UNIVERSITAT DE BARCELONA

The Long-Term Clinical and Functional Course of Borderline Personality Disorder

Evolución clínica y funcional del trastorno límite de personalidad a largo plazo

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A Irene y Miguel

A mis padres y hermano

A Per

We're on the borderline

Caught between the tides of pain and rapture

Then I saw the time

Watched it speedin' by like a train

Like a train

Will I be known and loved?

Is there one that I trust?

"Borderline"

Lyrics by Tame Impala

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CONTENTS

ABSTRACT

The present thesis aims to extend our knowledge on the long-term clinical and functional course of borderline personality disorder (BPD) and explore potential predictors of several long-term outcomes. To this end, we conducted a 10-year prospective study in a Spanish sample of BPD patients and, afterwards, we carried out a systematic review and meta-analysis of prospective studies that had followed BPD clinical samples over five years and beyond, which included our previous follow-up study.

At 10 years, over half of patients in our Spanish sample had achieved remission from BPD and significant improvements were observed in all BPD symptomatic domains, suicidal behavior and affective symptoms, with the exception of the cognitive domain that remained steady at a moderate level of severity over time. Neuroticism, Impulsivity and Aggression-hostility tended to normalization, whereas Activity and Sociability tended to impairment at follow-up. Comorbidity with other personality disorders (PDs) remained high, particularly with avoidant and obsessive-compulsive PDs. There was high comorbidity with affective, anxious and substance abuse/dependence disorders at follow-up. Regarding physical health, one third of patients reported to suffer from two or more medical illnesses at 10 years. Despite the symptomatic amelioration in some areas, there was only a slight improvement in social and occupational functioning over time. The rate of psychiatric hospitalization decreased substantially at follow-up. By contrast, over 60% of patients still received psychiatric treatment and individual therapy, and 10% of them were frequently treated by a general practitioner. Besides, there was an increase in the percentage of patients that attended any rehabilitation service and received a disability pension or another social benefit at follow-up.

In our follow-up study, a younger age of first BPD diagnosis showed a trend to be associated with a higher remission rate and, to a lesser extent, with greater improvements in the affective domain of the disorder. On the other hand, patients with an earlier BPD diagnosis did not show higher improvements either in the impulsive, cognitive and interpersonal domains of the disorder or in social functioning over time than those with a delayed one. However, patients with an earlier BPD diagnosis did not show higher improvement in social functioning over time than those with a delayed one. Additionally, we analyzed several predictors of the long-term quality of life (QOL) in our sample. Higher severity of childhood trauma affected negatively the long-term QOL, after controlling for initial BPD symptomatology and social functioning. Achieving remission from BPD was associated with a better QOL at follow-up. Physical health problems only impacted negatively on the QOL of those patients with a chronic BPD diagnosis.

Findings from our meta-analysis confirm the favorable prognosis of BPD in the long-term, providing evidence of its generalization in a variety of populations and assistance contexts. This is indicated by a mean remission rate of 60% among studies and improvements in depression and social/global functioning, with medium effect sizes, at five years of follow-up and beyond. However, the mean suicide rate was 4%, suggesting a high risk of suicide for these patients in the long-term. In terms of potential moderators of outcome, a younger age was correlated to a higher remission rate from BPD in the long-term. Female gender was associated with lower functional improvement. Treatment characteristics did not show significant effects on the long-term outcome in treatment-seeking BPD samples. Despite that, those samples who received controlled treatments, both specialized therapies and treatment as usual (TAU), and during a longer period appeared to be more likely to present greater functional improvement in the long-term, although this trend did not reach statistical significance.

To sum up, findings suggest that the course of BPD is characterized by symptomatic amelioration in the long-term, but with persistent symptomatic manifestations and a variety of psychiatric and medical comorbidities that might be suffered by a part of these patients. Social and global functioning seem to improve slightly over time, with some patients presenting disabling functional impairments in the long-term. A younger age and an earlier BPD diagnosis appear to be associated with higher likelihood of remission from BPD. Female gender seems to be correlated to more limited functional improvement. The severity of childhood trauma, the chronicity of BPD and poor physical health seem to affect negatively the long-term QOL of these patients. More evidence on the long-term effects of treatments is needed. Adapting treatments to gender differences and particularities in every stage of the lifespan, such as adolescence or the elderly, is recommended.

RESUMEN

El propósito de la presente tesis doctoral es profundizar en el conocimiento de la evolución a largo plazo del trastorno límite de personalidad (TLP), atendiendo tanto a variables psicopatológicas como de funcionamiento social y calidad de vida, y explorar los efectos de diversos predictores en dicha evolución.

Para ello, se llevó a cabo primeramente un estudio prospectivo a 10 años en una muestra clínica española de pacientes con TLP. En el seguimiento a 10 años, más de la mitad de los pacientes habían alcanzado la remisión del trastorno y se observaron mejoras significativas en todos los dominios sintomáticos del TLP, conducta suicida y síntomas afectivos, a excepción del área cognitiva que se mantuvo en un nivel moderado de severidad clínica. Los rasgos dimensionales de Neuroticismo, Impulsividad y Agresión-Hostilidad tendieron a la normalización, mientras que los de Actividad y Sociabilidad empeoraron en el seguimiento. La comorbilidad con otros trastornos de personalidad (TP) se mantuvo elevada, especialmente con los TP evitativo y obsesivo-compulsivo. Así mismo, se observó una alta comorbilidad con trastornos afectivos, de ansiedad y de abuso/dependencia de substancias en el seguimiento. En cuanto a la salud general, un tercio de la muestra informó sufrir polipatología médica a los 10 años. Pese a la recuperación clínica observada en algunas áreas, el nivel de funcionamiento social y ocupacional mostró únicamente una leve mejoría a largo plazo. Respecto al uso de recursos sanitarios y sociales, se redujo sustancialmente el porcentaje de pacientes que requirieron algún ingreso psiquiátrico en el seguimiento. En cambio, a los 10 años, más del 60% de los pacientes continuaban recibiendo tratamiento psiquiátrico y psicoterapia individual y el 10% acudían con frecuencia a su médico de atención primaria. Además,

aumentó el uso de servicios de rehabilitación y el número de pacientes que recibían una pensión por incapacidad u otra ayuda social.

En cuanto a potenciales predictores del curso a largo plazo en la muestra española, se observaron efectos positivos de recibir el diagnóstico de TLP por primera vez a edades más tempranas en incrementar la tasa de remisión del TLP y, en menor medida, en la mejoría de los síntomas afectivos del trastorno, en comparación con un diagnóstico más tardío. En cambio, los pacientes con un diagnóstico temprano mostraron una mejoría similar que aquellos con un diagnóstico tardío en las áreas sintomáticas impulsiva, cognitiva e interpersonal del trastorno, así como en el funcionamiento social a largo plazo. Por otro lado, una mayor severidad de experiencias traumáticas sufridas en la infancia mostró un impacto negativo en la calidad de vida de estos pacientes a largo plazo, tras controlar el nivel basal de sintomatología TLP y de funcionamiento social. En cambio, haber alcanzado la remisión del TLP a lo largo del seguimiento estuvo asociado significativamente con una mejor calidad de vida a largo plazo. Así mismo, sufrir problemas de salud general tuvo un impacto negativo significativo únicamente en la calidad de vida de los pacientes con un diagnóstico TLP crónico.

En un segundo momento, se realizó una revisión sistemática y meta-análisis de los estudios prospectivos a largo plazo en muestras con TLP publicados hasta el año 2017, incluyendo nuestro estudio en población española. Los resultados obtenidos confirman el pronóstico favorable del TLP a largo plazo, aportando evidencia de su generalización en diversas poblaciones y contextos asistenciales. Este curso favorable viene indicado por una tasa media de remisión del trastorno del 60% y mejoras moderadas en sintomatología depresiva y funcionamiento social y general, que fueron observadas en las diferentes muestras tras periodos de seguimiento de cinco años o más. No obstante, la tasa de suicidio media se situó en el 4%, lo que indica un riesgo elevado de muerte por

suicidio de estos pacientes a largo plazo. En cuanto a posibles predictores del curso, una edad media más joven en las muestras de pacientes con TLP se asoció a una mayor probabilidad de remisión del trastorno a largo plazo y un mayor porcentaje de mujeres, a una mejoría más leve en su funcionamiento social/general. El tratamiento psicoterapéutico recibido durante el seguimiento no mostró efectos significativos en la evolución a largo plazo. No obstante, se observó una tendencia a una mayor mejora funcional en aquellos pacientes que recibieron tratamientos controlados experimentalmente y de mayor duración al inicio del seguimiento, tanto alguna terapia especializada como el tratamiento habitual, comparado con aquéllos en estudios naturalistas. En concreto, una más larga duración de estos tratamientos podría estar asociada a una mayor mejoría en sintomatología depresiva y funcionamiento a largo plazo.

En conclusión, los resultados que componen la tesis indican que el curso del TLP está caracterizado por una mejoría sintomática a largo plazo, aunque con presentaciones crónicas del trastorno y una comorbilidad psiquiátrica y médica elevada en una parte de los pacientes. Por otro lado, el funcionamiento social/general parece mejorar de forma más atenuada a largo plazo, aunque observándose deficiencias funcionales incapacitantes en algunos pacientes. Ser más joven y recibir un diagnóstico de TLP más tempranamente se ha mostrado asociado a una mayor probabilidad de remisión del trastorno. Ser mujer se ha asociado a una disminución de las mejoras en ajuste social a largo plazo. Las experiencias traumáticas tempranas, la cronicidad del trastorno y otras enfermedades médicas comórbidas han mostrado un efecto perjudicial en la calidad de vida de estos pacientes a largo plazo. Las características de los tratamientos recibidos durante el seguimiento no mostraron un efecto diferencial significativo en la evolución a largo plazo de pacientes con TLP que buscan tratamiento. Recibir tratamientos controlados y más

duraderos parece impactar favorablemente en la mejora funcional y de la sintomatología depresiva a largo plazo. Se requiere más estudios longitudinales que investiguen la eficacia a largo plazo de los tratamientos disponibles. Así mismo, sería recomendable ofrecer tratamientos adaptados a las diferencias de género y a las diversas etapas del ciclo vital en las que se puede sufrir el trastorno, aunque sea menos frecuentemente, como la adolescencia temprana o la vejez.

ABBREVIATIONS

AMPD: Alternative Model for Personality Disorders

ADHD: Attention Deficit Hyperactivity Disorder

BDHI: Buss-Durkee Hostility Inventory

BPD: Borderline personality disorder

CBT: Cognitive-Behavioral Therapy

CGI/-S: Clinical Global Impression/-Severity

CLPS: Collaborative Longitudinal Personality Disorder Study

CTQ: Childhood Trauma Questionnaire

DBT: Dialectical-Behavior Therapy

DD: Delayed BPD Diagnosis

DIB/-R: Diagnostic Interview for Borderlines/-Revised

DSM: Diagnostic and Statistical Manual of Mental Disorders

ED: Early BPD Diagnosis

FFM: Five Factor Model

GAF: Global Assessment of Functioning

GAS: Global Assessment Scale

HDRS: Hamilton Depression Rating Scale

HSRS: Health-Sickness Rating Scale

ICD: International Classification of Diseases

MBT: Mentalization Based Therapy

MDD: Major Depressive Disorder

MINI: Mini International Neuropsychiatric Interview

MSAD: McLean Study of Adult Development

MQLI: Multicultural Quality of Life Index

PD: Personality Disorder

PTSD: Post-Traumatic Stress Disorder

QOL: Quality of Life

SASS: Social Adaptation Self-Evaluation Scale

SAQOR: Systematic assessment of quality in observational research

SCID-II: Structured Clinical Interview for DSM-IV - Axis II

SUD: Substance Use Disorder

TAU: Treatment as usual

ZKPQ: Zuckerman-Kuhlman Personality Questionnaire

WHO: World Health Organization

PROLOGUE

The present thesis is comprised of two research projects which were carried out under the supervision of Prof. Arturo Bados, as main thesis director, and the approval of the Doctorate Commission in the Faculty of Psychology at the University of Barcelona.

Firstly, a 10-year prospective naturalistic study was conducted in collaboration with the BPD Unit at the Hospital de la Santa Creu i Sant Pau and under the supervision of Dr. Joaquim Soler as thesis co-director. The empirical phase of this study lasted one year between 2012 and 2013, when a Spanish sample of patients with BPD that had participated in a previous clinical trial was reassessed 10 years later (Soler et al., 2005). This research work has been presented in several congresses until now and main findings were published in 2017 in the *Journal of Personality Disorders.*

A predoctoral stay was due between February and April in 2015 in the Laboratory for the Study of Adult Development at McLean Hospital in Belmont, which was financially supported by a research grant from the Fundació Montcelimar. During this stay, the empirical research of the 10-year follow-up study was supervised by Prof. Zanarini.

Secondly, a meta-analytic review of prospective studies on the long-term course of BPD was conducted at the University of Barcelona, which included the former follow-up study. This meta-analysis has been recently published in the *European Psychiatry*.

To sum up, the main findings that comprise the present thesis have been reported in the following articles:

Original Research 1: 10-year follow-up study

ARTICLE 1

Álvarez-Tomás, I., Soler, J., Bados, A., Martín-Blanco, A., Elices, M., Feliu-Soler, A., Pérez, V., & Pascual, J.C. (2017). Long-term course of borderline personality disorder: a prospective 10-year follow-up study. *Journal of Personality Disorders, 31*(5), 590-605.

Preliminary data and additional results of this study were also reported in the following posters and communications:

Poster 1:

Álvarez-Tomás, I, Soler, J., Martín-Blanco, A., Feliu, A., Elices, M., Pérez, V., & Pascual, J.C. (2013, February). *Evolución a largo plazo del Trastorno Límite de Personalidad: Datos preliminares de un estudio de seguimiento a 10 años en una muestra española.* [Long-term course of Borderline Personality Disorder: Preliminary data of a 10-year follow-up study in a Spanish sample.] Poster presented at the V Simpósium en Trastorno Límite de Personalidad, Hospital General de Catalunya, Barcelona.

Preliminary results on clinical and functional features shown by a part of the follow-up sample, while continuing the recruitment process of the study.

Communication 1:

Álvarez-Tomás, I. (2014, April). *Evolución del TLP a largo plazo: Estudio de seguimiento a 10 años.* [The long-term course of BPD: a 10-year follow-up study.] Communication presented at the X Congreso Nacional de Trastornos de la Personalidad, Barcelona. See it on: http://hdl.handle.net/2445/132363.

Results on BPD remission (by the Diagnostic Interview for Borderlines-Revised, DIB-R), main clinical indexes and social functioning in the overall follow-up sample.

Communication 2:

Álvarez-Tomás, I. (2014, October). *Differential long-term course related to early and delayed diagnosis of borderline personality disorder*. Communication presented at the 3rd International Congress on Borderline Personality Disorder and Allied Disorders, Rome. See it on: http://hdl.handle.net/2445/132358.

Results on the effects of the age when BPD was first diagnosed on the long-term course of BPD symptomatology, BPD remission (by DIB-R), suicidality and social functioning.

Poster 2:

Álvarez-Tomás, I., Bados, A., Soler, J., Martín-Blanco, A., Feliu, A., Elices, M., Pérez, V., & Pascual, J.C. (2015, March). *Predictors of the Long-Term Quality of Life in BPD Patients: A 10-year Follow-up Study*. Poster presented at the 3rd Annual NASSPD Conference, Boston, Belmont. See it on: http://hdl.handle.net/2445/132366.

Results on the predictive effects of age, childhood trauma, initial BPD symptoms, dimensional personality traits, and social functioning on the QOL of BPD patients in the long-term.

Poster 3:

Álvarez-Tomás, I., Soler, J., Bados, A., Martín-Blanco, A., Elices, M., & Pascual, J.C. (2016, November). *Early and delayed BPD diagnosis and its relationship to long-term remission in adulthood*. Poster presented at the 3rd CORE Seminar "Creixent en salut mental: La salut mental en les primeres etapes de la vida", Hospital Parc Taulí, Sabadell, Barcelona. See it on: http://hdl.handle.net/2445/132367.

Results on the effects of an early or delayed BPD diagnosis on long-term BPD remission (by DIB-R and Structured Clinical Interview for DSM-IV-Axis II, SCID-II).

Poster 4:

Álvarez-Tomás, I., Bados, A., Soler, J., Martín-Blanco, A., Elices, M., Carmona, C., Domínguez-Clavé, E., & Pascual, J.C. (2018, September). *Physical health, health care utilization and long-term quality of life in remitted and non-remitted BPD patients: A 10-year follow-up study in a Spanish sample*. Poster presented at the 5th International Congress on Borderline Personality Disorder and Allied Disorders, Sitges, Barcelona. See it on: http://hdl.handle.net/2445/132368.

Results on prevalence of physical illnesses and health care utilization at 10-year follow-up, and the relative impact of BPD remission and physical health condition on the long-term QOL of subjects diagnosed with BPD.

Original Research 2: Meta-analysis of long-term prospective studies

ARTICLE 2

Álvarez-Tomás, I., Ruiz, J., Guilera, G., & Bados, A. (2019). Long-term clinical and functional course of borderline personality disorder: a meta-analysis of prospective studies. *European Psychiatry*, *56,* 75-83.

Preliminary findings of this meta-analytic review were also reported in the following communications:

Communication 3:

Álvarez-Tomás, I., Bados, A., Guilera, G., & Ruiz, J. (2016, September). *Prospective long-term course of Borderline Personality Disorder in adulthood: A systematic review.* Communication presented at the 4th International Congress on Borderline Personality Disorder and Allied Disorders, Vienna. See it on: http://hdl.handle.net/2445/132362.

Preliminary findings on long-term remission in BPD adults and the effect of potential moderators on its course, by the meta-analytic review of literature published within the period 1990-2015.

Communication 4:

Álvarez-Tomás, I., Bados, A., Ruiz, J., Guilera, G. (2017, September). *Borderline personality disorder and functioning in the long term: A meta-analysis of prospective studies*. Communication presented at the XV ISSPD Congress "Personality disorder, functioning and health", Heidelberg. See it on: http://hdl.handle.net/2445/132364.

Preliminary findings on social and global functioning of BPD adults in the long-term and the effect of potential moderators on its course, by the meta-analytic review of literature published within the period 1990-2015.

1. INTRODUCTION

1.1. <u>BORDERLINE PERSONALITY DISORDER: A DIAGNOSIS IN PROCESS</u>

BPD is receiving increasing attention in the scientific literature since the disorder was given official status in the Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III; American Psychiatric Association, APA, 1980), due to its clinical complexity and its impact on the general health, functional level and QOL of those who suffer it (Zanarini, 2012; IsHak et al., 2013; Doering, 2019). Besides, new therapeutic approaches have recently emerged, which offers a promising context for the treatment of this disorder and promotes new research into the field (Stoffers et al., 2012; Cristea et al., 2017; Oud, Arntz, Hermens, Verhoef, & Kendall, 2018).

Epidemiologic studies have also brought to light the high prevalence of BPD in most developed countries. Some studies indicate that BPD occurs in about 1% of the general population (Torgersen, Kinglen, & Cramer, 2001; Coid, Yang, Tyrer, Roberts, & Ullrich, 2006; Lenzenweger, Lane, Loranger, & Kessler, 2007), although one study have suggested that the prevalence of BPD could be as high as 6% (Grant et al., 2008). In our region, Catalonia, a recent study estimated 2% lifetime-prevalence and 0.7% year-prevalence of BPD, according to official health registries (Salvador-Carulla et al., 2014). Moreover, this disorder is very frequent in clinical populations, where it is reported that at least 9% of outpatients and between 15% and 25% of inpatients present a BPD diagnosis (Zimmerman, Rothschild, & Chelminski, 2005; Torgersen, 2005).

Beyond its recognition as a differentiated diagnostic category in the DSM-III, the conceptualization of BPD diagnosis has continued to evolve, not without controversy, in recent literature (Zandersen, Henriksen, & Parnas, 2019). Previously, borderline psychopathology was an issue mainly addressed from a psychodynamic framework, where it was considered as a syndrome between psychosis and neurosis. Therefore, a

main objective of early longitudinal research on BPD, in the 80s and 90s, was to demonstrate the validity of the disorder by studying its stability over time and its differential course patterns in comparison with other psychiatric disorders, namely psychotic and affective disorders, and other personality disorders (Gunderson, 2009; Sanislow, Marcus & Reagan, 2012). Moreover, longitudinal studies also aimed to test the persistence of the BPD psychopathology over time, which has consistently characterized the conceptualization of all personality disorders in the consecutive diagnostic classifications until now. It is interesting to note that pervasiveness of PDs has been recently considered as "relative" in the DSM-5 Alternative Model for Personality Disorders (AMPD) (APA, 2013) and the forthcoming International Classification of Diseases-11 (ICD-11) (World Health Organization, WHO, 2018; Bach & First, 2018), in accordance to the extensive evidence indicating the plasticity of PDs over time (Skodol, 2008; Morey & Hopwood, 2013).

Another point of controversy has been the validity of categorical and dimensional models to define accurately the borderline pathology and other personality disturbances (Morey & Hopwood, 2013). This point has been addressed by longitudinal research comparing the course of dimensional traits and categorical symptoms over time, and their predictive associations with functional impairment in the long-term (See section 1.3.3 and 1.4). However, current evidence from prospective studies on the long-term course of BPD used the categorical diagnosis of the disorder as inclusion criteria, mainly according to the DSM (See Table 2 below, and Table 9.1 in section 4.3.1), rather than the most recent dimensional models of the DSM-5 AMPD and ICD-11, due to the fact that these models were not accepted in diagnostic classifications at the onset of the follow-up period of these studies.

Despite the nosological controversies, categorical DSM criteria for BPD have suffered little change between editions, suggesting an acceptable homogeneity of the clinical entity that has been studied by prospective research up to now. Since DSM-III, BPD was defined by eight diagnostic criteria that has been maintained in consecutive editions (See Table 1). The only relevant change was the addition in the DSM-IV (APA, 1994) of a ninth criterion on cognitive disturbances that were formerly assessed by the DIB diagnostic interview (Gunderson, Kolb, & Austin, 1981), which was broadly used in prospective studies. Changes in diagnostic criteria and established diagnostic measures might involve confounding effects on observed outcomes, representing a challenge to the future research on this area (Stone, 1993; Karaklic & Bungener, 2010).

In this respect, one question that arises is how the current evidence on the long-term course of BPD will accommodate to the novel dimensional models of diagnosing PDs. Both the DSM-5 AMPD and the ICD-11 introduce five pathological dimensional traits as descriptors of PDs diagnoses. Both systems include the domains of Negative Affectivity, Detachment, Antagonism/Dissociality, and Disinhibition, and differ only in one domain (i.e., Anankastia in ICD-11 and Psychoticism in DSM-5), showing a satisfactory correspondence between them (Bach et al., 2017) and with the Five Factor Model (FFM) traits (Gore & Widiger, 2013). However, both classifications preserve the categorical criteria for BPD in some manner, which facilitates a gradual transition between diagnostic systems in research and clinical practice. In the DSM-5, the dimensional model is exposed for research purposes in Section III but all categorical PD diagnoses continue to apply in Section II, whereas the ICD-11 offers the option to add a borderline pattern qualifier that mirrors the categorical DSM diagnosis for BPD. Despite that, it is clear that the dimensional models of personality pathology will become essential for future research in BPD, offering a new framework to understand the course and

mechanisms of change of dysfunctional personality traits over time (Hopwood, Zimmerman, Pincus, & Krueger, 2015).

Table 1. Categorical diagnostic criteria for BPD according to DSM classifications

	A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by **five (or more)** of the following:
Criterion 1	Frantic efforts to avoid real or imagined abandonment (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
Criterion 2	A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
Criterion 3	Identity disturbance: markedly and persistently unstable self-image or sense of self.
Criterion 4	Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
Criterion 5	Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
Criterion 6	Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
Criterion 7	Chronic feelings of emptiness.
Criterion 8	Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
Criterion 9 [a]	Transient, stress-related paranoid ideation or severe dissociative symptoms.

Note. [a] Incorporated in DSM-IV and consecutive classifications.

1.2. THE COURSE OF BPD DURING ADULTHOOD: GENERAL OVERVIEW

In early conceptualizations, BPD was considered as a chronic disorder with poor prognosis. Schmideberg (1959) first described the disorder as characterized by "a stable instability". The clinical practice supported this pessimistic prognosis, due to the demandingness, disturbing and frightening behaviors showed by these patients during the

psychiatric assistance and the lack of effective treatments available at that time (Paris, 1988; Sanislow et al., 2012; Stone, 2016). It is well documented that stigmatizing attitudes towards BPD patients were common among treatment providers, who tended to describe them as "difficult" or "treatment resistant", influencing negatively the expectations of outcome related to this disorder (Aviram, Brodsky, & Stanley, 2006). Moreover, theoretical assumptions about the persistence of personality features during the lifespan also reinforced this perspective, attributing a chronic course to personality disorders (Newton-Howes, Clark, & Chanen, 2015).

The empirical evidence on the course of BPD was scarce before the inclusion of the diagnosis into the DSM-III. Findings of early longitudinal studies seemed to confirm the invariability of the borderline pathology in the first years of follow-up, indicating little improvement in functioning (Karaklic & Bungener, 2010; Paris, 1988; Zanarini, Frankenburg, Hennen, Reich & Silk, 2005a). However, these studies suffered from extensive methodological limitations: small and heterogeneous samples, varying diagnostic criteria for borderline pathology between studies, diverse outcome measures, mostly non blind assessments, variable number of years of follow-up in the same study, and high attrition rates (Najavits & Gunderson, 1995; McDavid & Pilkonis, 1996; Zanarini et al., 2005a). Since then, there has been growing evidence that supports the view that a more favorable course could be expected for these patients (Biskin, 2015; Leichsenring, Leibing, Kruse, New, & Leweke, 2011; Karaklic & Burgener, 2010; Sanislow et al., 2012). A summary of findings from early long-term longitudinal studies is displayed in Table 2.

