M, Bolhofner K, Zimerman B. Psychotic phenomena in 257 young children and adolescents with bipolar I disorder: Delusions and hallucinations (benign and pathological). *Bipolar Disorders*. 2008;10(1):45-55. doi:10.1111/j.1399-5618.2008.00480.x
389. Jairam R, Srinath S, Girimaji SC, Seshadri SP. A prospective 4-5 year follow-up of juvenile onset bipolar disorder. *Bipolar Disorders*. 2004;6(5):386-394. doi:10.1111/j.1399-5618.2004.00149.x
390. Swann AC, Daniel DG, Kochan LD, Wozniak PJ, Calabrese JR. Psychosis in mania: specificity of its role in severity and treatment response. *The Journal of clinical psychiatry*. 2004;65(6):825-829.
391. Shapiro J, Timmins V, Swampillai B, et al. Correlates of psychiatric hospitalization in a clinical sample of Canadian adolescents with bipolar disorder. *Comprehensive Psychiatry*. 2014;55(8):1855-1861. doi:10.1016/j.comppsych.2014.08.048
392. Mazzarini L, Colom F, Pacchiarotti I, et al. Psychotic versus non-psychotic bipolar II disorder. *Journal of affective disorders*. 2010;126:55-60. doi:10.1016/j.jad.2010.03.028
393. McElroy SL, Altshuler L, Suppes T, Keck Jr. PE, Frye MA, Denicoff KD et al. Axis I Psychiatric Comorbidity and Its Relationship to Historical Illness Variables in 288 Patients With Bipolar Disorder. *American Journal of Psychiatry*. 2001;158(3):420-426. doi:10.1176/appi.ajp.158.3.420
394. Shapiro J, Timmins V, Swampillai B, et al. Correlates of psychiatric hospitalization in a clinical sample of Canadian adolescents with bipolar disorder. *Comprehensive psychiatry*. 2014;55(8):1855-1861. doi:10.1016/j.comppsych.2014.08.048
395. Paul E. Keck, M.D.; Susan L. McElroy, M.D.; Stephen M. Strakowski, M.D.; Scott A. West, M.D.; Kenji W. Sax, Ph.D.; John M. Hawkins, M.D.; Michelle L. Bourne, B.A.; Patrick Haggard BS. 12-Month Outcome of Patients With Bipolar Disorder Following Hospitalization for a Manic or Mixed Episode. *Am J Psychiatry*. 1998;155(May):646-652. doi:10.1176/foc.1.1.44
396. MacQueen GM, Young LT, Joffe RT. A review of psychosocial outcome in patients with bipolar disorder. *Acta Psychiatrica Scandinavica*. 2001;103(3):163-170.
397. Judd LL, Schettler PJ, Solomon DA, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. *Journal of affective disorders*. 2008;108(1-2):49-58. doi:DOI: 10.1016/j.jad.2007.06.014
398. MacQueen GM, Young LT, Robb JC, Cooke RG, Joffe RT. Levels of functioning and well-being in recovered psychotic versus nonpsychotic mania. *Journal of affective disorders*. 1997;46(1):69-72.
399. Zhang H, Wisniewski SR, Bauer MS, Sachs GS, Thase ME, Investigators STEP for BD (STEP-B. Comparisons of perceived quality of life across clinical states in bipolar disorder: data from the first 2000 Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) participants. *Comprehensive psychiatry*. 2006;47(3):161-168. doi:10.1016/j.comppsych.2005.08.001
400. Carlson GA, Kotov R, Chang SW, Ruggero C, Bromet EJ. Early determinants of four-year clinical outcomes in bipolar disorder with psychosis. *Bipolar Disorders*. Published online 2012. doi:10.1111/j.1399-5618.2012.00982.x

401. Martinez-Aran A, Torrent C, Tabares-Seisdedos R, et al. Neurocognitive impairment in bipolar patients with and without history of psychosis. *The Journal of clinical psychiatry*. 2008;69(2):233-239.
402. Strakowski SM, Williams JR, Sax KW, Fleck DE, DelBello MP, Bourne ML. Is impaired outcome following a first manic episode due to mood-incongruent psychosis? *Journal of Affective Disorders*. 2000;61(1-2):87-94. doi:10.1016/S0165-0327(99)00192-5
403. Wozniak J, Faraone SV, Martelon M, Mckillop HN, Biederman J. Further Evidence for Robust Familiality of Pediatric Bipolar-I Disorder: Results from a Very Large Controlled Family Study of Pediatric Bipolar-I Disorder and a Meta-Analysis. *J Clin Psychiatry*. 2012;73(10):1328-1334. doi:10.4088/JCP.12m07770
404. Birmaher B, Axelson D, Goldstein BI, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: The course and outcome of bipolar youth (COBY) study. *American Journal of Psychiatry*. 2009;166(7):795-804. doi:10.1176/appi.ajp.2009.08101569
405. Strober M. Relevance of early age-of-onset in genetic studies of bipolar affective disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1992;31(4):606-610.
406. Faraone S V, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. *Biological Psychiatry*. 2003;53(11):970-977.
407. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: An analysis from the global burden of disease study 2010. *PLoS ONE*. 2015;10(2):1-14. doi:10.1371/journal.pone.0116820
408. Björkenstam E, Cheng S, Burström B, Pebley AR, Björkenstam C, Kosidou K. Association between income trajectories in childhood and psychiatric disorder: a Swedish population-based study. *Journal of Epidemiology and Community Health*. Published online 2017:jech-2016-208513. doi:10.1136/jech-2016-208513
409. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *The Journal of clinical psychiatry*. 2009;70(8):1078-1090. doi:10.4088/JCP.08r04505
410. Mehrhof SZ, Fiksenbaum LM, Bettridge AM, Goldstein BI. Markedly increased prevalence of migraine headaches in adolescents with bipolar disorder. *Bipolar disorders*. Published online July 2020. doi:10.1111/bdi.12972
411. Hayes JF, Miles J, Walters K, King M, Osborn DPJ. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatrica Scandinavica*. 2015;131(6):417-425. doi:10.1111/acps.12408
412. Statistical Bulletin 2017 — prevalence of drug use | www.emcdda.europa.eu. Accessed December 29, 2017. http://www.emcdda.europa.eu/data/stats2017/gps
413. Hirneth SJ, Hazell PL, Hanstock TL, Lewin TJ. Bipolar disorder subtypes in children and adolescents: demographic and clinical characteristics from an Australian sample. *Journal of affective disorders*. 2015;175:98-107. doi:10.1016/j.jad.2014.12.021