In the 80s, four 15-year retrospective studies were published, which were the first to explore the course of BPD in the longer term: the Austen Riggs (Plakun, Burkhardt, & Muller, 1985), Chestnut Lodge (McGlashan, 1986), Montreal (Paris, Brown, & Nowlis,

Table 2. Longitudinal studies on the long-term course of BPD in adulthood excluded from meta-analysis

Study	Type	Country	BPD Measure & Criteria BL (FU)[a]	BPD N BL (FU)	% female (mean age)	Years FU	Control groups	Excl.[b]	Main Outcome Results
Pre-DSM-III									
Werble, 1970	P	US	Clinical diagnosis	41 (28)	---	6-7	No	(1)	None of BPD patients presented a psychotic episode over follow-up.
Carpenter, Gunderson, & Strauss, 1977	P	US	Clinical diagnosis-GC	24 (14)	---	5	Schz	(1)	Better social and occupational functioning in BPD patients compared to those with Schz.
DSM-III									
Pope, Jonas, & Hudson, 1983	R	US	Chart review DSM-III	33 (27)	82 (--)	4-7	Schz BD	(1) (2)	66.7% remained BPD. 6% suicide rate. None of BPD patients developed schizophrenia over follow-up BPD without comorbid MDD showed poorer functioning than BPD with comorbid MDD and BD or Schz.
Kroll, Carey & Sines, 1985	R	US	Chart review GC	15 (13)	100 (--)	20	No	(1) (2)	Middle-low socio-economical level. 2 died by suicide, 3 by natural causes. Only 1/3 of completers were considered recovered.
Austen Riggs study Plakun, Burkhardt & Muller, 1985	R	US	Chart review DSM-III	237 (63)	62 (40)	14	Schz MDD	(1) (2)	GAS=67; BPD without comorbid MDD functioned better than Schz, but was comparable to MDD; BPD with comorbid MDD functioned more poorly than BPD without comorbid MDD.
Chestnut Lodge study McGlashan, 1983, 1985, 1986	R	US	Chart review DSM-III or GC (Telf. Interv. DSM-III or DIB)	94 (81)	56 (47)	15 (2-32)	Schz UD	(1) (2)	50% DIB, 44% DSM-III remained BPD 3% suicide (2/81); 9 patients died by other causes. HSRS=64; 2/3 were working full-time. Some were living alone, as a "studious avoidance of relationships". Better levels of vocational engagement and global outcome, compared to patients with UD or Schz.

(continued)

Table 2. Longitudinal studies on the long-term course of BPD in adulthood excluded from meta-analysis

Study	Type	Country	BPD Measure & Criteria BL (FU)[a]	BPD N BL (FU)	% female (mean age)	Years FU	Control groups	Excl.[b]	Main Outcome Results
DSM-III									
Montreal study Paris, Brown, & Nowlis, 1987	R	Canada	Chart review GC (Telf. Interv. DIB)	322 (100)	84 (39)	15 (8-28)	None	(1) (2)	Middle-low socioeconomic level 8.5% suicide, 30 years mean age suicide. 13% died by other causes. 25% remained BPD; HSRS=63; 61% comorbid MAD
Paris & Zweig-Frank, 2001			(Telf. Interv. DIB-R)	(64)	83 (51)	27			10% suicide, 37 years mean age suicide 18% died by other causes 7.8% remained BPD; GAF= 63; 22% dysthymia, 3% TDM, 5% substance abuse; poorer outcome when comorbid dysthymia.
Columbia study/PI500 Stone, 1987, 1990	R	US	Chart review DSM-III or BPO	206 (188)	70 (37)	15	Schz	(1) (2)	9% suicide, 30y mean age suicide, 13% dead other causes GAS=63-67; 28% rehospitalization. Better global functioning and less rehospitalization than Schz. Women: 7% suicide; 51.5% married, 25% with children. 75% working or household half/full-time. Men: 13.4% suicide; 29% married, 15% with children. 50% working or household half/full-time.
Kullgren & Armelius 1990	P	US	Interview BPO or DIB	45 (31)	---	5	None	(1)	45% remained BPO, 57% DIB.
DSM-IV									
Yoshida et al., 2006	R	Japan	Chart review	72 (19)	58 (--)	13	None	(1) (2)	7% suicide GAF=60.7; 42% lived with parents, 37% married, 10% alone.

Note. R= Retrospective study; P= Prospective study; US= United States of America; BL= baseline; FU= Follow-up; Telf. Interv.= Telephone Interview; GC= Gunderson Criteria; BPO= Borderline Personality Organization by O. Kernberg (1967); Schz= Schizophrenia; MDD= Major Depressive Disorder; BD= Bipolar Disorder; UD= Unipolar Depression; [a] Only reported when the measure was different at follow-up and baseline; [b] Excl.=Reasons for exclusion from meta-analysis: (1) No validated & standardized BPD diagnostic interview, (2) No prospective study.

1987) and Columbia (Stone, 1990) studies. At 15 years, similar results on global functioning were informed, indicating a tendency towards functional recovery in patients diagnosed with BPD and a better prognosis compared to those suffering from schizophrenia (Stone, 1993, 2016; Paris, 1988, 2002; Karaklic & Burgener, 2010). In these studies, the Global Assessment Scale (GAS) and the Health-Sickness Rating Scale (HSRS) scores were around 60, with levels close to normality, and most patients were working and had a social network. All the studies reported suicide rates close to 9%, except for the Chestnut Lodge study (i.e., 3% suicide rate). Findings of the Montreal and Columbia studies suggest that suicide is more likely to occur after age 30. All studies informed that rehospitalization rate declined after the first few years (Paris, 1988, 2002). In the Montreal and Chestnut Lodge studies, remission from BPD was reported for 75% and 50% of the patients at 15 years of follow-up, assessed by the DIB and the Gunderson criteria, respectively (Paris et al., 1987; McGlashan, 1983). The Montreal study lately reported results at 27-year follow-up (Paris & Zweig-Frank, 2001). At that time, the percentage of subjects with BPD diagnosis decreased to 8%, whereas the suicide rate increased to 10.3%. No differences were reported in the mean Global Assessment of Functioning (GAF) score compared to the 15-year follow-up and social functioning was slightly lower than normative scores in the general population. This study informed of relevant percentages of comorbid affective disorders in the remaining cohort (5% major depression; 22% dysthymia), being associated the presence of comorbid dysthymia with poorer clinical and functional outcome.

Despite the relevant contributions of these follow-back studies into the field, there are substantial methodological limitations to be considered: low reliability of BPD diagnosis retrospectively assessed by chart review, data collected by non-blind coders, only one post-baseline assessment during follow-up, and control groups for comparison

showing high diagnostic overlaps or being absent (Paris, 1988; Stone, 1993; Zanarini et al., 2005a; Karaklic & Bungener, 2010). The generalization of findings might also be compromised by the high attrition rate in the Austen Riggs and Montreal studies, and the high socio-economical level of the samples in all but the Montreal study (Stone, 1993; Paris, 2002). However, consistent findings were recently reported by a follow-back study in Japan, confirming a favorable outcome of BPD in a different socio-cultural environment. This study followed 19 BPD patients at 13 years, reporting a mean GAF score of 60.7 and a suicide rate of 7%, but presenting similar methodological limitations (Yoshida et al., 2006). Another confounding factor to take into account is the potential effect of uncontrolled treatments received, which were different between retrospective studies: all patients in the Chestnut Lodge, Columbia and Austen Riggs studies received long-term psychotherapy, whereas many in the Montreal study received only intermittent treatment. Moreover, all samples were only recruited in inpatient settings (Paris, 1988, 2002; Stone, 2016).

More recently, two prospective studies have been conducted, with improved methodological robustness, on the course of BPD during adulthood: the McLean Study of Adult Development (MSAD; Zanarini et al., 2005a) and the Collaborative Longitudinal Personality Disorder Study (CLPS; Gunderson et al., 2000; Skodol et al., 2005). Both studies represented a great advance over previous research in several aspects: the prospective design with repeated assessments that were performed every two years of follow-up, the use of reliable instruments that were administered by trained interviewers who were blind to baseline diagnosis, the presence of clearly operationalized comparison groups with representative sample sizes, the data collection considering both categorical and dimensional personality models, and a wide variety of clinical and functional measures (e.g., Axis I comorbidity, physical health, different social and functional

indexes, life events, treatment variables, etc.). Besides, both studies have offered rigorous data to compare BPD with other personality disorders in terms of their course patterns, and also with major depressive disorder in the case of CLPS, which have contributed to determine the validity of the disorder (Zanarini et al., 2005a).

As previous research, these studies focused their efforts on following treatment-seeking samples, which adds clinical relevance to the findings but also implies that the effect of subsequent treatments might confound the results on long-term prognosis (Gunderson et al., 2000; Paris, 2002). In this respect, both studies reported data on treatment use along the follow-up period in a descriptive manner, without analyzing it as a potential moderator of the long-term outcome (Zanarini, Frankenburg, Hennen, & Silk, 2004; Hörz, Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010; Bender et al., 2006). This is a common drawback among current naturalistic longitudinal research on the course of the disorder, especially when there is growing evidence of effective treatments for BPD in recent times (Stoffers et al., 2012; Calati & Courtet, 2016; Cristea et al., 2017; Oud et al., 2018).

On the other hand, several follow-up post-treatment studies have recently provided results on the long-term clinical and functional outcome in treated BPD samples, differentiated by the initial intervention subgroups (Stevenson, Meares & D'Angelo, 2005; Bateman & Fonagy, 2008; Davidson, Tyrer, Norrie, Palmer, & Tyrer, 2010; Antonsen et al., 2015; Sahin et al., 2018). These follow-up clinical studies mainly aimed to compare the effects of some specialized therapy for BPD, i.e., conversational therapy, mentalization based therapy (MBT), cognitive-behavioral therapy (CBT) for PDs, and a psychodynamic & cognitive-behavioural combination programme, with TAU on the long-term outcome (Stevenson et al., 2005; Bateman & Fonagy, 2008; Davidson et al., 2010; Antonsen et al., 2015). As an exception, one study examined the impact of BPD

severity on the long-term efficacy of two specialized therapies, i.e., dialectical-behavior therapy (DBT) and object-relational psychotherapy, and TAU (Sahin et al., 2018). Among them, only two studies informed of a better long-term outcome associated to specialized therapies over TAU (Bateman & Fonagy, 2008; Antonsen et al., 2015). This stands in contrast to findings from a recent review, indicating greater beneficial effects of specialized therapies over TAU on overall BPD severity in the short-term (Oud et al., 2018). Accordingly, some concerns have been raised about the consistency of therapeutic achievements in the long-term, pointing out the lack of evidence on the long-term effects of therapeutic interventions and its relevance to determine more definitive treatment outcomes (Stevenson et al., 2005; Bateman & Fonagy, 2008; Davidson et al., 2010; Antonsen et al., 2015).

In the methodological realm, an outstanding contribution of the MSAD and CLPS studies was the operationalization of key concepts to describe the course of BPD. "Remission" from BPD was defined in these studies as no longer meeting BPD diagnostic criteria, assessed by validated interviews, during a concrete period of time (2, 4, 6, or 8 years in the MSAD; two or 12 months in the CLPS). "Relapse" or "recurrence" was described as meeting BPD criteria after achieving a concrete period of remission (Zanarini, Frankenburg, Hennen & Silk, 2003; Zanarini, Frankenburg, Reich & Fitzmaurice, 2012; Gunderson et al., 2011). Regarding the functional course, the MSAD introduced the term "recovery" that was defined as a combination of symptomatic remission and a good level of functioning, represented by a GAF score of 61 or higher, which meant that one had at least one emotionally sustaining relationship with a close friend or life partner/spouse, and was able to work or go to school consistently, competently, and on a full-time basis, including being a houseperson (Zanarini et al.,

2012). In contrast, the CLPS considered functional remission only when a GAF score greater than 70 was sustained for two months (Gunderson et al., 2011).

Despite that these definitions have clearly represented a guideline to further research, there are some relevant variations to point out in the operationalization of these concepts in other longitudinal studies. In this line, it is relevant to notice that both the MSAD and CLPS studies mainly reported cumulative remission rates, which correspond to the percentage of subjects who achieved a concrete period of remission (i.e., 2-12 months or 2-4-6-8 years) throughout the whole length of follow-up (e.g., 10 or 16 years). This is similar for cumulative rates of relapse/recurrence and recovery (or functional remission) in the studies (Zanarini et al., 2012; Gunderson et al., 2011). The MSAD study also informed of the temporal points when particular changes appeared for the first time; e.g., time-to-remission was defined as the follow-up period at which remission was first achieved, and similarly to time-to-recurrence, time-to-recovery, and so on (Zanarini et al., 2012). This is a critical difference between findings reported by these two follow-along studies and other longitudinal research that has reported remission rates at specific time points in the long-term: the former retrospective studies (McGlashan, 1986; Paris et al., 1987; Paris & Zweig-Frank, 2001), other naturalistic prospective studies, including our 10-year follow-up study (Links, Heslegrave & Van Reekum, 1998; Riihimäki, Vuorilehto & Isometsä, 2014; Álvarez-Tomás et al., 2017; Zeitler et al., 2018), and long-term follow-up post-treatment studies (Stevenson et al., 2005; Bateman & Fonagy, 2008; Davidson et al., 2010; Antonsen et al., 2017; Sahin et al., 2017). Furthermore, Zeitler et al. (2018) has recently questioned the use of the GAF to define functional recovery, because this measure is based in predetermined criteria of social adjustment which may not properly capture idiosyncratic life preferences. These authors have proposed another

conceptualization of recovery based on a self-report scale of life satisfaction, in addition to symptomatic remission, which is more related to subjective QOL.

Findings from contemporary follow-along studies will be deeply explained in the next section, which summarizes the current evidence from prospective research on the long-term course of BPD in adulthood. According to previous authors (Najavits & Gunderson, 1995; Ng, Bourke & Grenyer, 2016; Stone, 2016), we considered as long-term those follow-ups lasting five years and beyond, whereas those of less than five years were defined as short-term. It is generally accepted that some time is required to observe changes in personality traits, which tend to be more stable than certain symptoms over time. In this line, outcome measures in the long-term may offer a more accurate picture of the course prognosis of BPD than those in the short-term (Paris, 2002; Stone, 2016).

1.3. PROSPECTIVE EVIDENCE ON THE CLINICAL AND FUNCTIONAL COURSE OF BPD IN THE LONG-TERM

1.3.1. BPD diagnosis: rates of remission and relapse/recurrence

As stated above, the MSAD and CLPS mainly informed of cumulative rates of remission and relapse (or recurrence) over time. The MSAD study informed that 73.5% of patients with BPD had remitted at least for a 2-year follow-up period and only 5.6% had presented a subsequent recurrence over six years (Zanarini et al., 2003). Cumulative rates of remission and relapse/recurrence over 10 years in both studies are displayed in Table 4. In the MSAD, 88-93% of patients had achieved a 2-year remission, depending on computing methods, but 30% had experienced a subsequent recurrence over 10 years (Zanarini et al., 2007; Zanarini, Frankenburg, Reich & Fitzmaurice, 2010a). In the MSAD, cumulative rates declined as longer periods of sustained remission were studied, although the likelihood of symptomatic recurrence also decreased after longer sustained

remissions (Zanarini et al., 2010a; Zanarini et al., 2012). Similarly, the CLPS reported that 85% of BPD patients had experienced a 12-month remission and 12% a consequent relapse over 10 years (Gunderson et al., 2011). More recently, the MSAD informed of cumulative rates of remission over 16 years, which ranged from 99% when remission lasted two years to 78% when lasted eight years. In contrast, cumulative rates of recurrence ranged from 36% after 2-year remission to 10% after an 8-year sustained remission (Zanarini et al., 2012). Comparing to other disorders, both studies concluded that the likelihood of remission from BPD appears to increase more slowly than from other PDs and major depressive disorder (MDD), but reaching similar levels in the longer term (Gunderson et al., 2011, Zanarini et al., 2012).

Other prospective studies have reported remission rates at specific follow-up points between five and 14 years after the study inclusion, considering both naturalistic (Links et al., 1998; Riihimäki et al., 2014; Álvarez-Tomás et al., 2017; Zeitler et al., 2018) and follow-up post-treatment studies (Stevenson et al., 2005; Bateman & Fonagy, 2008; Davidson et al., 2010; Antonsen et al., 2015). Findings of these studies, including our own follow-up research, are summarized in the Article 2, where remission rates are displayed in Table 9.1 (See section 4.3.1). Percentages of BPD remission widely ranged from 31% to 81% in naturalistic studies and from 13% up to 93% in follow-up post-treatment studies. This variability is analyzed with meta-analytic methods in our review and results are discussed in depth in the general discussion below.

1.3.2. BPD symptomatology: Are there acute and temperamental symptoms?

Apart from the course of the diagnosis, naturalistic studies have separately analyzed the trajectories of borderline symptoms. This issue is relevant to better understand the course of borderline psychopathology over time, even in subthreshold manifestations, and orient the clinical practice with these patients.

In this realm, the MSAD concluded that the overall BPD symptomatology tend to improve over time, but at different speeds. This study reported at 6-year follow-up that, despite the significant decreases observed in general, the affective symptoms of BPD were the least likely to resolve (from 95-99% of prevalence at baseline to 61-79% at follow-up), and the impulsive symptoms, the most likely to do so (from 81% to around 25% for self-mutilation and suicide efforts). In contrast, the cognitive and interpersonal symptoms were more heterogeneous in this regard. To interpret these findings, the authors proposed a "complex" model of the borderline psychopathology which differentiates between acute and temperamental symptoms by their resistance to change, being the latter the most enduring ones over time (Zanarini et al., 2003). This model has been confirmed by prospective evidence reported in this study over 10 and 16 years of follow-up. At 10 years, one-half of the symptoms were identified as acute, due to a substantial decline in rates to the point that only 15% of subjects who exhibit them at baseline still presented them at follow-up. The median time-to-remission for each BPD symptom over the 10 years was also consistent with this classification, which is displayed below in Table 3 (Zanarini et al., 2007). In this line, it has been also reported higher cumulative remission rates and lower cumulative recurrence rates for acute symptoms compared to temperamental ones over 16 years of follow-up (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2016). To sum up, this model states that core symptoms of behavioral impulsivity (e.g., self-mutilation, suicide efforts), affective instability, serious identity

disturbances, and active attempts to manage interpersonal difficulties seem to resolve the most quickly, whereas chronic dysphoria and anger, general impulsivity, and interpersonal symptoms related to abandonment and dependency issues appear to be more resistant to change (Zanarini, 2012).

Concurrently, the CLPS studied the course of each DSM-IV criteria for BPD and proposed a "hybrid" model, similar to the former one, that classify BPD criteria into symptomatic behaviors, more changeable, reactive, and stress responsive; and traits, more resistant to change and representing core dimensions of the disorder (McGlashan et al., 2005). However, the evidence on these subtypes of BPD criteria is mixed. By two years, identity disturbance, abandonment fears, and self-injurious behavior were the least frequent and most changeable criteria (i.e., symptomatic behaviors), whereas affective instability, intense anger, and impulsivity were the most frequent and stable (i.e., trait-like criteria) (McGlashan et al., 2005). However, these differences in course patterns between subtypes were not confirmed by results at the 10-year follow-up, reporting similar rates of decline for all criteria over time (Gunderson et al., 2011). More recently, a similar classification has been successfully tested in the 10-year data from the CLPS using trait-state-occasion modeling, which is also displayed in Table 3 (Conway, Hopwood, Morey, & Skodol, 2018). Whatever the case, the CLPS reported that the mean number of criteria met for BPD sharply decreased in the first year (from 6.7 to 4.3) and declined more steadily until the 10th year (Gunderson et al., 2011).

Beyond this controversy, there is considerable evidence indicating that marked symptomatic changes in borderline pathology may occur during the first years of follow-up and keep gradually declining in the long-term. Besides the above, the McMaster study also reported that impulsive features showed a steeper decrease over the first two years in those patients who achieved full remission at seven years (Links, Heslegrave, & Van

Reekum, 1999). On the other hand, Zeitler et al. (2018) reported that BPD patients who achieved remission, but not recovery by GAF, still fulfilled some BPD criteria at 14 years of follow (54% dissociation, 42% affective instability; 42% suicidality or self-mutilating behavior), indicating that subthreshold BPD characteristics may persist beyond diagnostic remission. In this line, findings of the MSAD reported at the 10th and 16th year also indicate that some patients keep struggling with symptomatic disturbances in the longer term: among impulsive symptoms, 18% of patients reporting self-mutilation acts, 13% suicide attempts, and 19% adult verbal aggression toward others; among cognitive symptoms, 43% non-delusional paranoia, 37% odd thinking, 26% unusual perceptions, and over 20% depersonalization and derealization (Zanarini et al., 2008; Zanarini, Frankenburg, Wedig, & Fitzmaurice, 2013; Zanarini et al., 2017). Moreover, dysphoric states decreased in this study by 63% over 10 years, although remaining significantly more frequent for BPD than for other PDs (Reed, Fitzmaurice & Zanarini, 2012). Similarly, negative perceptions of self-worth declined significantly over 20 years but BPD patients remained experiencing them more often than those patients with other PDs (Gad et al., 2019).

Table 3. Classification of BPD pathology by the MSAD and CLPS

MSAD: "Complex" model 22 BPD symptoms by DIB-R (+2 DSM-III-R)	CLPS: "Hybrid" model 9 BPD Criteria by DSM-IV
ACUTE	**BEHAVIORAL SYMPTOMS**
Affective symptoms Affective instability	Affective instability

Cognitive symptoms
  Quasi-psychotic thought
  Serious identity disturbance
	Stress-related paranoia
	Identity disturbance

Impulsive symptoms
  Substance abuse/dependence
  Sexual deviance
  Self-mutilation
  Manipulative suicide efforts
	Suicidal behavior and self-harm

Interpersonal symptoms
  Stormy relationships
  Devaluation/manipulation/ sadism
  Demandingness/entitlement
  Treatment regressions
  Countertransference problems
	Abandonment fears

TEMPERAMENTAL	**TRAITS**

Affective symptoms
  Chronic/major depression
  Chronic feelings of helplessness/hopelessness
  Chronic anger/frequent angry acts
  Chronic anxiety
  Chronic loneliness/emptiness
	Intense anger
	Chronic emptiness
	*Affective instability**

Cognitive symptoms
  Odd thinking/unusual perceptual experiences
  Non-delusional paranoia	

Impulsive symptoms General impulsivity	Impulsivity

Interpersonal symptoms
  Intolerance of aloneness
  Abandonment/engulfment/annihilation concerns
  Counterdependency/conflict over help
  Dependency/masochism
	Unstable relationships

Note. MSAD= McLean Adult Development Study; CLPS= Collaborative Longitudinal Personality Disorder Study; *Affective instability was classified as Temperamental by McGlashan et al. (2005)

1.3.3. Axis II comorbidity and personality dimensional traits: the overlap between personality disorders

It is well-documented that comorbidity between PD diagnoses is common. Cross-sectionally, the CLPS informed that patients in all PD subgroups had a median of one comorbid PD at baseline, and those with BPD had at least two of them (McGlashan et al., 2000). Over the first six years of follow-up, the MSAD reported declining rates of most types of comorbid Axis II disorders in BPD patients, which are displayed in Table 4 (Zanarini, Frankenburg, Vujanovic et al., 2004). None of these studies reported prospective data on Axis II comorbidity in the longer term.

In terms of dimensional FFM traits, the CLPS reported that the differential stability was lower in patients with BPD compared to those with other PDs over six years of follow-up (i.e., schizotypal, avoidant and obsessive-compulsive PDs), especially on the traits of Neuroticism and Conscientiousness. These traits showed a greater mean-level change in the BPD group, lowering Neuroticism and raising Conscientiousness faster than in the other groups (Hopwood et al., 2009). These findings were partially replicated by the MSAD over 10 years of follow-up, supporting a lower differential stability in BPD on Conscientiousness and greater mean-level decreases on Neuroticism compared to other PDs (Hopwood & Zanarini, 2010a). Moreover, the MSAD examined the dynamic associations between BPD symptoms and FFM traits over 10 and 16 years. This study concluded that acute symptoms were associated with low Agreeableness, and temperamental symptoms with high Neuroticism (Hopwood, Donnellan, & Zanarini, 2009). Moreover, it reported that the reduction in BPD symptoms was strongly associated with decreasing Neuroticism and increasing Agreeableness and Conscientiousness, and to some degree extraversion over 16 years of follow-up (Wright, Hopwood, & Zanarini, 2015).

1.3.4. Axis I comorbidity and its course over time

The MSAD informed that most rates of comorbid Axis I disorders significantly decreased in patients with BPD and other PDs over six years of follow-up but remained higher in the BPD subgroup, particularly for mood and anxiety disorders (Zanarini, Frankenburg, Hennen, Reich et al., 2004). Rates of comorbid Axis I disorders showed a similar declining trend over 10 years (See Table 4). However, most Axis I disorders showed an intermittent course among BPD patients over this time, with remissions being frequent but also recurrences (Silverman, Frankenburg, Reich, Fitzmaurice & Zanarini, 2012; Zanarini, Reichman, Frankenburg, Reich & Fitzmaurice, 2010; Zanarini et al., 2011; Zanarini, Hörz et al., 2011). More recently, a German study reported that almost three quarters of the sample presented some comorbid Axis I disorder at 14-year follow-up, e.g., 43% post-traumatic stress disorder (PTSD), 35% affective disorders, 26% substance use disorders (SUD), 17% other anxiety disorders, confirming the relevance of Axis I comorbidity in the long-term course of BPD (Zeitler et al., 2018).

1.3.5. Completed suicide and other premature deaths

Suicide is an adverse consequence of suffering from BPD, which is more prevalent in subjects with this diagnosis than in the general population (Pompili, Girardi, Ruberto, & Tatarelli, 2005). In our review, the rates of completed suicide observed in prospective studies are displayed in Table 9.1 (See section 4.3.1). More recently, the MSAD has reported that the incidence of suicide over 24 years was 5.9% for BPD compared to 1.4% for other PDs. Of interest is that the incidence of premature death by other causes was also studied, which was 14% for BPD patients compared to 5.5% for those with other PDs. The most common causes of non-suicide deaths were cardiovascular (n=11), substance-related complications (n=5), cancer (n=4), and accidents (n=4). These findings indicate that patients with BPD are at risk of premature

death by suicide and other causes that are often related to physical health problems (Temes, Frankenburg, Fitzmaurice & Zanarini, 2019).

1.3.6. Use of mental health resources

Both the MSAD and CLPS studies informed of the lifetime treatment utilization reported at baseline by diagnostic subgroups (Zanarini et al., 2001; Bender et al., 2001). The patients with BPD were more likely to receive most types of psychosocial treatment and standing medications, and in greater amount, than those patients with other PDs or MDD. In both samples, around 95% of patients with BPD had received individual therapy and over 70% had previous psychiatric hospitalizations. Taking psychotropic medications was also common to BPD patients, who were more likely to have received standing medications that patients with other PDs and MDD. Besides, the MSAD reported that BPD patients were younger when they first received individual therapy (mean age 18 vs. 22 years) and standing medications (mean age 22 vs. 26 years), and these treatments lasted longer, in comparison to patients with other PDs (Zanarini et al., 2001). This is consistent with findings of the McMaster study, indicating that BPD patients, compared to those with borderline traits, were younger at their first outpatient psychiatric contact (mean age 18 vs. 25 years) and at their first psychiatric hospitalization (mean age 23 vs. 28 years), and also had more psychiatric hospitalizations prior to the inclusion in the study (Links et al., 1988).

Regarding treatment use over follow-up, both the MSAD and CLPS studies informed of a pattern of declining participation in most treatment modalities for all subgroups, which was more marked over six and 10 years of follow-up, but maintaining baseline differences in percentages of treatment utilization by diagnosis (Bender et al., 2006; Zanarini, Frankenburg, Hennen & Silk, 2004; Hörz, Zanarini, Frankenburg, Reich & Fitzmaurice, 2010). Both studies informed of a reduction in the need for psychiatric

hospitalization over time in BPD patients, which appeared to be more slight during the first years of follow-up (CLPS, from 31% at first year to 22% at the third one; MSAD, from 79% at baseline to 60% at two years and to 33-29% at 6-10 years). On the contrary, the use of individual therapy showed the major decline by the first years, but still remained considerably common among BPD patients in the long-term: 85% vs. 64% at three years in the CLPS, 96% vs. 75-73% at 6-10 years in the MSAD. Besides, almost 70% of BPD patients in the CLPS received medication consultations throughout the first three years, and over 70% of BPD patients in the MSAD were taking standing medication over the whole 10-year follow-up period. Moreover, polypharmacy in this study only decreased slightly over six years, from 66% to 51% of BPD patients taking two or more medications (Zanarini, Frankenburg, Hennen & Silk, 2004).

It is notable that most BPD patients in these studies were highly treated over follow-up, which might modulate the natural course of the disorder, restricting the generalizability of their findings to treated samples. The confounding effects of uncontrolled treatments is a common drawback of other naturalistic studies following seeking-treatment samples. For instance, the German 14-year naturalistic study and our own research followed BPD samples who received some modality of dialectical-behavior therapy early during follow-up (Zeitler et al., 2018; Álvarez-Tomás et al., 2017). Moreover, the majority of naturalistic studies recruited samples in psychiatric units, except for the Vantaa study that did so in primary care services. In this study, the use of mental health resources by BPD patients was more moderate than in the MSAD and CLPS studies: only 24% received any psychiatric care and 59% any psychosocial treatment during the 5-year follow-up (Riihimäki et al., 2014).

On the other hand, all participants in the follow-up clinical studies received some kind of controlled treatment at the onset of the follow-up period, which are described in

our review and summary information is displayed in Table 9.2 (See section 4.3.1). Among them, four studies reported some information on treatment utilization over the follow-up post-treatment period (Stevenson et al., 2005; Bateman & Fonagy, 2008; Davidson et al., 2010; Antonsen et al., 2017). The Boscot study informed that the use of hospital services remained high in the overall BPD sample over the 6-year follow-up, with about 54% of patients receiving inpatient treatment and around 65% emergency room visits (Davidson et al., 2010). This study and the MBT trial found significant differences in the amount of mental health resources received during follow-up in favor of the specialized therapy subgroups, i.e., less days of hospitalization and lower number of emergency visits (Davidson et al., 2010; Bateman & Fonagy, 2008). Moreover, the MBT trial reported a shorter length of psychiatric outpatient and psychopharmacological treatments received by BPD patients in the specialized therapy subgroup over five years postdischarge (Bateman & Fonagy, 2008). In contrast, Antonsen et al. (2017) reported, over six years, a decrease in rates of inpatient hospitalization (from 57 and 44% to 13 and 10%, depending on treatment group) and any use of psychiatric health care (from 100 and 89% to 63 and 53%), without significant differences between treatment subgroups. Stevenson et al. (2005) also informed of a progressive reduction in time of hospitalization over five years in a BPD sample that had initially received a specialized therapy, but this study had not a TAU group for comparison.

1.3.7. Physical health and health care utilization

The MSAD has studied the impact of struggling with BPD on the prevalence of several health problems, poor health-related lifestyle choices and health care utilization over time. This study reported that patients who achieved remission from BPD over the first six years were less likely to suffer from chronic fatigue, fibromyalgia, or temporomandibular joint syndrome (25% vs. 42%), obesity (24% vs. 41%), osteoarthritis

(8% vs. 17%), diabetes (2% vs. 11%), hypertension (5% vs. 13%), chronic back pain (39% vs. 63%), and urinary incontinence (5% vs. 19%). Over half of non-remitted BPD patients reported to suffer multiple medical conditions in comparison to one quarter of those who remitted. Poor health-related lifestyle choices (i.e. one pack per day smoking, daily alcohol use, lack of regular exercise, daily use of sleep medication, and overuse of pain medication) were more likely reported by non-remitted than remitted BPD patients. Non-remitted BPD patients were more likely to have had at least one medically related emergency room visit and a medical hospitalization than those who remitted (Frankenburg & Zanarini, 2004). Similar differences were found between recovered and non-recovered BPD patients over 10 years of follow-up. Prevalence rates are displayed in Table 4 (Keuroghlian, Frankenburg, & Zanarini, 2013).

These findings indicate that suffering from BPD seems to be associated with higher risk of chronic medical illnesses, poor healthy habits and use of health care resources. Consistent with that, the Vantaa study also reported that a concurrent BPD diagnosis in depressed patients was associated with a greater number of visits to the primary care physician over five years (Riihimäki et al., 2014).

Of interest is that BPD patients were more likely to experience pain and rate it as more severe than patients with other PDs in the MSAD (Biskin, Frankenburg, Fitzmaurice & Zanarini, 2014). Consequently, the prevalence of opioid medication prescribed to BPD patients was almost twice as greater as that prescribed to those with other PDs. It is notable that a quarter of BPD patients were being treated with opioid pain medications 16 years after the study inclusion, with the risk that accompanies its regular use (Frankenburg, Fitzmaurice & Zanarini, 2014).

1.3.8. Global and social functioning, and quality of life: achieving full recovery

The MSAD reported an improvement in the social functioning of patients with BPD over the first six years of follow-up, but remaining significantly more impaired than those with other PDs, particularly in the area of vocational achievement (Zanarini, Frankenburg, Hennen, Reich & Silk, 2005b).

Over 10 years, about 60% of BPD patients who did not have good psychosocial functioning at baseline achieved it at follow-up. The poor psychosocial functioning of BPD patients was mainly due to poor vocational but not social performance (Zanarini, Frankenburg, Reich & Fitzmaurice, 2010b). BPD patients were subsidiary 3 times more of economic aid than patients in the control group. Over 40% of BPD patients were receiving a disability reliance (Zanarini, Jacoby, Frankenburg, Reich & Fitzmaurice, 2009). On the other hand, one-half of BPD patients achieved full recovery at least two years over the 10-year follow-up, although one third lost this recovery afterwards (Zanarini et al., 2010b). Cumulative rates of recovery and functional remission over 10 years are displayed in Table 4. In the CLPS, social functioning of BPD patients showed a modest but statistically significant improvement over time, although they appeared more impaired than those with other PDs and MDD. Percentage of full-time employment rose from 19% to 36% in the BPD group, although this increase was less than those in the other groups. Marriage or cohabitation rates were similar in all groups, rising from 23% to 41% for BPD patients at 10 years (Gunderson et al., 2011).

Lately, the MSAD reported that BPD patients were less likely to achieve sustained recoveries lasting four to eight years than those with other PDs. By 16-year follow-up, cumulative rates of recovery for the BPD sample ranged from 60% (lasting two years) to 40% (lasting eight years) compared to 85% and 75%, respectively, for the other PDs sample (Zanarini et al., 2012). By 20 years, cumulative rates of 2-year recovery remained

steady and only 39% of BPD patients achieved an excellent recovery (GAF score higher than 71, by adding the absence of a comorbid disorder to previous conditions for recovery). These findings indicate that the likelihood of full recovery seems to reach a stable ceiling in the longer term (Zanarini, Temes, Frankenburg, Reich, & Fitzmaurice, 2018). Consistently, a German naturalistic study reported that only 44% of borderline patients achieved recovery by GAF at a mean follow-up period of 14 years (Zeitler et al., 2018). This study also assessed by self-report how much satisfied with life were the BPD patients at this time, which has been related to their subjective QOL (Thadani, Pérez-García, & Bermúdez, 2018). In the German study, the rate of recovery was similar when it was used the satisfaction with life as criterion instead of the GAF score (49%), which supports the use of subjective perceptions of wellbeing to assess the full recovery of these patients (Zeitler et al., 2018).

However, changes in subjective QOL of BPD adults has not been yet studied prospectively by naturalistic studies in the long-term. Only two post-treatment follow-up studies have studied this aspect, reporting an increase in subjective QOL over six years in the overall BPD samples, regardless the initial treatment received (Davidson et al., 2010; Antonsen et al., 2017). However, in the first study the QOL in BPD patients remained poor and comparable to values reported for other severe mental health populations (Davidson et al., 2010).

Table 4. Prevalence rates in MSAD and CLPS at 10-year follow-up

Outcome	MSAD [1]	CLPS [2]
Cumulative BPD Remission/Relapse 1) Zanarini et al., 2010, 2012 2) Gunderson et al., 2011	93% 2-year remission 30% recurrence 86% 4-year remission 15% recurrence 63% 6-year remission [a] 43% 8-year remission [a]	91% 2-month remission 85% 12-month remission 21% relapse after 2 months 11% relapse after 12 months
Cumulative BPD Recovery 1) Zanarini et al., 2010, 2012 2) Gunderson et al., 2011	50% recovery (2y+) 34% loss of recovery 47% 2-year recovery [a] 40% 4-year recovery [a] 31% 6-year recovery [a] 21% 8-year recovery [a]	21% Functional remission
Axis II comorbidity [b] 1) Zanarini et al., 2004	*Remitted vs. Non-remitted %BL - %FU* 36-16% vs. 85-72% Avoidant 42-8% vs. 56-45% Dependent 16-3% vs. 13-2% OC 19- 3% vs. 27-8% Passive aggressive 22-1% vs. 34-27% Self-defeating 23-2% vs. 31-8% Paranoid 2-0% vs. 3-2% Schizotypal 1-1% vs. 1-0% Schizoid 8-2% vs. 16-6% Histrionic 7-2% vs. 19-2% Narcissistic 19-2% vs. 31-3% Antisocial	

Axis I comorbidity
1) Zanarini et al., 2010
   Zanarini et al., 2011
   Zanarini, Hörz et al., 2011
   Silverman et al., 2012
	%BL - %FU
	22 - 2% Anorexia
	24 - 2% Bulimia
	28 - 17% EDNOS
	62 - 7% Drug abuse/dependence
	50 - 9% Alcohol abuse/dependence
	45 - 23% Panic disorder
	50 - 7% Social phobia
	11 - 4% GAD
	15 - 10% OCD
	58 - 21% PTSD	

Mental health utilization 1) Hörz et al., 2010 2) Bender et al., 2006	**%BL - %FU** 96 - 73% Individual therapy 84 - 72% Standing medication 79 - 29% Psychiatric hospitalization	**%BL - %FU** 85-64% Individual therapy [c] 69-68% Medication [c] 31-21% ER visits [c] 31-22% Hospitalization [c]
Physical health & health care utilization 1) Keuroghlian et al., 2013	*Ever-recovered vs. Never-recovered* **%BL - %FU** 20-16% vs. 34-37% Syndrome 16-25% vs. 44-50% Obesity 4-12% vs. 16-27% Osteoarthritis 1-4% vs. 6-14% Diabetes 39-48% vs. 46-58% Hypertension 39-48% vs. 46-58% Chronic back pain 2-4% vs. 11-22% Urinary incontinence	

Table 4. Prevalence rates in MSAD and CLPS at 10-year follow-up

Outcome	MSAD [1]	CLPS [2]
Physical health & health care utilization 1) Keuroghlian et al., 2013	*Ever-recovered vs. Never-recovered* **%BL - %FU** 43-40% vs. 61-64% Multiple poor health-related lifestyle choices 87-91% vs. 91-94% PC physician visit 16-17% vs. 38-40% Med. ER visit 16-17% vs. 38-40% Med. hospitalization	
Global & Social Functioning 1) Zanarini et al., 2009 Zanarini et al., 2010 2) Gunderson et al., 2011	26% good functioning at baseline 60% attained good functioning at follow-up 80% lost good functioning at follow-up 41% - 44% Receiving SSDR	**%BL - %FU** 19-36% Full-time employment 23-41% Married or cohabiting

Note. MSAD= McLean Adult Development Study; CLPS= Collaborative Longitudinal Personality Disorder Study; 2y+ = at least 2 years; BL= Baseline; FU= Follow-up; OC= Obsessive compulsive; EDNOS= Eating Disorder Not Otherwise Specified; GAD= Generalized Anxiety Disorder; OCD= Obsessive-Compulsive Disorder; PTSD= Post-Traumatic Stress Disorder; PC= Primary care; Med.= Medical; ER= Emergency room; SSDR=Social Security Disability Reliance; [a] Cumulative rates estimated for 10 years in survival analyses over 16 years; [b] Rates of Axis II comorbidity were only reported over the 6-year follow-up; [c] Rates of treatment use were only reported over the first 3 years in the CLPS study.

1.4. PREDICTORS OF THE CLINICAL AND FUNCTIONAL LONG-TERM COURSE OF BORDERLINE PERSONALITY DISORDER

Despite the consistent evidence indicating a favorable prognosis for BPD in general terms, a good outcome appears to be an elusive target for a sizable part of these patients even though they had been treated for long periods. For this reason, it seems crucial to identify relevant aspects that allow us to predict this variability between individuals on their clinical and functional trajectories. In fact, this has been a recurrent concern of the research on the long-term course of BPD.

Early 15-year retrospective studies examined several predictors of good and poor global functioning (assessed by GAS and HSRS). In these studies, a good global functioning in the long-term was predicted by the following factors: high intelligence, being unusually talented or physically attractive (if female), the absence of parental

divorce and narcissistic entitlement, and the presence of physically self-destructive acts during the index admission. In contrast, the predictors of poor global functioning were: affective instability, chronic dysphoria, younger age at first treatment, length of prior hospitalization, antisocial behavior, substance abuse, parental brutality, a family history of psychiatric illness, and a problematic relationship with one's mother (Paris et al., 1987; Stone, 1990; McGlashan, 1985; Paris, Nowlis, Brown, 1988; Plakun, 1991). In sum, retrospective findings pointed out that the likelihood of recovery from BPD may increase in subjects with socially-valued capacities, absence of hereditary or other early developmental determinants, such as childhood traumatic experiences, prevalence of externalizing over internalizing BPD symptoms, absence of a comorbid substance abuse disorder and antisocial behavior, and lesser amount of prior psychiatric interventions, although none of these factors independently showed a strong predictive power of the long-term outcome (Paris, 1988).

Prospectively, the MSAD analyzed the impact of multiple baseline predictors (i.e., demographic characteristics, treatment history, adverse and protective childhood experiences, family history of psychiatric disorders, lifetime Axis I disorders, comorbid Axis II disorders, dimensional traits, previous social and vocational competence, and adult adversity) on time-to-remission and time-to-attainment of recovery over 10 and 16 years, controlling for initial severity of BPD pathology (Zanarini, Frankenburg, Hennen, Reich & Silk, 2006; Zanarini et al., 2014). Seven baseline predictors of earlier time-to-remission from BPD were reported: younger age (25 years or younger), absence of childhood sexual abuse, no family history of substance use disorder, good vocational record, absence of an anxious cluster PD, low Neuroticism and high Agreeableness. Absence of prior psychiatric hospitalizations, less severity of other forms of child abuse, no family history of mood disorders, and no comorbid PTSD also showed significant

bivariate associations with shorter time-to-remission. In contrast, higher intelligence, female gender, the age of onset of symptoms or the age of first treatment were not significant predictors of this outcome (Zanarini et al., 2006). More recently, most of these predictors have also shown significant effects on the time-to-attainment of recovery over 16 years, with some relevant variations to note: the absence of childhood sexual abuse, but not other types of abuse, was not significant to predict an earlier recovery whereas it did so for remission; by contrast, other predictors related to vocational and social competence, such as higher intelligence, higher extraversion, and number of friends, were more predictive of earlier recovery than remission. Gender and age of onset of symptoms and first treatment also showed no significant effects on time-to-attainment of recovery (Zanarini et al., 2014).

On the whole, findings from the MSAD study expand previous evidence from retrospective research, specifying that predictors related to social and vocational capacities, e.g., high intelligence quotient (IQ), high extraversion, are particularly relevant to predict earlier functional recovery, whereas some childhood traumatic experiences impact more negatively on symptomatic remission. According to previous studies, factors related to less emotional instability and internalizing symptoms, i.e., traits of low Neuroticism and high Agreeableness, and the absence of an avoidant PD, were predictive of a better outcome. This study also confirms the negative impact of the presence of a psychiatric family history and prior psychiatric hospitalizations, but not of other factors indicating an early onset of psychopathology, i.e., age of onset of symptoms and first treatment, on the long-term outcome. Gender was not a relevant predictor of outcome in the MSAD, in contrast to the interactions between gender and other predictors that were suggested by one retrospective study (Stone, 1990; Stone, Hurt, & Stone, 1987).

In fact, there is little evidence from longitudinal research on the predictive effects of gender and age of first BPD diagnosis in the long-term course of BPD, which stands in contrast to results from cross-sectional research, indicating significant differences in clinical presentations of BPD by gender (Bayes & Parker, 2017) and stages of life (Winsper et al., 2015; Beatson et al., 2016).

Regarding age, findings of the MSAD support the positive effects of a younger age on earlier remission and recovery. By contrast, the CLPS found little influence of age on the improvement of borderline criteria over six years, although informed of a worsening tendency in functioning for older BPD patients (35-45 years) midway through the follow-up (Shea et al., 2009). The latter is consistent with findings of two retrospective studies that reported a fall in functioning after age 50, suggesting an "inverted U" pattern over time (McGlashan, 1986; Stone, 1990). Riihimäki et al. (2014) reported that older age (35 years and above) was associated to longer duration of depression and shorter time to work, if in the labor force, in patients with BPD and co-occurring depressive disorders, indicating that age might moderate the effects of comorbid mood disorders on the long-term course.

Further evidence has confirmed interactions between the co-occurrence of other Axis I/II disorders and remission from BPD. The MSAD reported positive reciprocal effects between the absence of a comorbid avoidant, dependent and self-defeating PD and shorter time-to-remission from BPD over six years of follow-up (Zanarini, Frankenburg, Vujanovic et al., 2004). In terms of Axis I comorbidity, the MSAD reported that the presence of a comorbid SUD, PTSD, mood disorder, eating disorder or other anxiety disorders predicted a delayed time-to-remission from BPD over six years, particularly the first one (i.e. 4 times more delayed with a comorbid SUD). On the other hand, to achieve remission from BPD was associated with more substantial declines in Axis I comorbidity

(Zanarini et al., 2004). Regarding the interactions of BPD and mood disorders, the CLPS informed of significant reciprocal effects between BPD and MDD, delaying the time-to-remission from each disorder over 10 years, whereas BPD and bipolar disorders were independent, except for bipolar II that delayed BPD time-to-remission (Gunderson et al., 2014). Similarly, the McMaster study reported that there is an association between higher rates of comorbid Axis I and II disorders and the absence of remission from BPD predicted over seven years of follow-up (Links, Heslegrave, Mitton, Van Reekum & Patrick, 1995).

BPD psychopathology and FFM personality traits have been also studied as predictors of social functioning in BPD patients. The MSAD informed that both predictive factors were strongly correlated and predicted the level of social functioning over 10 years. Among FFM traits, FFM Extraversion and Agreeableness were the most incrementally predictive of a better social functioning. BPD features were negatively associated with the long-term social functioning, being cognitive and impulse action features the most predictive of a poorer outcome (Hopwood & Zanarini, 2010b). In this line, this study also reported that achieving remission from BPD predicted a better vocational and social functioning over six years of follow-up (Zanarini, Frankenburg, Hennen, Reich & Silk, 2005). Poor psychosocial outcome for BPD subjects was also predicted by impulsivity, negative affectivity, and antisocial traits at baseline, and by comorbid MDD at 8-year follow-up in a recent study (Soloff & Chiappetta, 2017).

Prospective evidence on the predictors of QOL in BPD adults is scarce. In contrast, there has been more interest for this aspect in longitudinal research studying the long-term course of personality disturbances suffered in the adolescence and youth. In this field, the Children in the Community (CIC) study informed of the prospective associations between the presence of several PD diagnoses in young adults and the

consequent QOL reported 11 years later in a community sample. This study concluded that Cluster B PDs in young adulthood predicted higher impairment in overall long-term QOL than other PD clusters, after controlling for demographic variables, comorbid Axis I disorders and physical illness. Particularly, the presence of borderline symptoms predicted later impairment in the perceived physical health and environmental context (Chen et al., 2006). Cross-sectionally, a BPD diagnosis in adults has been associated to poorer QOL, not only to the mental and social dimensions of QOL but also to the physical one, in comparison with the general population (IsHak et al., 2013). On the other hand, a review concluded that some dimensional FFM traits show significant correlations with the subjective well-being in the general population, being negative for Neuroticism and positive for Extraversion and Agreeableness (DeNeve & Cooper, 1998).

As it has been said, several psychotherapeutic interventions have demonstrated to be effective for BPD (Stoffers et al., 2012; Calati & Courtet, 2016; Cristea et al., 2017; Oud et al., 2018), suggesting that receiving a psychotherapeutic treatment might provide a beneficial effect on the natural course of the disorder in the long-term. Particularly, there is current evidence indicating a greater efficacy of specialized treatments for BPD over the usual mental health assistance on reductions of BPD psychopathology in the short-term, which suggests that the type of treatment received might be a potential predictor of the long-term outcome in treatment-seeking BPD samples (Stoffers et al., 2012; Cristea et al., 2017; Oud et al., 2018). However, findings in this respect from current follow-up clinical trials are mixed (Stevenson et al., 2005; Bateman & Fonagy, 2008; Davidson et al., 2010; Antonsen et al., 2015). Moreover, the length and intensity of therapeutic interventions have also been studied as predictors of outcome, with conflicting results until now. Perry, Banon, and Ianni (1999) concluded that longer treatments appears to be more effective for personality disorders, although this association has not been confirmed

for BPD (Omar, Tejerina-Arreal, & Crawford, 2014). Regarding the intensity of therapy, Davidson and Tran (2014) concluded that this factor does not affect the efficiency in treating depression and suicidal behaviors in patients with BPD. By contrast, another review has informed of greater improvements in depression, self-harm and social functioning associated to more intensive treatments (Omar et al., 2014).

2. GENERAL APPROACH AND RESEARCH JUSTIFICATION

The current evidence from longitudinal research brings to light a more favorable prognosis for BPD in the long-term than it was hypothesized in early conceptualizations. According to these studies, achieving remission from the disorder seems to be common among BPD patients, and recurrences less frequent, after 10 or 15 years of follow-up. Dimensional FFM traits of Neuroticism, Agreeableness, and Conscientiousness, which have been associated to BPD features, also tend to improve over time. Additionally, there seem to be significant reductions in comorbidity with Axis II and I disorders in the long-term, although evidence on the former has been not reported until now in the longer term. Notwithstanding, the long-term course of BPD presents some drawbacks in the clinical and functional realms. Previous evidence suggests that some BPD symptoms sharply decrease over time whereas others may remain longer, producing distress even in remitted patients. Moreover, a part of these patients will keep struggling with comorbid Axis I/II disorders and increasing physical health problems in the long-term. In addition, previous research informed of lesser improvements in functional outcomes, although there are differences in findings among studies. In this sense, of note is the fatal outcome of the high rates of premature death by suicide compared to the general population, despite the variability in rates reported among studies.

However, these studies have been mainly conducted in the United States (US) and Canada, which reduces the generalization of findings to different social and assistance contexts. In this line, the present thesis aims to test previous evidence in a Spanish sample of BPD patients followed at 10 years, which may add to recent findings from other populations. Besides, this thesis intend to contribute, through a meta-analysis of prospective studies, to draw generalizable conclusions on the long-term course of BPD during adulthood with regard to both clinical and functional outcomes.

On the other hand, longitudinal research has been interested in studying several predictors of long-term outcome. However, current evidence is scarce in contrast to the vast scope of this task, which means to take into account multiple potential predictors and outcomes. In this line, it is of great relevance to develop further exploratory research to accumulate evidence on the predictive effects of specific factors on particular outcomes related to the long-term course of BPD. As far as we are aware, there are not prospective studies until now that reported on the predictive effects of the age of first BPD diagnosis on the long-term outcome. Moreover, there is no evidence on predictive factors of the long-term QOL of these patients. Consistently, the purpose of the present thesis is to fill this gap analyzing these aspects in the clinical sample of BPD patients in our 10-years follow-up study. Additionally, we also aim to study the effects of potential moderators in our meta-analysis of prospective studies, where possible, to provide further evidence on predictive factors of the long-term course of the disorder. In the following sections, these general goals shall be translated into the specific objectives and hypothesis of the two research studies that comprise the present thesis.

3. ORIGINAL RESEARCH 1:

10-YEAR FOLLOW-UP STUDY

3.1. <u>OBJECTIVES & HYPOTHESIS</u>

Firstly, this study aimed to describe the long-term clinical and functional course of BPD in a Spanish sample, in terms of the following aspects: (1) presence/absence of BPD diagnosis, (2) characteristic BPD symptomatology, (3) dimensional personality traits, (4) general psychiatric symptoms, (5) comorbidity with other personality disorders, (6) comorbidity with Axis I disorders, (7) use of health and social resources, (8) physical health, and (9) social functioning. This primary objective was mainly addressed in Article 1 (See section 3.3.1). The descriptive findings on physical health and health care utilization at follow-up were reported in Poster 4 (Álvarez-Tomás et al., 2018).