414. Geller B, Tillman R, Bolhofner K, Zimerman B. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Archives of General Psychiatry*. 2008;65(10):1125-1133. doi:10.1001/archpsyc.65.10.1125
415. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Development and psychopathology*. 2006;18(4):1023-1035. doi:10.1017/S0954579406060500
416. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Archives of general psychiatry*. 2006;63(10):1139-1148. doi:10.1001/archpsyc.63.10.1139
417. Birmaher B. Longitudinal course of pediatric bipolar disorder. *The American Journal of Psychiatry*. 2007;164(4):537-539. doi:10.1176/appi.ajp.164.4.537
418. Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disorders*. 2001;3(4):202-210. doi:10.1034/j.1399-5618.2001.30405.x
419. Srinath, S., Reddy, Y.C., Girimaji, S.C., Seshadri, S.P., Subbakrishna DK. A prospective study of bipolar disorder in children and adolescents from India. *Acta Psychiatr*. 1998;Scand(98):437–442.
420. Jairam R, Srinath S, Girimaji SC, Seshadri SP. A prospective 4-5 year follow-up of juvenile onset bipolar disorder. *Bipolar Disord*. 2004;6(5):386-394. doi:10.1111/j.1399-5618.2004.00149.x
421. Romero S, DelBello MP, Soutullo CA, Stanford K, Strakowski SM. Family environment in families with versus families without parental bipolar disorder: A preliminary comparison study. *Bipolar Disorders*. 2005;7(6):617-622. doi:10.1111/j.1399-5618.2005.00270.x
422. Romero S, Birmaher B, Axelson DA, et al. Negative Life Events in Children and Adolescents with Bipolar Disorder. *J Clin Psychiatry*. 2010;70(10):1452-1460. doi:10.4088/JCP.08m04948gre.Negative
423. Neria Y, Bromet EJ, Carlson GA, Naz B. Assaultive trauma and illness course in psychotic bipolar disorder: findings from the Suffolk county mental health project. *Acta psychiatrica Scandinavica*. 2005;111(5):380-383. doi:10.1111/j.1600-0447.2005.00530.x
424. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *The Lancet*. 2016;387(10027):1561-1572. doi:10.1016/S0140-6736(15)00241-X
425. Vieira IS, Pedrotti Moreira F, Mondin TC, et al. Childhood trauma and bipolar spectrum: a population-based sample of young adults. *Trends in psychiatry and psychotherapy*. 2020;42(2):115-121. doi:10.1590/2237-6089-2019-0046
426. Andreu Pascual M, Levenson JC, Merranko J, et al. The Effect of Traumatic Events on the Longitudinal Course and Outcomes of Youth with Bipolar Disorder. *Journal of Affective Disorders*. 2020;274:126-135. doi:10.1016/j.jad.2020.05.131
427. Martland N, Martland R, Cullen AE, Bhattacharyya S. Are adult stressful life events associated with psychotic relapse? A systematic review of 23 studies. *Psychological medicine*. 2020;50(14):2302-2316. doi:10.1017/S0033291720003554
428. Goldstein TR, Birmaher B, Axelson D, et al. Psychosocial functioning among bipolar youth. *Journal of affective disorders*. 2009;114(1-3):174-183. doi:10.1016/j.jad.2008.07.001

429. Birmaher B, Axelson D, Goldstein B, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *The American Journal of Psychiatry*. 2009;166(7):795-804. doi:10.1176/appi.ajp.2009.08101569
430. Delbello MP, Hanseman D, Adler MA, Fleck DE, Strakowski SM. 12-Month Outcome of Patients With Bipolar Disorder Following Hospitalization for a Manic or Mixed Episode. *Am J Psychiatry*. 2007;164(April):582-590. doi:10.1176/foc.1.1.44
431. Geller B, Zimerman B, Williams M, et al. Six-month stability and outcome of a prepubertal and early adolescent bipolar disorder phenotype. *Journal of child and adolescent psychopharmacology*. 2000;10(3):165-173. doi:10.1089/10445460050167278
432. Best MW, Bowie CR, Naiberg MR, Newton DF, Goldstein BI. Neurocognition and psychosocial functioning in adolescents with bipolar disorder. *Journal of Affective Disorders*. 2017;207(June 2016):406-412. doi:10.1016/j.jad.2016.09.063
433. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000;39(12):1543-1548.
434. Biederman J, Faraone S V, Wozniak J, et al. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *Journal of Psychiatric Research,*. 2005;39(6):611-622.
435. Torres I, Garriga M, Sole B, et al. Functional impairment in adult bipolar disorder with ADHD. *Journal of Affective Disorders*. 2017;227(September 2017):117-125. doi:10.1016/j.jad.2017.09.037
436. Martinez-Aran A, Vieta E, Torrent C, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar disorders*. 2007;9(1-2):103-113. doi:10.1111/j.1399-5618.2007.00327.x