Secondly, we were interested to explore the impact of the age of onset of BPD diagnosis on the long-term clinical and functional outcome. In this line, we studied the differential clinical and functional course patterns in subjects with early (ED) and delayed (DD) BPD diagnosis, considering the age when BPD was first diagnosed. This secondary objective was addressed in Communication 2 and Poster 3 (Álvarez-Tomás, 2014; Álvarez-Tomás et al., 2016).

Thirdly, this research intended to explore the impact of several factors on the long-term QOL of BPD patients. In this respect, the objectives were to identify relevant baseline predictors of the QOL of BPD patients in the long-term and to study the influence of BPD remission and physical health condition at follow-up on the long-term QOL. These objectives were addressed in Poster 2 and 4, respectively (Álvarez-Tomás et al., 2015, 2018).

Regarding the first objective, we formulated the following hypothesis on the basis of former evidence:

1. BPD diagnosis will tend towards remission, indicated by a remission rate at 10-year follow-up that may range between 30% and 80%.

2. It is expected a statistically significant reduction of the overall BPD symptomatology from baseline to 10-year follow-up, observed in the total scores of SCID-II Borderline Subscale and DIB-R, and in each BPD symptoms domain by DIB-R (i.e. affect, cognition, impulse action, and interpersonal relationships).

3. It is expected a higher decrease of acute symptoms over temperamental symptoms of BPD from baseline to 10-year follow-up, indicated by differences in the amount of change between DIB-R domains, in the way that the larger effect size will be found in the impulsive domain and the lowest in the affective one, due to the fact that acute symptoms are more prevalent in the former and temperamental symptoms in the latter.

4. The percentage of patients presenting suicide attempts and self-mutilation acts will decrease significantly from baseline to 10-year follow-up.

5. It is expected statistically significant reductions in general psychiatric symptoms of depression and hostility/aggression from baseline to 10-year follow-up.

6. In terms of dimensional personality traits, Neuroticism-Anxiety, Impulsivity-Sensation seeking, and Aggression-Hostility will decrease significantly from baseline to 10-year follow-up, presenting high effect sizes.

7. It is expected to observe significant declining rates of comorbidity with other PDs from baseline to 10-year follow-up.

8. It is expected a suicide rate up to 9% at 10-year follow-up.

9. It is expected a reduction in the rate of psychiatric hospitalization, individual therapy and use of psychotropic medications from baseline to 10-year follow-up.

10. Social functioning will moderately improve from baseline to 10-year follow-up.

There were not predetermined hypotheses for the exploratory study of the predictive effects of the age of first BPD diagnosis.

To study potential predictors of QOL of BPD patients in the long-term we drew the following exploratory hypothesis:

1. It is expected that QOL of BPD patients at 10 years will be predicted by the following baseline factors: age, severity of childhood traumatic experiences, BPD symptoms, FFM dimensions, and level of social functioning.

2. BPD remission will be associated with better physical health and lesser use of health care services at 10 years.

3. It is expected that both BPD remission and better physical health at 10-years will interact to predict higher QOL in the long-term.

3.2. <u>METHODS</u>

This is a naturalistic prospective study that was conducted in the BPD Unit at the Hospital de la Santa Creu i Sant Pau in Barcelona. The research methods of this study were mainly described in Article 1 (See section 3.3.1). Additional information was displayed in Communication 2, and Poster 2, 3, and 4 (Álvarez-Tomás, 2014; Álvarez-Tomás et al., 2015, 2016, 2018). A general overview of the procedures used in the study is explained below.

3.2.1. Participants

The initial sample of this study comprised 64 outpatients with BPD as primary diagnosis who had participated in a former clinical trial (Soler et al., 2005). Inclusion criteria were: (1) age between 18 and 45 years, (2) meeting DSM-IV-TR criteria for BPD by SCID-II and DIB-R interviews (First, Spitzer, & Gibbon, 1997; Zanarini, Gunderson, Frankenburg, & Chauncey, 1989), (3) BPD severity scores by the Clinical Global Impression-BPD-Severity (CGI-BPD-S) of 4 or more (Guy, 1976; Pérez et al., 2007).

Exclusion criteria were: (1) current diagnosis of mental retardation, organic mental disorder, schizophrenia, drug-induced psychosis, alcoholism or dependence on other substance, bipolar or major depression disorders, (2) having participated in another study over the previous three months.

Only six subjects of the initial sample might not be localized at follow-up. From those subjects who were localized, 12 refused to participate in this study or did not complete the follow-up assessments. Participants did not receive any remuneration. Contacting with relatives, it was known that five subjects from the initial sample had died by suicide over the follow-up period.

Finally, 41 subjects were reassessed at 10-year follow-up, which represents a drop-out rate of 36%. The follow-up sample included 92.7% of women and the mean age at baseline was 26.9 years ($SD = 6.3$). Dropouts and continuers were similar at baseline in age, gender, and other relevant sociodemographic characteristics, clinical features, and level of social functioning. Comparative analyses between dropouts and continuers are deeply described in Article 1 (See section 3.3.1).

For the study of differences in course patterns related to the age of first BPD diagnosis, we grouped the follow-up sample, using the mean age as cutoff point, into the ED and DD subgroups (ED subgroup ≤ 25 years; DD subgroup > 25 years). The ED and DD subgroups comprised 23 and 18 subjects, 91.3% and 94.4% women, with a mean age at baseline of 22.6 years ($SD = 3.7$) and 32.3 years ($SD = 4.4$), respectively. No differences were found between subgroups on dropout rate (Álvarez-Tomás, 2014; Álvarez-Tomás et al., 2016).

In Poster 4, the 40 subjects of the follow-up sample who were assessed by both DIB-R and SCID-II were grouped into two subgroups, the remitted ($n=22$) and non-

remitted (*n*=18) BPD patients, according to our restrictive operationalization of remission defined below in section 3.2.3 (Álvarez-Tomás et al., 2018).

3.2.2. Procedure

The recruitment and assessment processes in the initial study are described in a previous article (Soler et al., 2005). Participants in the initial study were recruited from the psychiatric services at the hospital. The initial assessment process lasted four weeks. It consisted of three assessment interviews by an experienced psychiatrist. Subjects from the initial sample were contacted 10 years later by postal mail. The objectives and procedure of the present study were explained to the subjects in the first contact in person or by phone. They were requested to participate in the current study, with independence from their assistance condition. The recruitment period at follow-up lasted 12 months.

All the components of the follow-up assessment were scheduled in one day. It comprised two consecutive interviews, one conducted by a psychiatrist and another by a clinical psychologist, and self-report questionnaires. In the first interview, the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998; Bobes, 1998) was completed by a psychiatrist. Lately, participants filled out all self-report questionnaires. In the second interview, the DIB-R, the SCID-II confirmatory interview, and the 17-item Hamilton Depression Rating Scale (17-HDRS; Hamilton, 1960; Bobes et al., 2003) were completed. In this interview, data on socio-demographic features, social functioning, and clinical indexes were also registered. This study was conducted according to the Declaration of Helsinki and was approved by the Clinical Research Committee at the Hospital de la Santa Creu i Sant Pau.

3.2.3. Variables & Instruments

Table 5 displays the variables and instruments which were used in the present study. Variables were registered on the following areas: sociodemographic data and functional features, clinical indexes, BPD symptomatology, Axis I and II comorbidity, general psychiatric symptoms, dimensional personality traits, social functioning, and QOL. In Table 5, variables are classified as constant or modifiable with regard to their expected likelihood to change over time. Constant variables were only considered as potential moderators/predictors in some analyses. These variables were mainly registered at follow-up, due to the fact that the aim of the initial trial differed from the study of the course of the disorder. The majority of modifiable variables were registered at both assessments, except for some data which were not analyzed in test-retest analyses.

In this study, remission was defined as not meeting diagnostic criteria for BPD in the last two years prior to the follow-up assessment. Initially, remission from BPD was only measured by the DIB-R (DIB-R Total score <6). Early analyses were run with this operationalization of remission and results were informed in preliminary posters and communications (Poster 1; Communication 1 and 2). Lately, we decided to apply a more restrictive operationalization of remission from BPD, measured by both the DIB-R and the SCID-II interviews, due to the variations in DIB-R diagnostic cut-offs observed in previous literature. This restricted definition of remission was used to analyze the data reported in Article 1 and Poster 2, 3, and 4 (Álvarez-Tomás et al., 2015, 2016, 2018), which are explained in section 3.3.1 and 3.3.2. In these cases, the sample for the analyses on remission comprised the 40 subjects who were evaluated by both the DIB-R and SCID-II interviews at baseline and follow-up assessments.

Table 5. Variables and instruments used in the 10-year follow-up study

	Constant Variables	**Instruments**	**Modifiable Variables**	**Instruments**
Sociodemographic data & Functional Indexes	Gender Country of birth	Self-report	Age Marital status Education Living arrangements No. children Location of residence No. previous residence moves Currently studying Domestic tasks Employment Occupational level Social benefits Presence physical illness *Type of physical illnesses* [a] *Serious accidents* [a] *Use of medical services* [a]	Self-report
Clinical Ind exes	Family psychiatric history Lifetime disorders Age 1st mental health consultation Age 1st BPD diagnosis Age 1st BPD treatment Childhood trauma	Self-report CTQ-SF	Psychiatric hospitalizations Use of mental health resources Suicidality	DIB-R & Self-report DIB-R
Psychopathology & Dimensional personality traits			BPD symptomatology DSM-IV PD diagnosis Dimensional Personality Traits Hostility Depression *Axis I comorbidity* [a]	DIB-R SCID-II ZKPQ BDHI 17-HDRS MINI
Social Functioning & QOL			Social Functioning *Quality of Life* [a]	SASS MQLI

Note. The nomenclature and the psychometric characteristics of the instruments used are described in Table 6. [a] Modifiable variables only assessed at follow-up.

Sociodemographic and functional features, and some clinical indexes (i.e., family psychiatric history, lifetime disorders and mental health treatment background) were informed by the subjects in a clinical interview, according to the research protocol. The age of first BPD diagnosis was asked to the participants as follows: "At what age were you first given the diagnosis of BPD by a specialist?" The age of first mental health consultation refers to the first contact of the subject with any kind of mental health intervention, whereas the age of first BPD treatment indicates the age when the subject received the first specialized treatment for BPD. Other variables were assessed by specific instruments, whom psychometric properties are displayed below in Table 6.

Table 6. Psychometric properties of instruments used in the follow-up study

Revised Diagnostic Interview for Borderlines (DIB-R) Zanarini et al., 1989 Tragesser et al., 2010 Barrachina et al., 2004	Semi-structured interview that assesses BPD symptomatology within the past two years on four domains: Affect, Cognition, Impulse Action Patterns, and Interpersonal Relationships. Section scores are obtained for each domain and converted into scaled section scores. We used section scores to study each domain due to their stability over time. The DIB-R total score consists of the sum of all scaled section scores and ranges from 0 to 10. The Spanish version has shown good psychometric properties: internal consistency, sensitivity, and specificity. In this version, the cut-off in DIB-R total score for BPD diagnosis is $\geq$6.
Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) First et al., 1997 Gómez-Beneyto et al., 1994	Semi-structured interview that covers the DSM-IV personality disorders and two additional categories (depressive and passive-agressive PDs). Firstly, the SCID-II Personality Questionnaire was completed and, lately, those items that screened positive were assessed by interview, considering the prior 2-year period. The Spanish version has been shown good properties to distinguish between PDs and good interrater reliability.
Zuckerman-Kuhlman Personality Questionnaire (ZKPQ) Zuckerman & Kuhlman, 1993 Zuckerman et al., 1993 Gutiérrez-Zotes et al., 2001 Gomà-i-Freixanet & Valero, 2008	Self-report questionnaire that evaluates the Alternative Five-Factor Model personality traits. It consists of 99 dichotomous items sorted into 5 factor scales: Neuroticism-Anxiety (N-Anx), Activity (Act), Sociability (Sy), Impulsive-Sensation Seeking (ImpSS) and Aggression-Hostility (Agg-Host). Zuckerman et al. (1993) proposed some correspondences with the FFM: N-Anx and Sy are similar to Neuroticism and Extraversion; Agg-Host and Imp-SS are opposite to Agreeableness and Conscientiousness. The Spanish version has shown good internal consistency of all the scales and good discriminant validity by the lack of correlation among scales. There are normative data of the ZKPQ for the Spanish population.

(continued)

Table 6. Psychometric properties of instruments used in the follow-up study

Clinical Global Impression-Borderline Personality Disorder - Severity CGI-BPD-S Pérez et al., 2007	The CGI-BPD-S scale is an adaptation of the CGI scale designed to assess severity in patients with BPD. It contains 10 items that score the nine relevant psychopathological domains of BPD, plus an additional global score. The modified scale showed good validity and reliability, and adequate sensitivity to change.
MINI International Neuropsychiatric Interview Sheehan et al., 1998 Bobes, 1998	Semi-structured interview that assesses the presence of lifetime and current Axis I diagnoses, according to the DSM-IV categories. The Spanish version has demonstrated an acceptable agreement with clinical diagnosis in primary health care.
17-item Hamilton Depression Rating Scale (17-HDRS) Hamilton, 1960 Bobes et al., 2003	Clinical scale that evaluates the severity of depression. It comprises 17 items, scoring from 0 to 2 or from 0 to 4. The total score ranges between 0 and 52. The Spanish version of the 17-HDRS showed an adequate discriminant validity, internal consistency; temporal stability; interrater reliability and sensitivity to change.
Buss-Durkee Hostility Inventory (BDHI) Buss & Durkee, 1957 Oquendo et al., 2001	Self-report questionnaire that evaluates hostility and aggression. BDHI total score ranges from 0 to 75, with a cutoff level of 27. The Spanish version has shown appropriate validity and test-retest reliability.
Childhood Trauma Questionnaire- Short Form (CTQ-SF) Bernstein & Fink, 1998 Heim et al., 2009	Self-report questionnaire that explores the occurrence of several traumatic events during childhood. It consists of 28 items grouped into five subscales: sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect. Each subscale score ranges from 5 to 25. The total score consists of the sum of subscale scores. The CTQ has good internal consistency, good specificity and sensitivity of cutoff scores to classify maltreated subjects.

3.2.4. Statistical analyses

All the analyses were run considering the follow-up sample, who completed both assessments in the study. The comparative analyses between repeated measures at baseline and 10-year follow-up in the overall sample are described in Article 1 (See section 3.3.1). In this paper, Student's t tests for paired samples were used for continuous measures and McNemar test with exact methods for dichotomous ones. Hedges's $\hat{g}$ was used to calculate effect sizes. Values were interpreted as small size ($\geq$.20), medium ($\geq$ .50), and large ($\geq$.80).

To study the effects of the age of first BPD diagnosis, we firstly analyzed descriptive data of the ED and DD subgroups on psychiatric antecedents, clinical indexes

and functional features. In Communication 2 and Poster 3, Chi-square analyses, or Fisher's exact tests where required, were run for comparisons between subgroups on psychiatric antecedents, suicide rate, and remission rate (Álvarez-Tomás, 2014; Álvarez-Tomás et al., 2016). In Communication 2, mixed factorial ANOVA analyses were run to compare the prospective changes in DIB-R total and section scores, and SASS total score between subgroups (Álvarez-Tomás, 2014). Hedges's $\hat{g}$ (standardized difference between the change of means of the ED y DD subgroups from baseline to follow-up, the denominator being the pooled standard deviation in the pretest) were also calculated to determine effect sizes in repeated-measures analyses, using similar criteria for interpretation as in Article 1. In Poster 3, a Student's t test for independent samples was run to compare the age of first mental health intervention between both subgroups (Álvarez-Tomás et al., 2016). Moreover, the risk ratio (RR) for remission and suicide was also calculated. A value of RR < 1 meant a reduced risk whereas a RR > 1 meant an increased risk of remission or suicide in the indicated subgroup. We considered that differences between subgroups were significant when the 95% confidence interval (CI) of the RR did not contain the value 1.

To explore potential predictors of the long-term QOL in Poster 2, Pearson's r correlations were run between several baseline variables (i.e., age, childhood trauma, initial BPD symptomatology, dimensional personality traits and social functioning) and the QOL reported at 10-year follow-up (Álvarez-Tomás et al., 2015). r values were interpreted as small size ($\geq$ .10), medium ($\geq$ .30), and large ($\geq$ .50). The most relevant three variables were introduced by forced entry method into a multiple linear regression analysis, to study their partial contribution to predict the long-term QOL.

In Poster 4, we reported the prevalence of various physical health illnesses and rates of primary care utilization at 10-year follow-up in the overall sample and in remitted

and non-remitted BPD patients (Álvarez-Tomás et al., 2018). Differences in percentages between these subgroups were analyzed with Fisher's exact tests. A MANOVA analysis was run to study the impact of BPD remission and current presence of any medical illness on the QOL at 10 years.

3.3. <u>RESULTS</u>

3.3.1. ARTICLE 1

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Long-term course of Borderline Personality Disorder: a prospective 10-year follow-up study

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Abstract

The aim of this prospective study was to expand previously reported evidence on the 10-year clinical and functional course of borderline personality disorder (BPD) in a Spanish sample. Participants diagnosed with BPD were assessed at baseline and at 10-years follow-up to evaluate BPD symptomatology and other relevant clinical measures, suicidal behavior, dimensional personality traits, Axis I and II comorbidity, use of mental health resources, and psychosocial functioning. At the 10-year follow-up, significant improvements were observed on BPD domains, suicidal behavior, and other clinical measures. Neuroticism, impulsiveness and aggression-hostility features trended towards normalization, whereas activity and sociability impaired over time. Comorbidity with Axis I and personality disorders remained high. Social functioning and occupational functioning were largely unchanged. These findings confirm the tendency towards a symptomatic remission of BPD over the long term with regard to symptom criteria and characteristic dimensional traits. However, psychosocial functioning remained impaired.

Keywords: Borderline personality disorder; long-term course; follow-up studies; dimensional personality factors; comorbidity; social functioning

Introduction

When borderline personality disorder (BPD) was first defined, it was considered a severe, chronic, untreatable disorder with poor prognosis. However, the publication of four large, retrospective 15-year follow-up studies in the 1980s (McGlashan, 1986; Paris, Brown, & Nowlis, 1987; Plakun, Burkhardt, & Muller, 1985; Stone, 1990) significantly altered this perception. Those studies all reported significant improvements in borderline symptomatology and global functioning. Moreover, the Montreal study subsequently found that these improvements continued at the 27-year follow-up (Paris, 2002; Paris & Zweig-Frank, 2001). The most striking finding in that study was the increase in the remission rate —from 75% at 15 years to 92% at 27 years— while overall functioning remained steady. Despite these positive changes, long-term BPD presents an important drawback, the persistence of residual affective symptoms and high suicide rates over time (up to 10.3% at 27 years) in spite of the overall improvement in the BPD symptomatology.

More recently, two rigorous prospective longitudinal studies involving large BPD clinical samples have reported results after 10 plus years of follow-up: the McLean Study of Adult Development (MSAD; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2005) and the Collaborative Longitudinal Personality Disorders Study (CLPS; Gunderson et al., 2000). The findings reported by these studies provided prospective evidence that the course of BPD is characterized by a tendency towards remission and symptomatic stabilization, even as functional impairments may persist in the long-term (Sanislow, Marcus, & Reagan, 2012; Zanarini, 2012). At 10 years of follow-up, the MSAD and CLPS studies reported cumulative remission rates, respectively, of 93% and 85%, although 30% and 11% of remitted patients, respectively, presented a subsequent symptomatic recurrence (Gunderson et al., 2011; Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010b). These studies also found a modest improvement in psychosocial

functioning over time, although functional recovery appeared more difficult to attain than clinical remission (MSAD, 50% recovery; CLPS, 21% functional remission) (Gunderson et al., 2011; Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010a; Zanarini et al., 2010b).

Although these studies provide valuable prospective data, they were conducted in North America and need to be replicated in other countries with different psychiatric care systems to confirm the generalizability of these findings. Our study was conducted in Catalonia, Spain, where universal coverage is provided by the public health system. It is unknown whether the characteristics of different health care systems could affect the expected long-term course of BPD. To date, as far as we are aware, there are no other prospective studies outside of North America that have reported long-term follow-up (10-years or more) in clinical cohorts of subjects with BPD.

In addition to the longitudinal prospective research described here, evidence in support of a hybrid diagnostic model of personality disorders has been growing in the past decade (Samuel & Widiger, 2008). In fact, this model was recently incorporated into the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*, American Psychiatric Association, 2013). According to this dimensional perspective, BPD is characterized by negative affectivity (i.e., high Neuroticism), disinhibition, and antagonism domains (i.e., low Conscientiousness and Agreeableness). In terms of personality traits, both the CLPS and MSAD studies found that a pattern of declining Neuroticism and increasing Conscientiousness was more likely in patients with BPD than in other personality disorders, although, at 10 years, differences were significant only for Neuroticism (Hopwood et al., 2009; Hopwood & Zanarini, 2010). Furthermore, longitudinal studies have extended evidence on temporal interactions between BPD symptomatology and dimensional traits, which supports the relevance of both aspects in understanding the long-term course of the disorder. It is also claimed that dimensional

models may offer further explanation for the highly prevalent Axis II comorbidity in BPD (Wright, Hopwood, & Zanarini, 2015).

In summary, the main aims of the present study were to study the long-term clinical and psychosocial functioning course of individuals with BPD in a Spanish sample. Secondarily, we also aimed to study changes in dimensional personality traits and the co-occurrence with other personality disorders at 10-year follow-up.

Method

Participants and procedure

This was a naturalistic prospective longitudinal study to follow a cohort of subjects whose primary diagnosis was BPD. The subjects were followed for 10 years. The initial sample comprised a total of 64 outpatients with BPD, recruited from the BPD Unit at the Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. All patients had participated in a clinical trial comparing olanzapine plus dialectical-behavioral therapy (DBT) versus placebo plus DBT for 12 weeks. That clinical trial did not involve any posttreatment follow-up (for details, see Soler et al., 2005).

All participants who completed the baseline preintervention assessments in the initial trial were considered for inclusion in this longitudinal follow-up study. Inclusion criteria were: (a) diagnosis of BPD according to *DSM-IV* criteria as assessed by the Structured Clinical Interview for *DSM-IV* Axis II Disorders and the Revised Diagnostic Interview for Borderlines (First, Spitzer, & Gibbon, 1997; Zanarini, Gunderson, Frankenburg, & Chauncey, 1989); (b) age 18-45 years, inclusive; and (c) Clinical Global Impression (CGI) severity of illness score ≥ 4 (Guy, 1976; Perez, et al, 2007). Exclusion criteria included a current diagnosis of schizophrenia, drug-induced psychosis, bipolar or

major depressive disorders, alcoholism or dependence on any other substance, mental retardation, or an organic syndrome with psychiatric symptoms.

Subjects were invited by letter to participate in the follow-up study. Participants received no remuneration for participating. For inclusion, all patients were required to sign the new informed consent form after receiving detailed information about the study protocol. The Clinical Research Ethics Committee at the Hospital de la Santa Creu i Sant Pau approved the study, which was carried out according to the Declaration of Helsinki.

Baseline assessments were conducted by an experienced psychiatrist and a clinical psychologist according to the assessment protocol of the original trial. At follow-up, participants were reinterviewed by a psychiatrist and a clinical psychologist, both of whom remained blind to the initial assessments.

All participants were interviewed at baseline and at 10 years to assess demographic data, psychiatric history, other clinical variables, and functional characteristics. Participants were assessed to evaluate the presence of suicidal behavior (suicide attempts/gestures and self-mutilations) and the use of mental health resources (psychiatric hospitalizations, individual psychotherapy, outpatient psychiatric treatment, rehabilitation services/home support and use of psychoactive drugs) in the 2-year period preceding both assessments. During this 2-year period prior to the follow-up assessment, subjects who no longer met the criteria for BPD assessed by both diagnostic interviews (DIB-R< 6 and SCID-II Borderline Subscale<5) were considered to be in remission.

Measures

Revised Diagnostic Interview for Borderlines (*DIB-R*). The DIB-R (Zanarini et al., 1989) is a semistructured interview that determines a diagnosis of BPD within the past two years. This instrument includes four sections that evaluate different symptomatic areas related to BPD. Section scores are obtained by adding the summary statements

within each section: Affect (0-10), Cognition (0-6), Impulse Action Patterns (0-10), and Interpersonal Relationships (0-18). They are converted into scaled section scores by assigning categorical values based on clinical criteria. The DIB-R total score consists of the sum of all scaled section scores and ranges from 0 (*no BPD severity*) to 10 (*high BPD severity*). We used the validated Spanish version (Barrachina et al., 2004), which has shown good psychometric properties regarding internal consistency (Cronbach's alpha 0.89), sensitivity (0.81) and specificity (0.94), with a cut-off for diagnosing BPD of ≥ 6 in the DIB-R total score. The interviewers were experienced psychologists and presented a high interrater reliability (within-class correlation 0.94). To study each area of BPD symptomatology, we used section scores instead of scaled section scores because they have shown more stability over time (Tragesser et al., 2010).

Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II). All participants completed the SCID-II Personality Questionnaire (First et al., 1997) and were then interviewed with the SCID-II to assess all items that screened positive, considering only the prior 2-year period in both assessments. The SCID-II interview covers the *DSM-IV* personality disorders and the appendix categories of depressive and passive-aggressive personality disorders. The Spanish version has been shown to have good properties for discriminating between Axis II personality disorders, and it also has good interrater reliability (Kappa, 0.85; Gómez-Beneyto et al., 1994).

Zuckerman-Kuhlman Personality Questionnaire (ZKPQ). The ZKPQ (Zuckerman & Kuhlman, 1993) was designed to assess the Alternative Five-Factor Model of personality traits. It consists of 99 dichotomous items sorted into five content scales: Neuroticism-Anxiety (N-Anx), Activity (Act), Sociability (Sy), Impulsive-Sensation Seeking (ImpSS), and Aggression-Hostility (Agg-Host). Zuckerman, Kuhlman, Joireman, Teta, and Kraft (1993) compared the ZKPQ factors with the Five-Factor Model

and concluded that N-Anx and Sy are similar to Neuroticism and Extraversion, whereas Agg-Host and Imp-SS are opposite to Agreeableness and Conscientiousness. The Spanish version of the ZKPQ (Gutiérrez-Zotes, Ramos, & Saiz, 2001) has shown good psychometric properties, and normative data have been provided for the Spanish population (Gomà-i-Freixanet & Valero Ventura, 2008).

17-item Hamilton Depression Rating Scale (*17-HDRS*). The 17-HDRS (Hamilton, 1960) was used to assess changes in affective symptoms from baseline to follow-up. HDRS total scores range from 0 to 54. We used the Spanish version, which has shown appropriate psychometric properties and sensitivity to change in depressive outpatients (Bobes et al., 2003).

Buss-Durkee Hostility Inventory (*BDHI*). The BDHI (Buss & Durkee, 1957; Oquendo et al., 2001 [Spanish version]) was designed to evaluate hostility and aggression. BDHI total scores range from 0 to 75, with a proposed cutoff level of 27. This scale has shown appropriate validity and test-retest reliability.

MINI International Neuropsychiatric Interview (*MINI*). The MINI (Sheehan et al., 1998) was used to assess Axis I comorbidity at follow-up. We used a Spanish version, which has demonstrated an acceptable agreement with clinical diagnosis in primary health care (Bobes, 1998).

Social Adaptation Self-Evaluation Scale (*SASS*). The SASS (Bosc, Dubini, & Polin, 1997) was used to evaluate social functioning, with SASS total scores ranging from 35 to 52 defined as normal. The Spanish version has shown good test-retest reliability and sensitivity to change over time in depressive patients (Bobes et al., 1999).

Data analysis

The data analysis included only those subjects who completed both baseline and 10-year follow-up assessments. Student's *t* test for paired samples was used to compare

continuous measures. McNemar's test with exact method was used to determine the differences between two related dichotomous variables.

For continuous data, Hedge's $\hat{g}$ effect sizes were calculated using the pooled *SD* and controlling for *r* pre-post correlations. For dichotomous figures, Hedge's $\hat{g}$ effect sizes were derived from odds ratios based on 2x2 tables (Chinn, 2000). In both cases, Hedge's $\hat{g}$ values were interpreted as small ($\hat{g} \geq 0.20$), medium ($\hat{g} \geq 0.50$), and large ($\hat{g} \geq 0.80$) effect sizes.

A modified Bonferroni procedure (Jaccard & Wan, 1996) was used to determine the statistical significance of *p* values in order to minimize both Type I and Type II error. This procedure was applied within the following subgroups of variables: (a) borderline symptomatology and current psychiatric symptoms, (b) suicidal behavior, (c) Axis II comorbidity (SCID-II), (d) dimensional personality traits, (e) use of mental health resources, and (f) socio-demographic and functional features.

Results

Baseline characteristics of the sample

Of the initial baseline sample of 64 individuals (56 female, 8 male; mean age 26.7 ± 5.7 years), 41 (64%) were assessed at the 10-year follow-up (completer group). A total of 23 subjects (36%) dropped out of the study: We were unable to locate 6 subjects (9.4%), 12 refused to participate in the follow-up assessment (18.7%), and 5 had committed suicide (7.8%). The resultant follow-up study sample included 41 participants (38 females; 92.7%) with a mean age at baseline of 26.9 years (*SD* = 6.3) (Figure 1.1).

Figure 1.1. Flowchart of the study participants **
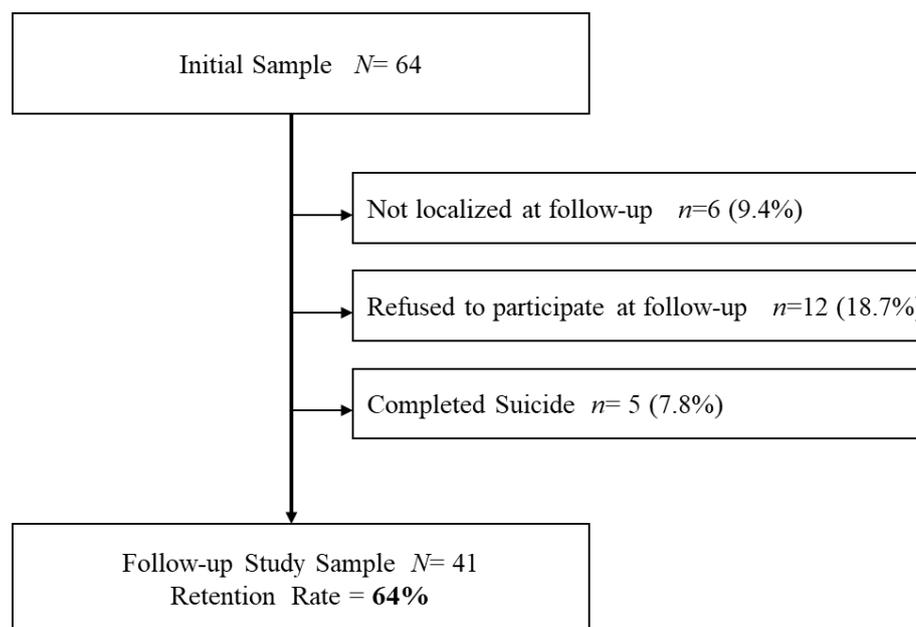
Note. ** Figure 1 in the original article

We compared the baseline characteristics of dropouts and completers to check for differences, finding no significant differences in age, gender, or other sociodemographic characteristics (except for education, marital status, and living arrangements). Dropouts were more likely to have completed high school or university (95.5% vs. 71.8%), be single or separated/divorced (77.3% vs. 48.7%), and live with their parents (94.7% vs. 48.5%) than completers (χ^2 = 5.0, *df* = 1, *p* = .026; χ^2 = 4.7, *df* = 1, *p* = .029; χ^2 = 11.4, *df* = 1, *p* = .001, respectively). No other significant differences between dropouts and completers were found in clinical severity (CGI-S mean score, 5.2 vs. 5.0, *t* = -0.71, *p* = .48), suicidal behavior (78.3% vs. 75.6% any suicide gesture/attempt past 2 years, *t* = 0.05, *p* = .81), prevalence of any comorbid personality disorder (56.5% vs. 46.3%, *t* = 0.61, *p* = .43), and social functioning (SASS total mean score, 28.5 vs. 30.2 [*n* = 38], *t* = -0.73, *p* = .47). Given the high suicide rate, we also compared this subset of patients who committed suicide to completers to check for a potential bias in BPD severity and suicidal behavior, although no differences were found between these groups at baseline.

Clinical characteristics at baseline and at 10-year follow-up

Clinical differences between the baseline and 10-year assessments are shown in Table 7.1. We found an overall improvement in BPD symptomatology between baseline and follow-up, indicated by significant decreases in the DIB-R total mean score (7.4 vs. 4.2, $p < .001$) and the SCID-II Borderline subscale mean score (7.3 vs. 4.3, $p < .001$), with both differences showing large effect sizes. At 10-year follow-up, the remission rate was 55% ($n = 22/40$), based on both diagnostic interviews. By BPD symptom domains, mean scores in Affect, Impulse Action Patterns, and Interpersonal Relationships DIB-R subscales significantly declined at 10-year follow-up, showing medium to large effect sizes. Only the Cognition subscale showed no significant differences between mean baseline and follow-up scores, although its values reached no clinically relevant levels in either of the assessments.

Significant differences for other clinical scales were also found, as shown in Table 7.1. Affective and hostility/aggression symptoms showed substantial decreases at 10 years, with large effect sizes.

Regarding suicidal behavior, the percentage of subjects who reported making at least one suicide gesture/attempt within the previous 2-year period declined significantly, from 75.6% at baseline to 17.1% at the 10-year follow-up. The percentage of multiple suicide attempters also decreased at follow-up. Rates of self-mutilation similarly declined between assessments. All these differences were statistically significant and showed large effect sizes.

In terms of Axis II comorbidity, there were no significant differences between baseline and follow-up in rates of co-occurring personality disorders. Despite the lack of statistical significance, the percentage of subjects with avoidant and obsessive-

compulsive personality disorders increased between assessments (from 10% to 27.5% and from 17.5% to 40%, respectively).

Table 7.1. Clinical features of the follow-up study sample (*N*=41) at baseline and at 10-year follow-up assessments **

	Baseline (BL)	Follow-up (FU)	BL vs. FU		
	M (SD)	*M (SD)*	*t*	*p*	*ĝ* [95% CI]
Borderline Symptomatology					
DIB-R Total Score	7.4 (1.1)	4.2 (3.7)	5.58	<.001*	1.28 [0.98, 1.58]
Affect	8.0 (1.6)	5.7 (3.8)	3.58	.001*	0.77 [0.52, 1.02]
Cognition	1.9 (1.0)	1.6 (1.8)	0.89	.38	0.21 [-0.01, 0.43]
Impulse Action Patterns	5.2 (1.7)	3.1 (3.0)	4.20	<.001*	0.92 [0.65, 1.18]
Interpersonal Relationships	8.6 (2.4)	5.2 (4.3)	4.53	<.001*	0.99 [0.72, 1.26]
SCID-II Borderline Subscale [a]	7.3 (1.3)	4.3 (3.4)	5.77	<.001*	1.36 [1.05, 1.67]
Current Psychiatric Symptoms					
17-HDRS total score	20.4 (3.8)	11.8 (11.2)	4.90	<.001*	1.09 [0.82, 1.37]
BDHI total score [b]	47.3 (7.9)	25.5 (14.2)	9.14	<.001*	2.32 [1.84, 2.81]
	n (%)	*n* (%)	b/c [c]	*p* [d]	*ĝ* [95% CI]
Suicidal Behavior					
Any suicide gesture/attempt	31 (75.6)	7 (17.1)	25/1	<.001*	1.74 [0.66, 2.82]
≥ 2 suicide gestures/attempts	25 (61)	5 (12.2)	20/0	<.001*	2.00 [0.48, 3.52]
Any self-mutilation [a]	34 (85)	11 (27.5)	24/1	<.001*	1.72 [0.64, 2.80]
≥ 2 self-mutilations [a]	26 (65)	8 (20)	19/1	<.001*	1.60 [0.51, 2.69]
Axis II Comorbidity (SCID-II) [a]					
Avoidant	4 (10)	11 (27.5)	0/7	.02	-1.44 [-1.24,-0.34]
Dependent	6 (15)	6 (15)	5/5	1.0	0.00 [-0.67, 0.67]
Obsessive-compulsive	7 (17.5)	16 (40)	2/11	.02	-0.93 [-1.74,-0.11]
Passive-Aggressive	8 (20)	11 (27.5)	5/8	.58	-0.25 [-0.87, 0.35]
Paranoid	9 (22.5)	13 (32.5)	4/8	.39	-0.37 [-1.03, 0.27]
Schizotypal	2 (5)	3 (7.5)	1/2	1.0	-0.37 [-1.74, 0.92]
Schizoid	1 (2.5)	1 (2.5)	1/1	1.0	0.00 [-1.52, 1.50]
Histrionic	3 (7.5)	1 (2.5)	3/1	.63	0.60 [-0.64, 1.82]
Narcissistic	2 (5)	3 (7.5)	1/2	1.0	-0.37 [-1.62, 0.92]
Antisocial	3 (7.5)	6 (15)	3/6	.51	-0.37 [-1.11, 0.37]
Any comorbid Axis II disorder	19 (47.5)	24 (60)	6/11	.33	-0.37 [-0.87, 0.22]

Note. 17-HDRS = 17-item Hamilton Depression Rating Scale; BDHI = Buss-Durkee Hostility Inventory; [a] *n*=40; [b] *n*=32; [c] b and c indicate the discordant pairs in the 2x2 tables for McNemar's test; [d] Exact two-tailed *p*-values; * Significant *p*-values according to Jaccard & Wan's correction; ** Table 1 in the original article.

In terms of axis I comorbidity at the 10-year assessment, 31.7% of completers showed affective disturbances (17.1% dysthymia, 14.6% current major depressive episode), and the prevalence of anxiety disorders was also high and clinically relevant (41.5% of subjects with generalized anxiety disorder and 17.1% with panic disorder). Finally, 24.4% of the sample presented drug dependence/abuse and 7.3% had alcohol dependence/abuse.

Dimensional personality traits

Figure 1.2 presents the mean values (*SD*) of the ZKPQ personality factors in the study sample at baseline and at 10-year follow-up. It also shows the comparative Spanish normative data in the general population (Gomà-i-Freixanet & Valero Ventura, 2008). Scores on all personality dimensions significantly decreased between baseline and follow-up (N-Anx, $t = 5.69$, $p < .001$; Imp-SS, $t = 5.48$, $p < .001$; Agg-Host, $t = 7.25$, $p < .001$; Act, $t = 2.64$, $p = .01$; Sy, $t = 7.21$, $p < .001$), and these differences showed medium and large effect sizes (N-Anx, $\hat{g} = 1.44$, 95% CI [1.06, 1.82]; Imp-SS, $\hat{g} = 1.40$, 95% CI [1.03, 1.78]; Agg-Host, $\hat{g} = 1.86$, 95% CI [1.42, 2.30]; Act, $\hat{g} = 0.68$, 95% CI [0.39, 0.97]; Sy, $\hat{g} = 1.93$, 95% CI [1.48, 2.38]).

Compared to normative data for an equivalent population group in age and gender, z scores on Neuroticism-Anxiety, Impulsive-Sensation Seeking and Aggression-Hostility in the study sample showed a trend towards amelioration and normalization from baseline to follow-up (N-Anx, $z = 1.69$ vs. $z = 0.05$; ImpSS, $z = 1.09$ vs. $z = -0.05$; Agg-Host, $z = 1.19$ vs. $z = -0.52$). By contrast, decreases in the Activity and Sociability subscales from baseline to follow up indicate a tendency toward impairment of these personality factors over time comparing to normative data (Act, $z = -0.28$ vs. $z = -0.84$; Sy, $z = -0.21$ vs. $z = -1.49$).

Figure 1.2. ZKPQ mean factor scores (SD) of the study sample at baseline and at 10-year follow-up **
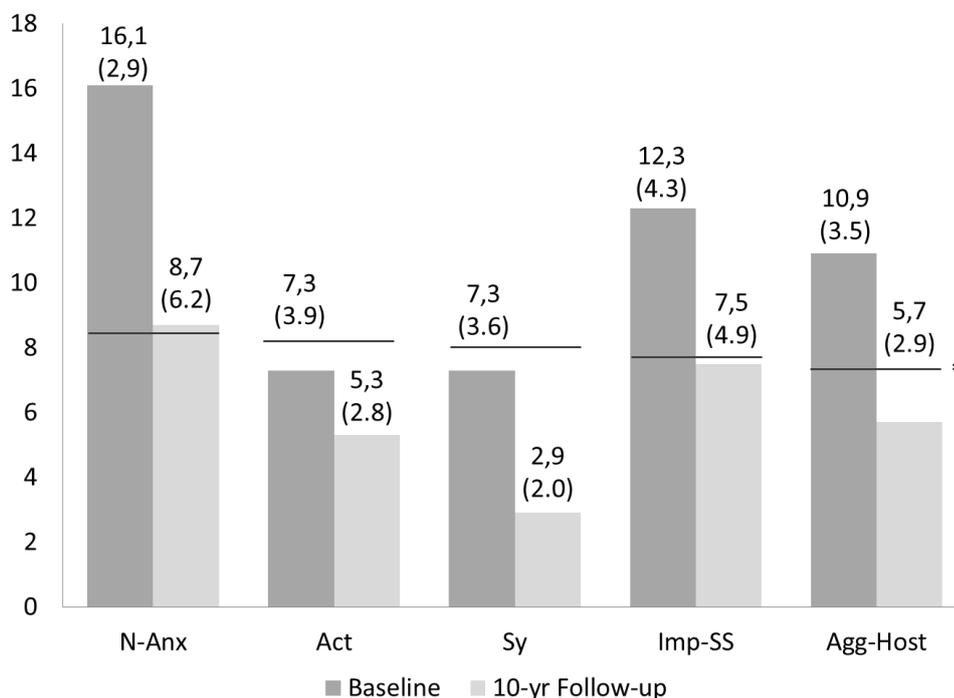
Note. N-Anx = Neuroticism-Anxiety; Act = Activity; Sy = Sociability; Imp-SS = Impulsive—ensation Seeking; Agg-Host = Aggression-Hostility. *Horizontal lines represent Spanish normative data (women 26-40 years old): N-Anx = 8.46 (4.52); Act = 8.29 (3.44); Sy = 8.02 (3.44); Imp-SS = 7.72 (4.21); Agg-Host = 7.28 (3.04); ** Figure 2 in the original article.

Use of mental health resources over 10-year follow-up

Table 7.2 presents prevalence data (baseline and at 10-year follow up) with regard to use of mental health treatment within the prior 2 years. We found relevant reductions from baseline to follow-up in all clinical treatment modalities comparing both assessments (46.3% at baseline vs. 22% at 10-year follow up for any psychiatric hospitalization; 95.1% vs. 61% for individual psychotherapy; and 90% vs. 67.5% for outpatient psychiatric treatment), with medium and large effect sizes, although only the decline in individual psychotherapy was statistically significant. The percentage of

subjects taking psychiatric medication decreased (nonsignificantly) from 89.5% to 71.1%, although the mean number of psychoactive drugs reported at both assessments was practically unchanged (2.6 [SD=1.5] vs. 2.1 [SD=1.7]; p = .12).

Over the 10-year follow-up period, more than half of the completers reported no psychiatric hospitalizations, although outpatient clinical treatments were common (75% individual psychotherapy, and 77.5% outpatient psychiatric treatment). It is noticeable that rehabilitation services emerged as necessary resources for a quarter of the sample over the 10 years of follow-up.

Table 7.2. Use of Mental Health Resources over 10-year follow-up **

Use Mental Health Resources	Baseline (BL)	Follow-up (FU)			BL vs. FU	
Last 2 years	n (%)	n (%)	b/c [a]	p [b]	$\acute{g}$ [95% CI]	
Any Psychiatric Hospitalization	19 (46.3)	9 (22)	15/5	.04	0.60 [0.05, 1.15]	
Individual Psychotherapy	39 (95.1)	25 (61)	15/1	.001*	1.47 [0.37, 2.56]	
Outpatient Psychiatric Treatment (n=40)	36 (90)	27 (67.5)	11/2	.02	0.92 [0.11, 1.73]	
Rehabilitation Services (n=39)	0 (0)	3 (7.7)	0/3	.25	-1.07 [-2.67, 0.55]	
Psychiatric Medication (n=38)	34 (89.5)	27 (71.1)	9/2	.07	0.81 [-0.02, 1.65]	
	M (SD)	M (SD)	t	p	$\acute{g}$ [95% CI]	
Nº Psychoactive Drugs (n=38)	2.6 (1.5)	2.1 (1.7)	1.60	.12	0.36 [0.12, 0.60]	
10 years period		n (%)				
No Psychiatric Hospitalization		22 (53.7)				
Individual Psychotherapy (n=40)		30 (75)				
Outpatient Psychiatric Treatment (n=40)		31 (77.5)				
Rehabilitation Services (n=36)		9 (25)				

Note. [a] b and c indicate the discordant pairs in the 2x2 tables for McNemar's test; [b] Exact two-tailed p-values; * Significant p-values according to Jaccard & Wan's correction; ** Table 2 in the original article.

Social and functional characteristics at baseline and at 10-year follow-up

Differences in social and functional characteristics between both assessments are shown in Table 7.3. The percentage of subjects being married or in a relationship remained steady. At baseline, almost half of the sample was living with their parents

(46.9%). By contrast, at the 10-year follow-up, most participants (87.5%) were living on their own or with a partner, a significant difference from baseline. The percentage of subjects with children also increased significantly (from 17.5% to 50%) over the 10-year period.

Table 7.3. Comparative socio-demographic and functional features of the study sample at baseline and at 10-year follow-up **

	Baseline (BL)	Follow-up (FU)		BL vs. FU	
	n (%)	n (%)	b/c [a]	p [b]	$ĝ$ [95% CI]
Socio-demographic features					
Marital Status (n=39)					
Married/In a relationship	20 (51.3)	20 (51.3)	9/9	1.0	0.00 [-0.51, 0.50]
Single/Separated/Divorced	19 (48.7)	19 (48.7)			
Living arrangements (n=32)					
With parents	15 (46.9)	4 (12.5)	11/0	.001*	1.68 [0.14, 3.20]
Alone or with a partner	17 (53.1)	28 (87.5)			
Having Children (n=40)	7 (17.5)	20 (50)	0/13	<.001*	-2.12 [-3.74, -0.50]
Functional features					
Education (n=39)					
College	6 (15.4)	9 (23.1)	1/4	.38	-0.75 [-1.90, 0.44]
Primary/High School	33 (84.6)	30 (76.9)			
Employed (n=33)	18 (54.5)	14 (42.4)	9/5	.42	0.31 [-0.27, 0.91]
Any social benefit (n=31)	8 (25.8)	14 (45.2)	5/11	.21	-0.43 [-0.98, 0.15]
Disability pension (n=31)	1 (3.2)	8 (25.8)	0/7	.02	-1.43 [-2.96, 0.09]
	M (SD)	M (SD)	t	p	$ĝ$ [95% CI]
SASS Total Score (n=32)	30.9 (9.5)	34.7 (10.6)	-1.93	.06	-0.47 [-0.74,-0.21]

Note. SASS = Social Adaptation Self-evaluation Scale; [a] b and c indicate the discordant pairs in the 2x2 tables for McNemar's test; [b] Exact two-tailed p-values; * Significant p-values according to Jaccard & Wan's correction; ** Table 3 in the original article.

In terms of functional characteristics, self-reported social adaptation assessed by the SASS scale showed a slight but nonsignificant improvement from baseline to follow-up, although mean total SASS scores remained below the normal range in both assessments. The majority of the study sample (84.6%) had at least high school

educational level at baseline and this percentage remained almost unchanged over the 10-year period. Similar rates of employment were also found at both assessments, with approximately half of the sample employed. However, the percentage of participants receiving any social assistance (due to health disabilities or social disadvantages) increased (nonsignificantly) from 25.8% to 45.2% over the study period. Similarly, the percentage of subjects receiving a permanent disability pension rose substantially (from 3.2% to 25.8%), although this difference did not reach statistical significance.

Discussion

Findings from this long-term prospective study in a Spanish sample provide further support for previously reported evidence on the positive prognosis of BPD in the long term. We found that more than half of subjects diagnosed with BPD at baseline no longer met the study criteria for BPD at 10 years. Moreover, we observed a significant clinical improvement on all BPD symptomatic domains that were initially impaired. Similarly, general psychiatric symptoms also improved markedly, although Axis I comorbidity rates were still high at follow-up and certain co-occurring personality disorders, such as avoidant and obsessive-compulsive disorders, increased but not significantly. Regarding personality dimensions, neuroticism, impulsiveness and aggression-hostility features all normalized over time; by contrast, activity and sociability dimensions worsened. We found a notable reduction in the use of mental health resources, although a relevant proportion of the subjects still required psychotherapy, pharmacotherapy, or rehabilitation interventions at 10 years. Our findings are consistent with, and confirm, previous evidence indicating that clinical improvement is not accompanied by a similar pattern in social and occupational functioning.

This study replicated the results on BPD symptomatology reported by previous longitudinal research studies (Gunderson et al., 2011; Zanarini et al., 2010b), although the 10-year remission rate was slightly lower in our sample. Several factors may have contributed to this divergence in remission rates, including methodological differences in the definition of remission, instruments used, baseline sample characteristics, or the cultural context and extent and type of mental health assistance received. Compared to the other long-term prospective studies, we reported remission rates only for the 2-year period prior to the follow-up assessment. By comparison, those other studies reported cumulative remission rates (lasting at least 12 or 24 months) over the 10-year follow-up. Thus, our index may be more sensitive to variations in particular symptoms in the most recent years due to the natural variability in the course of the disorder. Other relevant reasons for these differences in remission rates may be due to dissimilarities in terms of the intensity or specificity of clinical treatments. However, medium-term follow-up studies comparing outcomes from specialized psychotherapeutic modalities and treatment as usual have reported contradictory findings in terms of remission rates (Bateman & Fonagy, 2008; Davidson, Tyrer, Norrie, Palmer, & Tyrer, 2010). Notwithstanding this variation, of interest is the significant improvement observed over time on all BPD domains that were clinically relevant at baseline (i.e., Affect, Impulse action patterns and Interpersonal relationships). We found similar reductions to those reported in the MSAD study in terms of rates of suicide gestures/attempts or self-mutilation; nevertheless, in contrast to the MSAD study, five patients in our study (7.8%) committed suicide (Zanarini et al., 2010b).

We observed a marked improvement in affective and hostility symptoms in our sample, even though Axis I comorbidity was still clinically relevant at follow-up. As in previous studies (Paris, 2002; Silverman, Frankenburg, Reich, Fitzmaurice, & Zanarini,

2012; Zanarini et al., 2011), comorbidity with affective and anxiety disorders and alcohol/drug misuse was notable in the long term.

Regarding Axis II comorbidity, we observed an apparent increase in BPD comorbidity with avoidant and obsessive-compulsive personality disorders at 10 years. It is possible that the clinical improvement in BPD symptoms observed in our study —such as emotional dysregulation, interpersonal relationships, and, particularly, impulsivity — imply avoidant behaviors as an adaptation process to prevent conflicts or other social difficulties. In this sense, obsessive-compulsive traits might also play an adaptive role as an emotional control mechanism. Indeed, findings in the CLPS study suggest that subjects with obsessive personality disorder showed an improvement on psychosocial functioning over the 10-year follow-up (Gunderson et al., 2011). Considering the evidence from large studies with healthy samples using other Big Five models (Srivastava, John, Gosling & Potter, 2003) and also the findings of a meta-analysis of more than 150 studies on developmental changes in normal personality (Roberts & DelVecchio, 2000), dimensions such Agreeableness and Conscientiousness increase with age. As Durbin and Klein (2006) pointed out, the increase in conscientiousness that occurs during adult development may also lead to increases in obsessive-compulsive personality disorder. Although Durbin's hypothesis was not based on samples with individuals with personality disorders, it is possible that the rise in Axis II comorbidity observed is "artificial", in the sense that the observed increase may be related to aging and subsequent age-related changes in dimensional personality. Aside from the aforementioned hypothesis, the high rates of Axis II comorbidity may also be related to the high degree of chronicity in our sample (Sanislow et al., 2009; Zanarini, Frankenburg, Vujanovic, et al., 2004).

From a dimensional perspective, according to Wright et al. (2015), the overall improvement observed in BPD symptoms observed in our sample may be associated with amelioration in Neuroticism-Anxiety, Impulse-Sensation Seeking and Aggression-Hostility traits. These findings are also consistent with previous evidence from CLPS and MSAD studies (Hopwood et al., 2009; Hopwood & Zanarini, 2010). Nevertheless, we unexpectedly observed a significant decrease in other personality features such as Activity and Sociability, with mean scores at follow-up that were significantly below normative levels in the Spanish population.

When our findings are considered as a whole, it appears that improvement in clinical BPD symptoms such as emotional dysregulation (or neuroticism), impulsivity, and hostility appears to come at the cost of a reduction in general activity and social life. That is, the price for this "adaptation mechanism" to BPD involves the presence of more avoidant and obsessive features, as well as chronic affective and anxiety symptoms and isolation.

Our findings show that the use of mental health resources by BPD patients appears to decrease over time. In our sample, all types of mental health care decreased at follow-up, although a relevant portion of subjects continued to receive outpatient mental health care at the final follow-up (61% individual psychotherapy; 67% outpatient psychiatric treatment; and 71% standing medication orders). These findings are similar to the those reported in other prospective studies (CLPS, 64% individual therapy at 3 years; and MSAD, 73% individual therapy, 72% standing medication at 10 years) (Bender et al., 2006; Hörz, Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010). Our results are also consistent with previous evidence suggesting that BPD symptomatic remission is related to relevant reductions in the use of mental health treatments, especially more intensive forms (Zanarini, Frankenburg, Hennen, & Silk, 2004). In our study, over half of the

subjects no longer met criteria for BPD at follow-up; however, many of these patients presented other psychiatric problems, such as affective or anxiety symptoms, which may explain the continued demand for and use of mental health resources. In addition, our results indicate that the need for rehabilitation services, including functional and occupational interventions, grew over the course of the disorder, as evidenced by the fact that one quarter of participants received these interventions within the 10-year study period. Nevertheless, given the other disturbances in general functioning, this demand for rehabilitation services appears to be relatively modest.

Our findings suggest that clinical remission does not appear to be consistently associated with a similar improvement in psychosocial functioning. Although most participants were able to establish their own household and more than half had children, some difficulties in functioning remained constant. This was especially notable in the occupational realm, since the unemployment rate was unchanged (around half of the sample) and 45% of subjects were receiving social benefits at follow-up. These results are consistent with previous long-term prospective studies, indicating less improvement in social functioning compared to BPD symptomatic remission (Gunderson et al., 2011; Zanarini et al., 2010a, 2010b). This may imply that several aspects besides the patients' clinical condition could influence social adaptation and functioning. Economic factors, health and labor policies, and cultural issues may promote or discourage social and occupational integration of people with BPD. Given these findings, it seems clear that psychosocial functioning needs to be specifically addressed for BPD patients to be able to achieve a full recovery.

This study has several limitations. The retention rate and, consequently, the limited sample size at follow-up may have affected the findings. However, the influence of these factors may have been diminished by the fact that there were no significant

clinical differences at baseline between study completers and dropouts. The lack of assessment of test-retest stability for the DIB-R interview is another limitation, although this is offset by the use of other measures. Moreover, additional information may have been missed due to the lack of multiple follow-up assessments. This was a naturalistic study and the intensity and specificity of the mental health assistance received during the 10-year period were not controlled. In addition, other potential socioeconomic, family, or medical factors that might affect general functioning were not evaluated. Lastly, there was no comparison group with other psychiatric disorders. Despite these limitations, this study provides new complementary data on the course of BPD in another population.

In summary, findings from the present study support an optimistic scenario with regard to the long-term course of BPD. Our results in a Spanish sample confirm the tendency toward symptom remission in the long term, a finding that has been reported in previous studies. However, symptom remission does not appear to equate with full recovery given that the amelioration of BPD symptoms is not necessarily associated with an improvement in psychosocial functioning. These findings suggest that BPD patients might benefit from therapeutic interventions aimed at treating the functional disabilities in daily life that often remain after clinical remission (Pascual et al., 2015).

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3.3.2. Additional results

Communication 2: *Differential long-term course related to early and delayed diagnosis of borderline personality disorder*

http://hdl.handle.net/2445/132358

Poster 3:   *Early and delayed BPD diagnosis and its relationship to long-term remission in adulthood*

http://hdl.handle.net/2445/132367

Communication 2 and Poster 3 reported the results of our 10-year follow-up study about the predictive effects of the age of first BPD diagnosis on the long-term course (Álvarez-Tomás, 2014; Álvarez-Tomás et al., 2016).

The mean age of first BPD diagnosis was 20.6 years ($SD = 2.5$) in the ED subgroup and 31.4 years ($SD = 4.8$) in the DD subgroup. In terms of psychiatric history, subjects with a delayed BPD diagnosis were more likely to report lifetime mood disorders (72% vs. 35%, $\chi^2 = 5.66$, $p < .05$). On the contrary, those subjects with an early BPD diagnosis reported more frequently to have suffered from mental disorders in early childhood (26% vs. 0%, $p < .05$). There were no significant differences in lifetime disruptive behavior or attention deficit hyperactivity disorder (ADHD) (17% vs. 0%), lifetime SUD (44% vs. 44%), and lifetime eating disorders (39% vs. 39%). Moreover, those subjects in the ED subgroup were more likely to have earlier received the first mental health intervention compared to those in the DD subgroup (14.4 years [$SD = 5.2$] vs. 21 years [$SD = 5.2$], $t = -4.08$, $df = 39$, $p < .001$).

The ED subgroup showed a higher remission rate than the DD subgroup at 10-year follow-up (by DIB-R and SCID-II), although this difference did not reach statistical significance (68.2% vs. 38.9%, $\chi^2 = 3.37$, $p = .06$). The likelihood of long-term remission

was 1.75 greater in the ED subgroup than in the DD subgroup (RR = 1.75, IC 95% [0.92, 3.34]). There was a non-significant difference in suicide rate between the ED subgroup and the DD subgroup (3% vs. 13%, p = .19, RR = 0.23, CI 95% [0.03, 1.9]).

There was no difference between the ED and DD subgroups in the reduction of the DIB-R total mean score over time (ED subgroup, M=7.00 [SD=1.51] at baseline, M=3.43 [SD=3.93] at follow-up; DD subgroup, M=7.39 [SD=1.54] at baseline, M=5.11 [SD=3.36] at follow-up). The interaction showed a large effect size, although it did not reach statistical significance (F [1, 39] = 1.29, p=.26; $\hat{g}$=0.83, 95% CI [0.19, 1.47]).

Regarding the DIB-R symptoms domains, there was a non-significant trend towards a greater improvement of the Affect DIB-R domain in the ED subgroup compared to the DD subgroup, showing a large effect size (ED subgroup, M=7.91 [SD=1.73] at baseline, M=4.65 [SD=3.97] at follow-up; DD subgroup, M=8.11 [SD=1.57] at baseline, M=7.00 [SD=3.14] at follow-up; F (1,39) = 2.83, p=.10; $\hat{g}$=1.27, CI 95% [0.59-1.94]). By contrast, impulsive, cognitive and interpersonal DIB-R domains showed similar amounts of improvement between subgroups. These interactions were not significant and effect sizes were small or medium (F (1, 39) = 0.23, p = .63, $\hat{g}$ = 0.31, [-0.31, 0.93]; F (1,39)=1.98, p=.16, $\hat{g}$=0.68, 95% IC [0.59, 1.94]; F(1,39)=0.23, p=.63, $\hat{g}$=0.31, 95% IC [-0.31, 0.93], respectively).

Moreover, there was no difference in the amount of improvement over time in the SASS total score between subgroups. This interaction was not significant and showed a small effect size (F [1, 30] = 0.02, p=.89, $\hat{g}$=0.02, [-0.62, 0.66]).

Graphics on the long-term trajectories of BPD symptomatology and social functioning in both subgroups may be consulted online (See it on *http://hdl.handle.net/2445/132358*).

Poster 2: *Predictors of the Long-Term Quality of Life in BPD Patients: A 10-year Follow-up Study*

http://hdl.handle.net/2445/132366

In Poster 2, several factors were studied as predictors of long-term QOL, operationalized as the MQLI total score at follow-up (Álvarez-Tomás et al., 2015). Higher CTQ total scores and lower SASS total scores at baseline showed significant independent correlations with higher MQLI total scores at follow-up, with medium effect sizes ($r=-.47$, $p=.002$; $r=.35$, $p=.04$, respectively). Younger age showed a moderate correlation to higher MQLI total scores at follow-up, although it did not reach statistical significance ($r=.30$, $p=.06$). Finally, the DIB-R total score and ZKPQ alternative FFM scores at baseline were not significantly associated with the MQLI total score at follow-up (DIB-R total score, $r=-.23$, $p=.17$; Neuroticism-Anxiety, $r=.12$, $p=.52$; Activity, $r=.18$, $p=.34$; Sociability, $r=.03$, $p=.87$; Impulsive-Sensation Seeking, $r=.26$, $p=.16$; Aggression-Hostility, $r=.05$, $p=.80$).

At a later stage, CTQ, SASS and DIB-R total scores were introduced into a predictive model of the MQLI total score at follow-up, which was tested by linear regression analysis. CTQ and SASS total scores were introduced as they had shown significant independent correlations with long-term QOL; DIB-R Total score, as BPD symptomatology has been considered a predictor of long-term QOL in former literature. Results showed that the CTQ total score was the most robust predictor of MQLI total scores at follow-up and its contribution was statistically significant ($\beta=-.40$, $p=.02$). By contrast, SASS and DIB-R total scores showed no significant effects on MQLI total scores at follow-up in this model ($\beta=.20$, $p=.22$; $\beta=-.15$, $p=.32$, respectively). This predictive model was significant and explained 29% of the variability of the MQLI total scores at follow-up ($R^2=.294$, $p=.01$).

Poster 4:   *Physical health, health care utilization and long-term quality of life in remitted and non-remitted BPD patients: A 10-year follow-up study in a Spanish sample*

http://hdl.handle.net/2445/132368

Poster 4 reported descriptive data on physical health conditions and use of medical resources of the study sample at follow-up, which are displayed below in Table 8 (Álvarez-Tomás et al., 2018). In the overall sample, 68% of BPD patients informed to suffer from at least a medical illness and 32% presented several comorbid medical illnesses at follow-up. Besides, 78% of BPD patients had been attended by a general practitioner at least once during the past year. There were no significant differences between remitted and non-remitted BPD patients on their physical health condition. By contrast, non-remitted BPD patients were more likely to become frequent users of primary care services, i.e., receiving more than 12 visits with a general practitioner the past year, than those who had remitted from BPD ($p = .03$).

Table 8. Prevalence of physical illnesses and use of medical resources at follow-up

Physical Health & Use of Medical Resources	Total (N=41)	Remitted (n=22)[a]	Non-remitted (n=18)[a]
Some current medical illness	**68%**	**59%**	**78%**
2 or more current medical illnesses	**32%**	**23%**	**44%**
Cardiovascular risk factors (BMI ≥30, diabetes, HBP)	12%	5%	22%
Musculoskeletal diseases (osteoarthritis, fibromyalgia, etc.)	20%	18%	22%
Neurological diseases (migraine, brain stroke, multiple sclerosis, etc.)	10%	9%	11%
Allergies & intolerances	12%	18%	6%
Asthma & other lung diseases (bronchitis, etc.)	15%	14%	17%
Sexually transmitted diseases (HIV, human papilloma virus, etc.)	5%	9%	0%
Endocrine diseases (hyper/hypothyroidism, irregular menstruation, etc.)	15%	5%	22%
Digestive diseases (hiatal hernia, pancreatitis, appendicitis, etc.)	10%	9%	11%
Use of primary care services last year	**78%**	**68%**	**89%**
Frequent users (+12 visits GP last year)	**10%**	**0%**	**22%****

Note. BMI=Body Mass Index; HBP=High Blood Pressure; HIV=Human Immunodeficiency Virus; GP=General Practitioner; [a] Subgroups comprised the 40 subjects who were evaluated by both the DIB-R and SCID-II interviews at baseline and follow-up assessments. ** Fisher's exact test: $p = .03$.

Furthermore, we analyzed the effects of presenting some medical illness at follow-up and achieving remission from BPD on the long-term QOL. Remitted BPD patients were significantly more likely to report higher MQLI total scores at follow-up than non-remitted ones, showing this association a large effect size (M=6.9, SD=0.37 vs. M=4.7, SD=0.46; F=14.5, df =1, p=.001, partial η^2=.29). Presenting some medical illness were associated to lower MQLI total scores, although this effect was not significant in the overall sample (M=5.3, SD=0.31 vs. M=6.38, SD=0.5; F=3.2, df =1, p=.08, partial η^2=.08). By contrast, presenting physical health problems at follow-up significantly impaired the long-term QOL of non-remitted BPD patients but not of the remitted ones (F=5.5, df =1, p=.03, partial η^2=.14). A graphic representing the effect of this interaction on the MQLI total scores at follow-up is displayed below.

Graphic 1. Differences in long-term QOL by BPD remission and physical health condition at follow-up
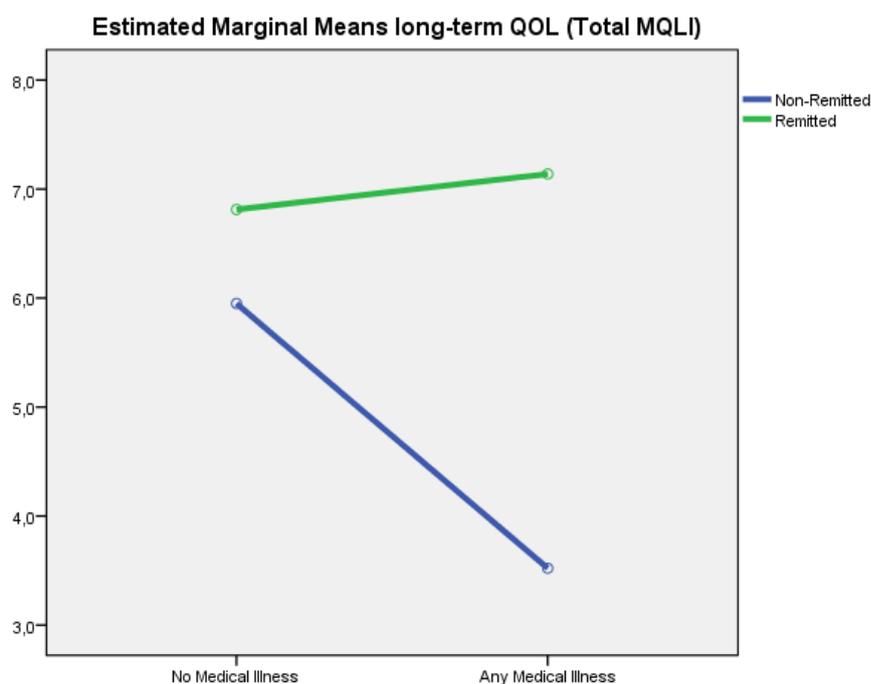
3.4. <u>SUMMARY OF FINDINGS</u>

In Article 1, we reported the main findings on prospective changes in clinical and functional features in our Spanish sample that characterize the long-term course of BPD. At 10-year follow-up, 55% of the sample achieved remission from BPD. Significant improvements in the overall BPD symptoms were reported at 10 years of follow-up, with medium and large effect sizes, except for the DIB-R Cognition domain which showed more stability over time. The follow-up sample showed substantial decreases as a group in depressive symptoms, hostility/aggression and suicidal behavior at 10 years, showing large effect sizes. However, the prevalence of affective and anxiety disorders was high at follow-up (31.7% affective disorders, 41.5% generalized anxiety disorder, 17.1% panic disorder). Moreover, 7.8% of the initial sample had committed suicide over 10 years.

The percentages of co-occurring personality disorders remained steady over time, although there was a non-significant increase of avoidant and obsessive-compulsive personality disorders, with large effect sizes. Dimensional personality traits of Neuroticism-Anxiety, Impulse-Sensation Seeking, and Aggression-Hostility decreased towards normalization whereas Activity and Sociability traits showed reductions below normality, with medium and large effect sizes.

Self-reported social functioning showed a non-significant slight improvement over time, with a small effect size, remaining the follow-up sample as a whole below normal levels of adjustment, compared to normative scores in the SASS scale that has been reported in the Spanish population (Bobes et al., 1999). However, it is noticeable that the majority of subjects lived alone or with a partner at 10 years and half of them had become parents over the follow-up period. Moreover, functional indexes showed great disparities between subjects in their occupational trajectories over time. Whereas the rate

of employment remained steady around half of the sample, receiving a disability pension became more common at follow-up (3% vs. 26%).

The use of mental health resources decreased at follow-up for all treatment modalities, with medium and large effect sizes, although only the reduction was statistically significant for individual psychotherapy. Despite that, almost three quarters of the sample took a mean of 2.1 psychoactive drugs at follow-up. It is also noticeable that rehabilitation services were required by one quarter of the sample over the 10 years of follow-up.

In terms of physical health, as stated in Poster 4 (Álvarez-Tomás et al., 2018), over two thirds of subjects with BPD in our study suffered from physical health problems at 10 years and one third presented several medical illnesses in the long-term. Moreover, the use of primary care services was frequent at follow-up, especially in those subjects that had not achieved remission from BPD. We also studied the relative impact of BPD remission and the physical health condition at follow-up on the long-term QOL. It is noticeable that remission from BPD significantly predicted a better QOL in the long-term regardless the current physical health condition, explaining 29% of variability on QOL by itself. The interaction between BPD remission and current physical health significantly explained 14% of variance, in the way that suffering from medical health diseases showed a negative impact on QOL only in non-remitted BPD patients.

Regarding the age of first BPD diagnosis as predictor of long-term outcome, those subjects who were earlier diagnosed with BPD showed a remission rate 1.75 greater (by DIB-R and SCID-II criteria, 68.2% vs. 38.9%) and a lower suicide rate (3% vs. 13%) than those with a delayed BPD diagnosis (Álvarez-Tomás et al., 2016). However, these differences between subgroups did not reach statistical significance, probably due to the limited sample size.

In terms of BPD symptomatic domains, subjects with a delayed diagnosis appeared to be more likely to maintain BPD affective features at follow-up than those with an early diagnosis. This interaction was not significant, although it showed a large effect size. There were not significant differences between subgroups in the amount of improvement of other BPD features from baseline to follow-up.

Lifetime mood disorders were more frequent in subjects with a delayed BPD diagnosis, whereas subjects with an early BPD disorder were more likely to report mental disorders in early childhood and to have earlier received the first mental health intervention.

Regarding social functioning, both subgroups showed a similar pattern of improvement in the long-term.

We also studied the impact of several potential predictors on the QOL of BPD adults in the long-term (Álvarez-Tomás et al., 2015). Higher severity of traumatic experiences suffered during childhood significantly predicted poorer QOL of BPD patients in the long-term, with a medium effect size ($r = -.47$, $p = .002$). The initial level of social functioning also appears to be directly correlated to the long-term QOL, with a medium effect size ($r = .35$, $p = .04$). Younger age was associated to higher long-term QOL, although this tendency did not reach statistical significance. Variations in BPD symptoms and FFM traits at baseline did not show significant predictive effects on the long-term QOL.

Secondly, we studied the relative contributions of childhood trauma severity, initial social functioning, and amount of BPD symptoms to predict the QOL over time. Among these factors the severity of childhood trauma was the only significant predictor, indicating that early traumatic experiences impact negatively on the long-term QOL of

BPD patients after controlling by initial variations in BPD symptoms and the level of social functioning.

3.5. <u>STRENGTHS & LIMITATIONS</u>

This study followed a well-defined sample of BPD patients after a long period of 10 years. Standardized and validated instruments were used at baseline and follow-up for measuring a variety of clinical and functional outcomes. However, the limited sample size affected the statistical power of analyzes, particularly when comparing subgroups. Besides, there was not a control group to compare the course of BPD with that of other disorders or with the normal development in the general population. Moreover, there were some limitations in the study of predictors of outcome, which was exploratory and restricted to specific areas of interest. Firstly, the age of first BPD diagnosis was self-reported and retrospectively assessed, and other potential predictors of outcome were not controlled in the analyses. Secondly, in the study of predictors of the long-term QOL, the initial level of QOL was not available and could not be considered.

4. ORIGINAL RESEARCH 2: META-ANALYSIS OF PROSPECTIVE STUDIES

4.1. <u>OBJECTIVES & HYPOTHESIS</u>

This meta-analysis aimed to review the current evidence on the long-term course of BPD in adulthood and pooled the prospective data reported by both naturalistic and post-treatment follow-up studies in different populations to draw general conclusions, where possible. The objectives of this research were to define the characteristic long-term course patterns of BPD during adulthood, both in clinical and functional domains, and to identify relevant moderators that might modulate these trajectories over time.

This research work was exploratory and, consequently, there were not predetermined hypothesis. Former literature was taken into account to define relevant outcome variables of the long-term course and potential moderators to consider for meta-analyses, deeply discussed in the sections 1.3 and 1.4.

When concrete moderators and outcome variables were determined by the available data for meta-analyses, we drew the following hypothesis:

1. BPD diagnosis will tend towards remission, indicated by a mean remission rate among samples that may range between 30% and 80%.

2. It is expected a statistically significant reduction in depression among samples.

3. It is expected a mean suicide rate up to 9% among samples.

4. Social functioning will moderately improve over time among samples.

5. A younger age will be associated to a higher likelihood of remission and improvements in depression and functioning in the long-term.

6. It is expected that gender will not show relevant a relevant impact on remission and functioning.

7. Higher rates of comorbidity with mood disorders at baseline will be associated to a lower BPD remission rate in the long-term.

8. A better social/global functioning at baseline will be associated to a better long-term outcome.

9. Receiving an initial controlled treatment will show beneficial effects on remission, depression and functioning in the long-term.

10. Receiving a specialized therapy will be associated to a higher likelihood of remission from BPD in the long-term, compared to TAU.

4.2. <u>METHODS</u>

Methods to perform the systematic review and consequent meta-analyses are mainly explained in Article 2, displayed in section 4.3.1. A methodological overview and additional information about some specific aspects will be addressed in the following paragraphs.

4.2.1. Systematic search & Selection of studies

A systematic review was initially conducted to identify relevant prospective research during the period between 1990 and 2015. The review period was lately extended to 2017, identifying an additional study which was included in the definitive meta-analyses reported in Article 2 and discussed in the present thesis. The search strategy used on both occasions was similar, which is defined in Article 2 (See section 4.3.1).

The selected studies comprised an adult BPD sample or subsample, diagnosed by a validated, semi-structured interview, and informed of repeated measures related to the course of the disorder at five years of follow-up or more. Both naturalistic longitudinal studies and post-treatment follow-up studies were selected and combined in the meta-analyses. We considered that both types of studies presented some similarities, which justify their combination: (1) all samples were recruited in clinical settings among those patients who were seeking treatment; (2) after inclusion, receiving treatment was allowed

in some degree in all studies; (3) the time lapse over the lifespan was five years or more in all participants, regardless of their degree of active engagement in some treatment intervention between assessments. In any case, all the samples in the included studies were composed by treatment seekers and our findings might only generalize to clinical populations.

4.2.2. Outcome variables & Moderators

The outcome variables on the clinical and functional course and their potential moderators were not determined in advance. Comparable measures reported by at least three studies were needed to identify an outcome variable and perform a meta-analysis. It resulted in four outcomes of interest: remission, completed suicide, depression, and functioning. Similarly, the moderators consisted of those factors reported by at least three studies (i.e. age at baseline, gender, time of follow-up, comorbidity with mood disorders at baseline, initial level of functioning, presence and type of controlled treatment and its length in months, and total hours of therapy). The concrete moderators analyzed for each outcome variable were limited by the data reported in the studies.

The outcome variables and moderators informed by each study are displayed in the Table 9.1. The measures that represent the outcome variables and moderators are explained in the Article 2 in sections 2.4 / 3.1.1, and 2.5 / 3.1.2, respectively. Besides, Table 9.2 summarizes the treatments received in follow-up clinical studies (See section 4.3.1). In short, all participants in follow-up clinical trials were prescribed some kind of experimental treatment during the early years and then were allowed to receive uncontrolled treatment in the community, as a naturalistic follow-up. By contrast, this experimental phase was absent in naturalistic studies although receiving treatment was also allowed. In fact, some naturalistic studies informed of almost three quarters of subjects receiving individual therapy during follow-up. Combining follow-up clinical

studies and naturalistic studies allowed us to analyze as moderators the impact of receiving an experimental treatment and other treatment characteristics (i.e., length, type and amount of therapy) on the outcome variables.

4.2.3. Quality assessment of studies

The adapted Systematic Assessment of Quality in Observational Research (SAQOR) guidelines proposed by Betancourt et al. (2013) were applied to assess the quality of both follow-up post-treatment and longitudinal studies. The SAQOR is a tool specially designed to assess the quality of the research in psychiatry, where observational methods are frequently implemented (Ross et al., 2011).

Regardless the original design and methods of the studies, in this review it was considered that: (1) the presence of BPD diagnosis at baseline was the exposure variable in all samples; (2) the aim was to study prospectively the association between BPD diagnosis at baseline and the outcome variables at follow-up, by meta-analytic procedures; (3) the variables identified as moderators (gender/age, psychiatric comorbidity, type of initial treatment, amount of therapy during follow-up, and other variables) might affect this association in each sample, thus the presence of control methods on these influential variables were evaluated in the studies; and (4) the presence of control groups was not assessed, since this data was not included in the meta-analyses.

The Annex contains the tables that display the definitive SAQOR ratings of the studies. Quality criteria are explained in the notes below the tables. Final SAQOR ratings were modified to maintain a similar sensitivity of the scale after removing the control group domain. Those ratings that needed consensus between the two raters are written in italics in the tables. Interrater agreement was calculated and reported in Article 2 (See section 4.3.1).

4.2.4. Meta-analyses

The meta-analytic methods are clarified in our paper (See Article 2, section 4.3.1). In summary, a meta-analysis was run for each outcome variable of interest. The relationship between the moderators and effect sizes was examined for all but one of these outcome variables (i.e., completed suicide), due to the homogeneity shown between the independent estimates of this variable among studies.

4.3. <u>RESULTS</u>

4.3.1. ARTICLE 2

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Long-term clinical and functional course of Borderline Personality Disorder: A meta-analysis of prospective studies

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Abstract

Background: This meta-analytic review is the first to synthesise findings from prospective research on the long-term course of borderline personality disorder in adult clinical populations. *Methods:* Systematic searches were conducted in Medline, PsycINFO, PsycArticles, PubMed and Scopus within the period 1990-2017. Inclusion criteria were: (1) adult BPD sample diagnosed by a validated, semi-structured interview; (2) at least two prospective assessments of outcomes; and (3) follow-up period ≥ 5 years. Quality of evidence was rated with the Systematic Assessment of Quality in Observational Research (SAQOR). Four outcomes were meta-analysed using mixed-effect methods: remission from BPD diagnosis, completed suicide, depressive symptoms, and functioning. Potential moderators regarding the natural course and the initial treatment received were studied. *Results:* Eleven studies met the inclusion criteria, with 837 participants from nine countries being followed. Between 50% and 70% of the BPD patients achieved remission in the long-term. Significant reductions in depression and functional impairment were also found. Mean suicide rate ranged from 2% to 5%. Younger age was associated with higher likelihood for remission. Being female was correlated with lower functional improvement. Despite some positive trends, there were no significant associations between treatment moderators and the long-term outcome.

Conclusions: Findings suggest that the course of BPD is characterised by symptomatic amelioration and a slight functional improvement in the long-term. Age and gender modulate the long-term prognosis and should be considered to adapt treatment resources. Further research is required to draw robust conclusions on the long-term effects of psychotherapeutic interventions.

Keywords: meta-analysis, borderline personality disorder, long-term, course, prognosis, therapy outcome.

1. Introduction

Over the last few decades, there has been growing evidence that the natural course of borderline personality disorder (BPD) is characterised by its plasticity, with consecutive periods of remission and relapse, and shows a trend towards symptomatic amelioration over time. Despite that, adults with BPD appear to frequently suffer from poor psychosocial functioning in the long-term [1, 2, 3]. Bearing this in mind, Paris suggested that treatment efficacy should be assessed in terms of their contribution to enhance the natural process of the disorder. In this respect, it is noteworthy to study the impact of psychotherapeutic interventions in patients with BPD in the long-term, both in the symptomatic and functional domains [2, 3].

Two main prospective studies provided evidence on a wide range of aspects related to the long-term course of adults with BPD: the McLean Study of Adult Development (MSAD) and the Collaborative Longitudinal Personality Study (CLPS) [4, 5, 6]. Both research projects demonstrated that it is common for BPD patients to experience periods of symptomatic remission over time, reporting high cumulative rates by 10 years (85% 12-month remission in CLPS; 93% 2-year remission in MSAD) [6]. At 16 years, the MSAD also reported that 78% of BPD patients had achieved a long-lasting remission of eight consecutive years [7]. Nevertheless, the recovery of psychosocial functioning was less consistent than symptomatic remission, oscillating between a steady functional impairment reported by the CLPS and a slight improvement by the MSAD [6]. Besides, patients with BPD were mostly not able to achieve normal levels of functioning in the long-term: only 33% had good functioning after 6 years in MSAD; and just 21% did so after 10 years in CLPS [8, 9].

Apart from the longitudinal research conducted in the US population, other naturalistic studies were carried out in different countries (i.e., Spain, Canada, Finland, and Germany) providing prospective data for a period of five years or more. Findings in these studies add to the evidence that the course of BPD is characterised by symptomatic improvement, although remission rates ranged widely from 31% to 81%, which were informed at different time points of follow-up [10, 11, 12, 13]. Álvarez-Tomás et al. also reported a slight improvement of psychosocial functioning in a Spanish sample followed up at 10 years, although dysfunctional levels of adjustment were maintained [10]. Moreover, only one third of subjects with BPD, on average, achieved both symptomatic and functional recovery at a 14-year follow-up in a German study [13].

Further analysis of potential moderators should be required to take into account variations on the course of BPD among studies. In this regard, previous longitudinal research pointed out the following factors as predictors of long-term outcomes: demographic characteristics, childhood experiences, stressful life events, treatment history, psychopathologic comorbidity, personality traits, and premorbid psychosocial functioning [14, 15, 16, 17, 18].

In addition to naturalistic research, clinical trials of psychotherapeutic interventions for BPD have recently shown greater interest in their long-term outcomes, reporting follow-up data for five years or more [19, 20, 21, 22, 23]. This longitudinal perspective on efficacy studies underlines the relevance of treatment as a potential factor of change over time. Nevertheless, findings are controversial among studies with respect to a differential impact of specialised therapies in comparison to treatment as usual (TAU) on diagnostic change and social functioning in the long-term. Bateman and Fonagy reported significant differences on remission favouring mentalisation-based treatment (MBT) over TAU (86% vs. 13%), but this effect was not found for other specialised

therapies [19, 20, 21]. Antonsen et al. reported better outcomes for the social functioning of a specialised therapy for personality disorders compared to TAU, in contrast to findings in the Boscot trial indicating a similar impact of treatment interventions [19, 21]. As far as we are aware, there are no published meta-analyses that synthesise current evidence on the long-term outcome of treatment interventions in BPD or that combine these findings with those from naturalistic prospective research. This may contribute to the study of long-term treatment effects in the context of the natural course of the disorder.

Thus, our objective was to conduct a meta-analysis of studies reporting the prospective results on the long-term course of BPD, considering both naturalistic and post-treatment follow-up research. In case of heterogeneity among studies, we were interested to study the effect of potential moderators related to the natural course (e.g., age, gender, time of follow-up, psychiatric comorbidity, and initial level of functioning) and those related to the treatment interventions received. The following questions were addressed: (1) What characterises the long-term course of BPD in adulthood, both in clinical and functional domains? (2) Are there significant moderators that influence the long-term course of the disorder?

2. Materials and methods

2.1. Search strategy

Our literature review was guided by the PRISMA standards for systematic reviews [24]. Bibliographic searches were conducted in Medline, PsycINFO, PsycArticles, PubMed, and Scopus to identify relevant literature during the period 1990-2017. The searching strategy was a combination of the following two steps: (1) either "borderline personality disorder" or "personality disorders" were used in addition to terms indicating a temporal dimension, i.e., "follow-up", "course", "longitudinal", "long-term", or "maintenance", in the title or abstract field; (2) the terms "borderline personality disorder"

and either "treatment*", "therap*", "psychotherap*", "intervention*", or "program*" were combined in the title field and added to similar temporal terms in the abstract field to identify follow-up clinical studies in BPD samples. We examined the references of all included articles to identify other relevant publications and contacted authors to obtain additional information. Dissertations and conference papers were also reviewed.

2.2. Selection criteria

Inclusion criteria were: (1) the presence of an adult BPD sample or subsample in the study, diagnosed by a validated, semi-structured interview; (2) at least two assessments with repeated outcome measures related to the course of BPD; and (3) a follow-up period of 5 years or more.

2.3. Data collection

Data extraction of the selected studies was independently completed by two investigators using an agreed coding protocol (available upon request). The authors of three studies were contacted to request additional information. A response was obtained from a study pending publication, which was included in the meta-analyses. The level of agreement between the coders was high (average agreement percentage = 95.53; average Kappa = .91).

2.4. Outcome variables

The comparable measures reported by at least three studies were considered as the minimum measures needed to successfully perform a meta-analysis, finally resulting in four outcomes of interest: remission, completed suicide, depression, and functioning.

As a measure of remission, the percentage of subjects who achieved diagnostic remission for BPD at a specific follow-up point was used; this measure differs from the cumulative remission rate, which is defined as the percentage of subjects who achieved a particular period of remission throughout the duration of the follow-up. Completed

suicide was computed as the number of subjects who completed suicide during follow-up divided by the total number of subjects included at baseline in the respective study. Depression and functioning were studied through the means of diverse instruments used in the studies. Their comparability was determined by consensus of the authors.

2.5. Definition of moderators

The potential factors reported by at least three studies were considered as moderators; age at baseline, gender, time of follow-up, comorbidity with mood disorders at baseline, initial level of functioning, presence and type of controlled treatment and its length in months, and total hours of therapy were studied.

As a measure of the initial level of functioning, we converted the mean scores of the functioning scales at baseline into a z-score, comparing the mean values in each study with those reported for these instruments in clinical populations from the corresponding countries, which mainly consisted of outpatients with anxiety or affective disorders [25, 26, 27, 28, 29, 30].

Regarding treatment, we analysed the impact of receiving a controlled treatment at the outset of the follow-up, comparing samples of naturalistic studies with those of follow-up clinical trials. Any treatment received in experimental conditions (e.g., predetermined prescription or length of treatment, attendance monitoring, etc.) was considered as a controlled treatment. Secondly, we compared those subgroups receiving specialised therapy for BPD or other personality disorders with those receiving TAU in follow-up clinical studies. Finally, we studied the length of the controlled treatment in these subgroups and, where possible, the total hours of formal therapy received, including both individual and group modalities. To this end, we calculated the total amount of hours of formal therapy, multiplying the number of therapy sessions by the hours per session.

2.6. Quality assessment

A quality assessment of studies was performed with the SAQOR, which was developed to assess quality in psychiatric research [31]. We followed the adapted guidelines used to assess both intervention and longitudinal studies in a former meta-analysis [32]. According to the purpose of the present review, quality was assessed considering the presence of BPD diagnosis as the exposure variable, regardless of the original design or aims of the studies. Gender/age, psychiatric comorbidity, type of initial treatment, amount of therapy during the follow-up, and other variables were considered among factors that might affect the association between BPD diagnosis and the long-term outcome. The control group domain was not applied, since the results of these samples were not analysed. The final SAQOR ratings were modified to maintain a similar sensitivity of the scale (See Table 9.1). Two of the authors completed the ratings, with an 89% average interrater agreement in domains' scores (average Kappa = .78) and an 82% in final ratings (Kappa = .63).

2.7. Meta-analyses

2.7.1. Effect size computation

For remission and completed suicide, the event rate itself was treated as a measure of effect size; event rates were converted into percentages. In the study of depression and functioning, the effect size used was Hedges' unbiased *g* standardised mean difference and was calculated by subtracting the mean scores at baseline from the mean at the follow-up, divided by the standard deviation within groups [33]. Since test-retest information is used to adjust the standard errors of the effect size estimates, we used test-retest correlation coefficients of .50, .60 and, .70 (presented here are those results based on a correlation of .50; the remaining analyses may be obtained upon request, but no

substantial differences were found). Hedges' g was computed in such a way that positive values indicate more of a particular outcome (i.e., more depression and more functioning).

2.7.2. Meta-analytic procedures

We ran four separate meta-analyses, one for each outcome variable of interest (i.e., remission, completed suicide, depression, and functioning). The likelihood of publication bias was tested using the Egger's regression test [34] in those meta-analyses with at least ten of the studies (i.e., remission and suicide) and the trim-and-fill procedure [35] in the remaining number [36].

To determine whether each set of independent estimates shared a common effect size, we computed the homogeneity Q statistic and the I^2 index (i.e., the estimated percentage of the total amount of variability that can be attributed to heterogeneity) [37, 38]. Since heterogeneity was observed in three of the four meta-analyses, effect sizes were combined under the random-effects model using the restricted maximum-likelihood estimation to estimate the amount of heterogeneity [39]. We obtained an estimate of the overall effect size (i.e., event rate or Hedges' g) for each outcome of interest, which was also tested by computing a 95% confidence interval (CI) and the associated p value.

To examine the relationship between the moderators and the effect sizes, a mixed-effects model was used (i.e., random-effects model with moderators), using restricted maximum-likelihood to estimate residual heterogeneity. For quantitative moderators, we report the estimated parameter, its 95% CI, the Q_M (i.e., heterogeneity accounted for by the moderator), and the associated p value. For categorical variables, we report the estimated effect sizes within each level of a moderator with the corresponding 95% CI, and the Q_B and its statistical significance. Analyses were conducted with the Comprehensive Meta-Analysis (CMA) software [40].

3. Results

3.1. Description of studies

A total of 1718 records were identified through database searching and other sources. Figure 2 describes the flow chart of the selection process. After removing duplicates, 769 records were screened that fulfilled inclusion criteria. Reasons for exclusion were: the design of the study was not prospective, the absence of a specified BPD sample, the lack of repeated outcome measures, and a follow-up period that did not course entirely through adulthood or was shorter than five years. Finally, twenty full-text articles corresponding to eleven prospective studies were selected and included in at least a meta-analysis.

Figure 2. Flow chart of selection process **
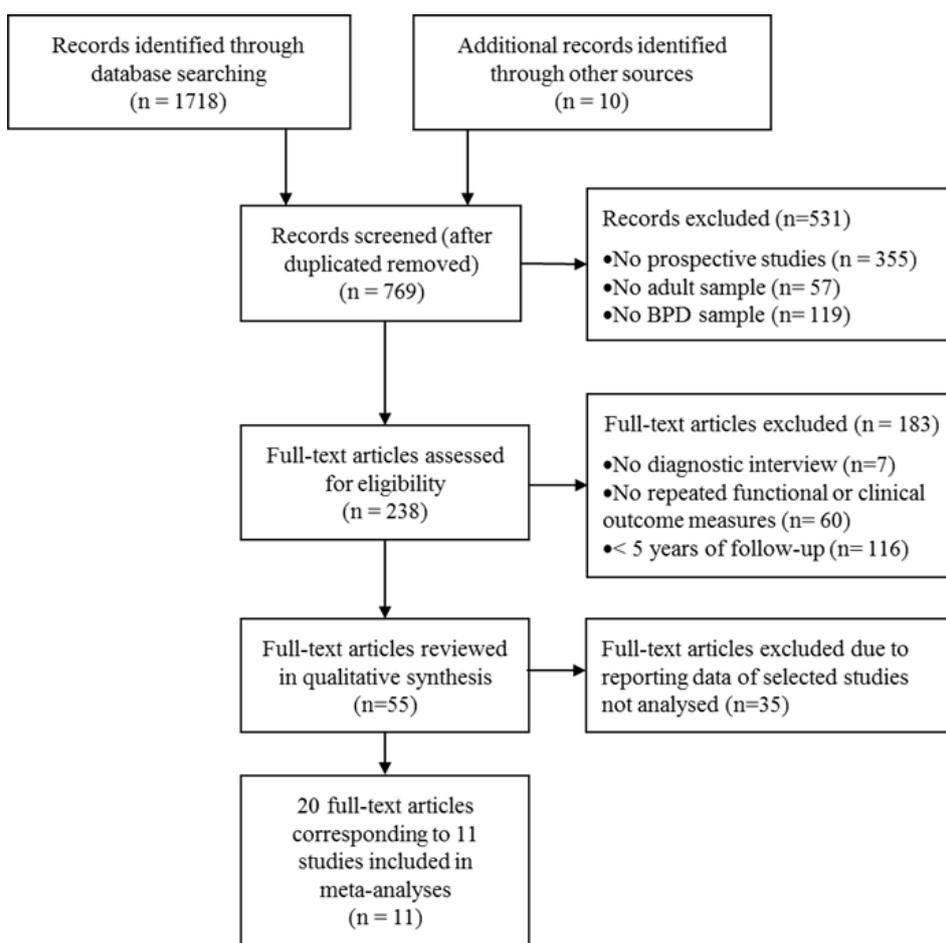
Note. ** Figure 1 in the original article

Table 9.1 describes the studies included in the meta-analyses and the outcome variables which were analysed from each of them. There were five clinical trials with long-term post-treatment follow-ups and six naturalistic studies without a controlled treatment phase. The methodological qualities of the studies are displayed in Table 9.1. The time from baseline to follow-up ranged from five to fourteen years, with a median value of six years. Overall, 837 participants from nine countries completed both assessments. The majority of studies showed a retention rate of more than 60 percent, with the exception of the naturalistic study with a fourteen-year follow-up [13]. Mean ages at baseline oscillated between 27 and 35 years, and the percentages of women were between 47% and 100%. Percentages of comorbidity with mood disorders at baseline fluctuated between 37.7% and 100%; this last percentage was due to one study conducted in a sample of primary care patients diagnosed with both major depressive disorder and BPD [12]. Recruitment settings in the rest of studies were outpatient or inpatient psychiatric services.

3.1.1. Measures of outcome

Selected studies reported follow-up data in several areas, i.e., the presence of BPD diagnosis and BPD symptomatic domains, dimensional personality traits, Axis II and Axis I comorbidity, general psychopathology, depression, anxiety, interpersonal problems, suicidal behaviour, psychosocial and global functioning, and quality of life. We only found comparable data for the four outcomes analysed (See Table 9.1).

Regarding remission, the CLPS was excluded from the meta-analysis due to its reporting of cumulative remission rates [9]. Aside from this type of measure, the MSAD also reported a specific remission rate at a six-year follow-up that was considered in the analyses [49]. The presence/absence of BPD diagnosis was generally assessed by

Table 9.1. Description of studies included in the meta-analysis (N = 837) **

Study Authors, year	Country	Quality [a]	Inclusion Criteria (measure)	Years FU (% Retention)	Presence/Type Controlled Treatment	Initial N (N at FU)	Mean Age (% Women)	% Mood disorder	Completed Suicide N (%)	Remission Rate (measure)	Depression/ Functioning measures
(1) Conversational Therapy Trial Stevenson et al., 1992, 2005 [23, 41][b]	Australia	Moderate	DSM-III (DIB)	6y (63)	CT/ Specialised therapy	48 (30)	29.4 (63.3)	---	0 (0)	40 (DIB)	---
(2) MBT Trial Bateman & Fonagy, 1999, 2001, 2008 [20, 42, 43]	UK	Moderate	DSM-III-R (SCID/DIB)	8y (93)	CT/ Specialised therapy	22 (22)	30.3 (68)	70	0 (0)	86	---
					CT/ TAU	22 (19)[c]	33.3 (47)	62	1 (4.5)	13 (ZAN-BPD)	
(3) Boscot Trial Davidson et al., 2006, 2010 Davidson, Norrie et al., 2006 Palmer et al., 2006 [21, 44, 45, 46]	UK	High	DSM-IV (SCID-II)	6y (72)	CT/ Specialised therapy	54 (43)	32.4 (83.3)	---	1 (1.9)	56	BDI-II/ SFQ
					CT/ TAU	52 (33)	31.4 (84.6)	---	1 (1.9)	52 (SCID-II)	
(4) Ullevål Trial Antonsen et al., 2017 Arnevik et al., 2010 [19, 47]	Norway	Moderate	DSM-IV (SCID-II)	6y (65)	CT/ Specialised therapy	27 (19)[d]	29 (85)	88	1 (3.7)	90	BDI/ GAF WSAS
					CT/ TAU	25 (15)[d]			0 (0)	93 (SCID-II)	
(5) SKIP Trial Sahin et al., 2017 [22]	Sweden	Moderate	DSM-IV ICD-10 (DIP-I)	5y	CT/ Specialised therapy 1	36 (35)[e]	31 (100)	37.7	---	---	GAF
					CT/ Specialised therapy 2	35 (32)[e]	30.6 (100)				
					CT/ TAU	35 (29)[e]	27.9 (100)				

(Continued)

Study Authors, year	Country	Quality [a]	Inclusion Criteria (measure)	Years FU (% Retention)	Presence/Type Controlled Treatment	Initial N (N at FU)	Mean Age (% Women)	% Mood disorder	Completed Suicide N (%)	Remission Rate (measure)	Depression/ Functioning measures
(6) McMaster Study Links et al., 1995, 1998 [11, 48]	Canada	Moderate	DSM-III (DIB≥7)	7y (65)	No controlled treatment	88 (57)	34.7 (93)	93	---	52.6 (DIB <7)	---
(7) MSAD Study Zanarini et al., 2003 [49]	US	High	DSM-III-R (DIB-R≥8 /DIPD-R)	6y (91)	No controlled treatment	290 (264)	26.9 (80.3)	96.9	11 (3.8)	68.6 (DIB-R <8 /DIPD-R)	GAF[f]
(8) CLPS Study Skodol et al. 2005, Gunderson et al., 2011 [9, 50]	US	High	DSM-IV (DIPD-IV)	10y (63)	No controlled Treatment	175 (111)	32.1 (75)	70.9	1 (0.6)	---	GAF[f]
(9) Vaanta Primary Care Depression Study Riihimäki et al., 2014 [12]	Finland	Moderate	DSM-IV (SCID-II)	5y (83)	No controlled treatment	35 (29)	32 (86)	100	---	31 (SCID-II)	17-HDRS BDI/ SOFAS
(10) Alvarez-Tomás et al., 2017 [10]	Spain	Moderate	DSM-IV (DIB-R≥6 /SCID-II)	10y (64)	No controlled treatment	64 (41)	26.9 (92.7)	54	5 (8)	55 (DIB-R<6 /SCID-II)	17-HDRS/ SASS
(11) Zeitler et al., 2018 [13]	Germany	Moderate	DSM-IV (DIB-R /SCID-II)	14.4y (35)	No controlled treatment	167 (58)	29.2 (100)	---	---	81 (IPDE <5)	---

Note. CT=Controlled Treatment; TAU=Treatment as usual; DIB=Diagnostic Interview for Borderline Patients; DIB-R=Revised Diagnostic Interview for Borderlines; DIBD-R=Diagnostic Interview for DSM-III-R Personality Disorders; DIPD-IV=Diagnostic interview for DSM-IV Personality Disorders; DIP-I= DSM-IV and ICD-10 Personality Disorders Interview; SCID=Structured Clinical Interview for DSM-III-R; SCID-II=Structured Clinical Interview for DSM-IV-Axis II; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder; IPDE=International Personality Disorder Examination; BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory-II; 17-HDRS=17-item Hamilton Depression Rating Scale; SFQ=Social Functioning Questionnaire; GAF=Global Assessment of Functioning; WSAS=Work and Social Adjustment Scale; SOFAS=Social and Occupational Functioning Assessment Scale; SASS=Social Adaptation Self-evaluation Scale. [a] SAQOR ratings: High = 5-4 Adequate domains; Moderate = 3-2 Adequate domains; Low ≤ 1 Adequate domain; [b] Waiting list control group was present in the original trial, although follow-up data was not reported for this group; [c] n=15 for remission outcome variable; [d] Initial n used to intent-to-treat analyses for depression, n at follow-up used for remission; [e] Intent-to-treat sample; [f] GAF scores only reported at baseline in these studies; ** Table 1 in the original article.

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similar instruments at baseline and follow-up, with the exception of two studies [13, 20].

Depressive symptoms were evaluated by the Beck Depression Inventory (BDI or BDI-II) and the 17-item Hamilton Rating Scale for Depression (HRSD-17). The Dysphoric Affect Scale (DAS) was used by the MSAD and was not considered comparable to the BDI/BDI-II and HRSD-17 due to the fact that this instrument identifies other dysphoric states apart from depression [51].

A variety of instruments were used as a measure of functioning, including (a) scales rated by clinicians: the Global Assessment of Functioning (GAF) and the Social and Occupational Functioning Assessment Scale (SOFAS), and (b) self-report questionnaires: the Social Functioning Questionnaire (SFQ), the Work and Social Adjustment Scale (WSAS), and the Social Adjustment Scale-Self-Report (SASS). Results on GAF scores were partially reported by three studies and were not analysed [9, 20, 49]. Besides, the MSAD was also excluded due to reporting specific indexes of psychosocial functioning [8, 52].

3.1.2. Treatment interventions

Table 9.2 illustrates the controlled treatment conditions compared in the follow-up clinical trials included in the meta-analyses. Controlled treatments lasted for one to three years and were mainly conducted in outpatient settings, with the exception of two groups who received a combination of day hospital and outpatient treatment [19, 20]. The hours of formal therapy fluctuated between 60 and over 600 hours, the latter reported by the MBT trial [20].

Among naturalistic studies, two studies followed up samples who initially participated in a clinical trial, although treatment subgroups were not individually studied at follow-up [10, 13]. Besides, three naturalistic studies informed of treatment use during follow-up in general terms. The CLPS and MSAD studies reported similar percentages

Table 9.2. Description of experimental treatment conditions in follow-up clinical studies **

Study	Type of Treatment	Treatment Setting	Description of Treatment conditions	Hours therapy (Months)
(1) Stevenson & Meares, 1992 Stevenson et al., 2005 [23, 41]	Conversational Therapy (ST)	Outpatient	2 sessions/week, 1h session duration. Manualized Psychodinamic-Interpersonal Psychotherapy. Optional inpatient stays when in crisis. Optional medication use. Therapists: 17 psychiatrists, 2 psychiatric nurses, 1 psychologist. Weekly supervision by audiotapes of sessions	96 (12)
(2) Bateman & Fonagy, 1999, 2001, 2008 [20, 42, 43]	Mentalization Based Therapy (ST)	Day Hospital Outpatient	DH: 18 months, 1 session/week psychoanalytic IT, 3 sessions/week analytic GT (1h each), 1/week psychodrama GT (1h), 1/week community meeting GT (1h). Average length=1.45y, 62% attendance at psychotherapy sessions. 1/month case management IT. Medication and 1/month psychiatric consultations.	612 (36)
			OT: 18 months 2 sessions/week analytic GT (180 hours over 18 months). 75% attendance at group therapy sessions. Medication and every 3 months psychiatric consultations. Optional inpatient stays when in crisis. Manualized psychotherapy. Therapists: nurses. 2/week Supervision.	
	TAU	Outpatient	18 months: No formal psychotherapy. 2/month individual community support by mental health nurses, 100% attendance. Medication and 2/month psychiatric consultations on average. Optional psychiatric DH (admission rate= 72%, average length stay=6 months). Optional inpatient stays when in crisis.	-- (36)
			18 months: Medication and psychiatric consultations, community support IT. Optional inpatient stays or psychiatric DH when in crisis. Psychotherapy but not MBT IT when recommended.	
(3) Davidson et al., 2010 Davidson, Norrie et al., 2006 Palmer et al., 2006 [21, 45, 46]	CBT-PD (ST) TAU	Outpatient	CBT-PD: 12 months, 30 IT sessions, 1h duration. CBT for Cluster B PDs. Manualized Psychotherapy. Trained therapists and weekly supervision. TAU: Idem as comparison group.	16 (12)
	TAU	Outpatient	Minimum Treatment: OT General practitioner care + Community mental health teams (CMH, 90% total sample). Optional psychological intervention when in crisis. Optional Accident and Emergency (A&E) visits when self-harm episodes (50% total sample) and inpatient stays when in crisis. Optional occupational and social attendance.	-- (12)

(Continued)

Study	Type of Treatment	Treatment Setting	Description of Treatment conditions	Hours therapy (Months)
(4) Antonsen et al., 2017 Arnevik et al., 2010 [19, 47]	Combination Programme (ST)	Day Hospital Outpatient	DH: 18 weeks, 3-4 days/week, psychodynamic GT, schema focused cognitive GT, anxiety cognitive behavioural GT OT combined psychotherapy: max 4y, weekly 1.5-h sessions GT, max 2.5y, weekly IT. Written manual. Relational psychotherapy, group analysis and self-psychology. Optional psychopharmacological consultations by psychiatrist.	117,5 (28)
	OIP (TAU)	Outpatient	No manual. No specific psychotherapeutic model, duration or intensity of treatment. Optional psychopharmacological consultations by psychiatrist.	60 (24)
(5) Sahin et al., 2017 [22]	Object-relational Psychotherapy (ORT)	Outpatient	2 sessions/week IT. Manualized psychotherapy. Trained therapists and supervision. Continuity of treatment after experimental phase was optional.	96 (12)
	Dialectical Behavior Therapy (DBT)	Outpatient	1 session/week IT, weekly 2h sessions GT. Optional phone calls with therapists between sessions. Manualized psychotherapy. Trained therapists and supervision. Continuity of treatment after experimental phase was optional.	144 (12)
	TAU	Outpatient	Usual treatment in psychiatric units	-- (12)

Note. ST= Specialised Therapy; TAU= Treatment as usual; CBT-PD=Cognitive Behavioural Therapy – Personality Disorders; OIP= Outpatient Individual Therapy; DH= Day Hospital; OT=Outpatient Treatment; GT= Group Therapy; IT= Individual Therapy. Community support by health professionals was not considered as formal therapy. When duration of sessions was not informed, it was computed 1 hour per session. Real over planned data on use of therapy was preferred for calculations; ** Table 2 in the original article.

of subjects in BPD samples who participated in individual therapy during the early years of follow-up, which tended to decrease over time (range, 85%-64% and 96%-75%, respectively) [53, 54]. Álvarez-Tomás et al. also reported that 75% of subjects received individual therapy over the 10-year period [10].

3.2. *Meta-analytic results*

There was no evidence for publication biases with respect to the four outcome measures studied in meta-analyses, according to the results of the Egger´s regression test (Remission, $t = 0.41$, $df = 10$, $p = .69$; Completed suicide, $t = 1.98$, $df = 8$, $p = .08$) and the trim and fill method (no study trimmed for depression and functioning).

3.2.1. Remission

Nine studies were analysed for remission, corresponding to twelve comparisons. The mean remission rate was 60% (49 - 71, 95% IC), although remission rates showed high heterogeneity among studies ($Q = 57.9$, $p < .001$; $I^2 = 80.9\%$). The percentages of remission in each study are displayed in Table 9.1.

The results of the effects of moderators are summarised in Table 9.3. Groups with a younger mean age at baseline were more likely to show higher remission rates at follow-up ($Q_M = 4.48$, $p = .03$). Greater percentages of women in the samples were associated with higher remission rates in the long-term, although this tendency did not reach statistical significance ($Q_M = 2.98$, $p = .08$). Time of follow-up, percentage of comorbidity with mood disorders at baseline, and initial level of functioning did not demonstrate a significant influence on long-term remission. No significant differences in mean remission rates were observed between groups receiving and not receiving an initial controlled treatment, i.e., clinical trials vs naturalistic studies (61% vs. 59%). Among clinical trials, the mean remission rate in groups receiving a specialised therapy was higher than in those receiving TAU (70% vs. 52%), although this difference was not

Table 9.3. Results in moderators' effects on remission, depression, and functioning

	Remission				Depression				Functioning			
Moderators	Estimate [95% CI]	Q_M	*(df)*	*p*	Estimate [95% CI]	Q_M	*(df)*	*p*	Estimate [95% CI]	Q_M	*(df)*	*p*
Mean Age	-0.13 [-0.25,-0.01]	4.48	(1)	.03	0.05 [-0.01, 0.12]	2.72	(1)	.10	0.02 [-0.04, 0.08]	0.41	(1)	.52
% Women	0.03 [-0.00, 0.06]	2.98	(1)	.08	0.01 [-0.07, 0.10]	0.13	(1)	.72	-0.03 [-0.05, -0.01]	7.24	(1)	.007
Time of Follow-up	0.11 [-0.08, 0.30]	1.23	(1)	.27	-0.07 [-0.25, 0.11]	0.52	(1)	.47	-0.09 [-0.23, 0.05]	1.68	(1)	.19
% Mood Disorders	0.01 [-0.07, 0.09]	0.04	(1)	.84	---	---	---	---	---	---	---	---
Mean Initial Level of Functioning (z score)	0.61 [-0.32, 1.54]	1.67	(1)	.20	0.18 [-0.28, 0.65]	0.60	(1)	.44	-0.00 [-038, 0.37]	0.00	(1)	.98
Length of Treatment	0.02 [-0.06, 0.12]	0.33	(1)	.57	0.04 [-0.02, 0.08]	3.01	(1)	.08	0.03 [-0.00, 0.07]	3.16	(1)	.07
Hours of Formal Therapy	0.00 [-0.00, 0.01]	1.02	(1)	.31	0.00 [-1.67, 0.07]	0.15	(1)	.70	0.00 [-0.01, 0.00]	1.13	(1)	.29
	Rate [95% CI]	Q_B	*(df)*	*p*	*g* [95% CI]	Q_B	*(df)*	*p*	*g* [95% CI]	Q_B	*(df)*	*p*
Initial Treatment		0.03	(1)	.85		0.22	(1)	.64		2.50	(1)	.11
No Experimental Treatment	59% [.42, .74]				-0.58 [-1.21, -0.06]				0.43 [0.17, 0.69]			
Experimental Treatment	61% [.45, .76]				-0.77 [-1.23, -0.30]				0.74 [0.45, 1.03]			
Type of Initial Treatment		0.57	(1)	.45		0.52	(1)	.47		0.08	(1)	.77
Specialized Therapy	70% [.41, .89]				-0.95 [-1.68, -0.23]				0.79 [0.26, 1.31]			
TAU	52% [.20, .83]				-0.58 [-1.30, 0.15]				0.70 [0.47, 0.93]			

statistically significant. No relevant impact of the length of treatment or the hours of formal therapy received was found.

3.2.2. Completed suicide

Seven studies were considered for completed suicide, which represented ten comparisons. The mean suicide rate was 4% (2 - 5, 95% CI); the values were homogeneous among studies ($Q = 8.68$, $p = .47$; $I^2 = .0\%$). The percentages of completed suicide in the studies ranged from 0% to 8%, as shown in Table 9.1. Due to the low heterogeneity presented among studies, the effects of moderators were not studied on this outcome variable.

3.6.3. Depression

Four studies were studied for depression, comprising six comparisons. Meta-analytic results showed a significant reduction in depressive symptoms at follow-up, indicated by a medium mean effect size ($g = -0.70$, [-1.04, -0.36] 95% CI, $p < .001$). However, there was high heterogeneity among the studies ($Q = 23.40$, $p < .001$; $I^2 = 78.6\%$).

The percentage of comorbidity with mood disorders at baseline was not studied as a moderator on depression because there were no data from at least three studies. No relevant impact of moderators on depression was found, except for the length of treatment. Longer treatments were associated with increased improvement in depression over time, although this trend did not reach statistical significance ($Q_M = 3.01$, $p = .08$).

3.2.4. Functioning

Five studies were synthesised for functioning, which represented nine comparisons. A significant improvement in long-term functioning was also found, with a medium mean effect size ($g = 0.66$, [0.43, 0.89] 95% IC, $p < .001$). However, there was high heterogeneity among studies ($Q = 25.54$, $p = .001$; $I^2 = 68.7\%$).

Groups with a higher percentage of women were more likely to present lower improvement in functioning at follow-up ($Q_M = 7.24$, $p = .007$); age at baseline, time of follow-up, and initial level of functioning showed no relevant impact on long-term functioning. The initial rate of comorbidity with mood disorders was also not studied for functioning because there were no data from at least three studies. Differences in functional improvement between groups from naturalistic studies and those from clinical trials receiving a controlled treatment were not significant, although the latter showed a greater estimated effect size ($g = 0.43$ vs. $g = 0.74$, $p = .11$). In clinical trials, receiving specialised therapies or TAU did not show a relevant impact on functional change. There was a non-significant relationship between longer treatments and higher functional improvement ($Q_M = 3.16$, $p = .07$), whereas the hours of formal therapy received did not have a relevant influence on functioning.

4. Discussion

This meta-analytic study synthesised current findings from prospective research on the long-term course of BPD in adulthood. In terms of mean remission rates, it is estimated that between 50% and 70% of patients diagnosed with BPD may achieve symptomatic remission at some point between five and fifteen years of follow-up; this finding is consistent with former literature indicating that BPD diagnosis leans towards increasing proportions of remission over time. The Montreal study retrospectively reported that 75% of patients with BPD achieved remission at fifteen years and over 90% did so at 27 years of follow-up [2]. Both the MSAD and CLPS studies also provided evidence for an enduring symptomatic remission of BPD, despite reporting cumulative rates of remission [6]. To our knowledge, our study is the first meta-analysis reporting estimated remission rates prospectively assessed at a specific point, which may be useful

in comparing the long-term effects of treatments for BPD patients over the course of the disorder.

Notably, depressive symptomatology and functioning in patients with BPD also lean towards improvement in the long-term. Findings are consistent with those reported by the CLPS and MSAD studies, indicating that the psychosocial functioning of BPD subjects may vary among individuals, but show a significant improvement over time as a group [6]. However, our results do not allow one to conclude whether individuals with BPD can reach normative functional adjustment in the long-term, although previous research indicates that a relevant proportion may suffer from persistent impairments over time [8, 9, 10, 13, 52]. In terms of depressive symptoms, the MSAD study also reported a significant decrease in dysphoric states in the long-term, which was more pronounced in recovered patients [51]. Despite this favourable outcome in clinical and functional realms, we found that the rate of completed suicide in BPD subjects might be expected to be between 2% and 5% during the second half of the decade of follow-up; percentages were lower than those based on previous follow-back research at fifteen and 27 years, which were between 8% and 10%. This fact is consistent with the hypothesis that completions are more likely to occur later in the course of the illness [1, 2].

We further investigated potential moderators for those outcomes which presented high heterogeneity in the meta-analyses. Regarding patients' age at baseline, we found that a diagnosis of BPD at a younger age was associated with higher percentages of remission in the long-term, whereas this moderator did not influence changes in depression and functioning. This is congruent with previous evidence indicating that BPD symptom severity may decline from adolescence to mid-adulthood, particularly in terms of the externalising manifestations of the disorder (i.e., impulsivity and suicidal behaviours) [55, 56, 57, 58]. Younger age has also been identified as a predictor of shorter

time to remission [14]. In contrast, the CLPS informed of similar rates of improvement in BPD symptoms in younger and older subjects over six years of follow-up [15]. This discrepancy in longitudinal findings suggests that age-related divergences might also be influenced by the duration of the illness, which is expected to be longer the older one becomes but with variations among subjects. Similarly, it would be useful to consider the age of onset and the duration of illness as specific moderators when studying the course of the disorder. In terms of functioning, cross-sectional research has reported, contrary to our findings, greater functional impairments in older age, when it is more likely to present worse physical health, poorer quality of life, and greater social assistance utilisation [56, 57, 58]. Nevertheless, this decline in functioning is more dramatically suffered in advanced age, whereas subjects comprising the study samples in our analysis were mostly in their 20s and 30s at baseline. Consistent with this hypothesis, the CLPS study reported that older participants only showed a higher decline in functioning midway through the follow-up [15].

A striking finding was that female gender was associated with a lower improvement in functioning, whereas there were no significant differences in gender with regard to changes in BPD diagnosis and depression in the long-term. These results are consistent with those informed by the MSAD, which did not report a significant impact of gender on time to remission over ten years [14]. Unfortunately, there is scarce evidence on gender differences regarding the functional course of BPD. In this respect, our findings indicate that the long-term functional recovery in women with BPD might be hampered by other causes apart from the persistence of the disorder. A possible explanation is that psychopathological divergences between genders in symptom severity and comorbidity might deeply interfere with the long-term functional outcome of BPD women, in spite of showing similar trends of clinical improvement over time. In this line, there is evidence

from cross-sectional research on gender differences that female BPD subjects present greater percentages of lifetime Axis I comorbidity and higher severity in general psychopathology, particularly in areas related to internalising patterns such as anxiety, depression, and somatisation [59, 60]. Additionally, BPD women are more likely to have a history of childhood sexual abuse and experience episodes of physical and sexual aggression during adulthood, which is related to higher psychosocial impairment [59, 61]. On the other hand, sociological studies have noted that gender roles determine different strains and benefits of normative social adaptation for men and women, which might also contribute to hindering psychosocial adjustment in female BPD subjects; for example, caregiving roles for women in the general population are associated with greater psychological distress and increased reductions in the protective benefits of employment for mental health, reporting higher rates of exposure to stressful life events involving significant others [62, 63].

Receiving an initial controlled treatment does not seem to increase the amount of clinical improvement in the long-term compared to the course of the disorder described in naturalistic studies. Besides, both specialised therapies and TAU seem to similarly improve the long-term clinical outcome, despite observing non-significant differences in mean remission rates between those groups. This contrasts with previous research indicating a higher efficacy of specialised therapies for BPD in the short-term [64, 65], which suggests that the differential effects of psychotherapeutic interventions might be diluted by the diverse mechanisms of change over the lifespan. On the other hand, the long-term functioning of BPD patients appears to be enhanced by any kind of controlled treatment, particularly those that are implemented over a longer period of time, although these trends did not reach statistical significance in our analyses. This might indicate that common components of psychotherapies are key factors in promoting changes in

psychosocial functioning in the long-term [66]. One aspect to note is that the methodological limitations of the selected studies may affect these results on treatment moderators. First, other confounding factors are likely to interfere with treatment efficacy in long-lasting post-treatment follow-ups, including the likelihood of receiving further treatment after the experimental phase. Secondly, most BPD subjects in naturalistic studies might also have received some form of uncontrolled treatment during the follow-up period [2, 64].

The length of follow-up was not relevant to explain the variations in the outcomes, suggesting a low pace of change in the long-term. This differs from the early years of illness when more dramatic shifts in BPD symptoms may occur [1, 14]. Additionally, no significant effects of the initial level of functioning and the percentage of comorbid mood disorders were found; this contrasts with findings from the CLPS indicating that a comorbid major depressive disorder is associated with a delayed time to remission from BPD, likely due to differences in the operationalisation of remission in this study [16].

There are strengths and limitations of this meta-analysis to consider. We included follow-along studies conducted in a variety of clinical settings and countries, which increases the generalisation of the findings. We also analysed the impact of several factors on the heterogeneity of the outcomes; however, the majority of selected studies reported results at follow-up lasting between five and ten years, largely restricting the scope of our findings to this time period. In general, the scarcity of selected studies and the small size of the BPD samples in most of them reduced the statistical power of the analyses and therefore may have affected the study of the effects of moderators. Additionally, the lack of data or the variability of measures used among studies restricted the analysis of other potential moderators and outcomes. Finally, we studied correlational relationships

between moderators and long-term outcomes and, therefore, we cannot establish causal links based on our findings.

5. Conclusion

Our findings confirm a pattern of clinical and functional improvement over time in patients diagnosed with BPD. It is tempting to think about the beneficial effects of psychotherapeutic interventions, specialised or not, on the functional long-term course, but further research on the long-term effects of psychotherapies is required to reach consistent conclusions in this regard. Moreover, longitudinal studies in untreated samples might also enrich our knowledge of the natural course of BPD and the study of treatment efficacy. In general, the consistent use of clinical and functional measures for BPD would facilitate meta-analytic research in this field.

Our results lead to the conclusion that BPD diagnosis at a younger age corresponds to a better clinical prognosis in the long-term, whereas similar rates of functional improvement are achieved by age over time. This justifies direct efforts towards the early detection of BPD, allowing the implementation of effective treatments during patients' youth to reduce the adverse effects of the disorder during this critical life stage. In addition, functional improvement in the long-term is hampered in women with BPD; accordingly, it is essential to incorporate a gender perspective to address psychosocial interventions for these patients, particularly due to the higher percentage of women among treatment-seekers with BPD diagnosis. Moreover, the use of study designs that allow gender comparisons would be recommended.

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Disclosure of interest

The authors declare that they have no competing interests.

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Note. References in this section are displayed in the format that was required by the journal of publication.

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4.4. <u>SUMMARY OF FINDINGS</u>

There were 11 studies which informed of prospective data in nine countries on the long-term course of BPD during adulthood, including our study in the Spanish population. Nine studies were analyzed for remission, indicating that 60% of the subjects with BPD diagnosis will achieve remission in the long-term. The 95% CI for this mean remission rate was 49%–71%. The mean suicide rate was 4% (2-5, 95% CI). Meta-analytic results showed a significant tendency towards improvement of depressive symptoms and functioning over time, with medium mean effect sizes ($g = -0.70$, $p < .001$; $g = 0.66$, $p < .001$; respectively), pooling data from four and five studies, respectively.

We analyzed the effect of several potential moderators on remission, depression and functioning, due to the heterogeneity of these variables among the studies. Samples with younger mean age at baseline were significantly more likely to present higher remission rates in the long-term. By contrast, the amount of improvement was similar for depression and functioning in younger and older samples. It is noticeable that higher percentage of women in the sample was significantly associated to lower amount of improvement in functioning, even though this negative correlation was not observed for remission rates and depression. No relevant impact of treatment moderators on remission was found. There was a non-significant trend of both specialized and usual treatments to increase the long-term functional adjustment over uncontrolled treatments in naturalistic studies. Only the length of controlled treatments showed beneficial effects on depression and functioning, with greater improvements as longer was the treatment, although this tendency did not reach statistical significance. The length of follow-up, the prevalence of comorbid mood disorders at baseline, and the initial level of functioning did not show relevant effects on long-term outcomes.

4.5. <u>STRENGTHS & LIMITATIONS</u>

This meta-analysis pooled prospective data of an extended number of BPD patients from different countries on relevant long-term outcomes, regarding clinical and functional areas. Moreover, the inclusion in the analyses of both naturalistic and follow-up post-treatment studies allowed us to study several treatment characteristics as moderators of long-term outcome. However, the availability of comparative data was restricted by the limited number of studies and the methodological variations among them, reducing the outcomes and potential moderators that were considered in the analyses. The statistical power in some analyses might be also reduced by the scarcity of studies and the small size of the samples. Moreover, we studied correlational relationships between moderators and outcomes, which impedes to draw definitive causal conclusions.

5. GENERAL DISCUSSION

The present thesis contributes to extend previous evidence on the long-term prognosis of BPD in two ways: firstly, describing specific course patterns for several clinical and functional areas and, secondly, exploring potential factors that may impact on the long-term outcome. Regarding the first aspect, our findings add to previous evidence indicating a favorable course of BPD in the long-term. Moreover, results of our meta-analysis also confirm the generality of this tendency towards improvement in different populations and socio-cultural contexts. In terms of identifying relevant predictors, our findings suggest that receiving a BPD diagnosis in a younger age might be associated with a better clinical outcome. Moreover, a younger age was also associated with higher remission rates from BPD in our meta-analysis. By contrast, female gender showed negative effects on functional rather than clinical improvement in the long-term, suggesting that social adjustment might be affected by gender differences. Contrary to our expectations, there were not relevant effects of treatment characteristics on the long-term outcomes, except for the length of therapy. In our follow-up study, an earlier age of first BPD diagnosis showed a trend to be associated with a higher remission rate and, to a lesser extent, with higher improvements in BPD affective symptoms (not so with the impulsive, cognitive and interpersonal symptoms). Several predictors of the long-term QOL were also studied in our sample. In the following paragraphs, we will extensively discuss our findings, firstly, on what is expected for these patients in the long-term and, secondly, on relevant predictors in light of several clinical and functional outcomes.

In our follow-up study, conducted in a Spanish sample, 55% of the subjects with BPD diagnosis achieved remission 10 years later. Consistently, findings of our meta-analytic review also indicate that remission from BPD is common in different populations after 5 years or more of follow-up, suggesting an estimated remission rate of 60% for these patients, with an expected variability from 49% to up to 72%. Our results are

consistent with those from the 15-year retrospective studies, reporting remission rates of 75% and 50%, although these studies presented some methodological limitations to take into account (Paris et al., 1987; McGlashan, 1983). By contrast, these percentages are slightly lower than the cumulative remission rates reported by the MSAD and CLPS studies in the long-term (Zanarini et al., 2010a; Zanarini et al., 2012; Gunderson et al., 2011). This might be attributed to the fact that the likelihood of relapse for a part of the sample may affect more negatively the remission rates assessed in a specific time point than the cumulative rates assessed over a long period, apart from other methodological considerations. This explanation is supported by findings indicating that cumulative rates decrease when longer periods of sustained remission are studied (Zanarini et al., 2010a; Zanarini et al., 2012).

In any case, our findings are consistent with those from MSAD and CLPS studies, indicating that BPD pathology tends to ameliorate in the long-term (Zanarini et al., 2007; Gunderson et al., 2011). In our follow-up study, general BPD symptomatology, assessed by SCID-II Borderline Subscale and DIB-R, and all clinically relevant BPD domains at baseline assessed by DIB-R, i.e., affective, impulsive, and interpersonal symptoms, presented significant reductions at 10 years. There were some differences in the amount of change observed between the symptomatic areas of the disorder although results did not confirm our expectations, according to the complex model of BPD pathology (Zanarini et al., 2003; Zanarini et al., 2007). The impulsive domain presented a large amount of change over time but also did so the interpersonal domain, which clusters a mixture of acute and temperamental symptoms in almost equal proportion. Affective features showed a more moderate improvement than the former, but still significant and clinically relevant, in spite of grouping mainly temperamental symptoms. Therefore, these findings suggest that the different course patterns drawn by acute and

temperamental symptoms might come together into a general trend of improvement in the long-term. Another reason to consider is the fact that grouping BPD features by domains may hamper the identification of variations among particular acute and temperamental symptoms, being the categorical domains more dependent on the specific expression of BPD pathology in each sample.

In terms of dimensional personality traits, we observed significant reductions in Neuroticism-Anxiety, Impulse-Sensation Seeking, and Aggression-Hostility at 10 years, as expected in light of the previous evidence (Hopwood et al., 2009; Hopwood & Zanarini, 2010a; Wright et al., 2015). This is accompanied in our sample by an improvement in BPD pathology, which provides evidence on the association of these dimensional traits with BPD symptomatology, as stated by Wright et al. (2015). Comparable decreases in Neuroticism-Anxiety and Aggression-Hostility, which have been previously associated to temperamental and acute symptoms respectively (Hopwood et al., 2009), supports the idea that both type of symptoms tend to improve in a more similar way in the long-term. Apart from this, there were unexpected decreases in the traits of Activity and Sociability towards impairment over time, which indicates reductions in the need for general activity, work, and social interactions. This might be associated with the increasing rates of comorbid avoidant and obsessive-compulsive PDs that we found in our sample at 10-year follow-up, which stands in contrast to previous evidence indicating a decreasing trend of Axis II comorbidity in the long-term (Zanarini, Frankenburg, Vujanovic et al., 2004). One reason for this could be that the development of avoidant and obsessive-compulsive traits might play an adaptive role for some patients, controlling emotional dysregulation and preventing conflict with others in some manner. In this line, it is possible that the high rates of Axis II comorbidity may be associated with the degree of chronicity in our sample, with almost half of patients suffering from

persistent BPD symptoms (Sanislow et al., 2009; Zanarini, Frankenburg, Vujanovic et al., 2004). Another explanation might be that the rise of Axis II comorbidity could reflect in part age-related changes in dimensional traits, which tend to increase in Agreeableness and Conscientiousness with age (Srivastava, John, Gosling, & Potter, 2003). According to Durbin and Klein (2006), the rise in Conscientiousness that tends to occur during adult development might have led to increases in obsessive-compulsive personality features.

In line with changes observed in dimensional traits, we found that symptoms of depression and aggression/hostility also tend to ameliorate at 10 years in our follow-up study, consistently with previous literature (Reed et al., 2012; Zanarini et al., 2017). Moreover, findings from our meta-analysis also suggest that significant reductions in depression are common in the long-term among BPD patients from different populations. Despite that, comorbidity with affective and anxiety disorders appears still clinically relevant in the long-term, as indicated by findings from our follow-up study and previous prospective research (Zanarini, Frankenburg, Hennen, Reich et al., 2004; Silverman et al., 2012; Zeitler et al., 2018).

Regarding suicidality, we found a substantial decrease in the prevalence of suicidal attempts and self-mutilation acts at 10 years, consistently with previous evidence (Zanarini et al., 2008). Despite this favorable outcome for the most part, the likelihood of completing suicide in our sample reached almost 8%, which represents a higher risk of suicide for these patients compared to the general population in Spain (i.e., mean rate between 20-39 years of 0.003% for women and 0.005% for both genders in a given year; Instituto Nacional de Estadística, INE, 2017). This finding is consistent with results from a previous review, indicating that completed suicide is significantly more frequent among BPD patients in comparison with the general population in the US, Norway and Canada (Pompili et al., 2005). However, we conducted a meta-analysis that yielded a more modest

expected suicide rate of 4%, when combining our results with those from other prospective studies over five years of follow-up and beyond (Stevenson et al., 2005; Bateman & Fonagy, 2008; Davidson et al., 2010; Antonsen et al., 2017; Zanarini et al., 2003; Gunderson et al., 2011). In this line, suicide rates reported by 15-year retrospective studies also showed oscillations from 3% to 9% (Plakun et al., 1985; McGlashan, 1986; Paris et al., 1987; Stone, 1990). These findings lead to conclude that completing suicide seems to be the fate for some of these patients in the long-term, although its likelihood may vary depending on other factors apart from the presence of the BPD diagnosis itself. Unfortunately, we were not able to analyze moderating effects on suicide due to the low heterogeneity of this outcome among selected studies. One reason for this might be that our review was only focused on long-term prospective studies, which restricted the evidence available for analyses and, thus, the variability observed in such a low-prevalent outcome. Accordingly, few studies have examined predictors of completed suicide rather than suicide attempts in BPD patients, due to methodological limitations (Pompili et al., 2005; Temes et al., 2019).

Findings from our follow-up study add to former evidence that the use of mental health treatments diminishes over time in BPD patients (Bender et al., 2006; Zanarini, Frankenburg, Hennen & Silk, 2004; Hörz et al., 2010). Despite that, outpatient interventions (i.e., psychiatric treatment and individual therapy) were still required by two thirds of our sample at follow-up, suggesting that BPD patients may benefit from these less intensive interventions in different stages along the course of the disorder. It is noteworthy that the use of rehabilitation services grew in the long-term, indicating the increasing relevance of functional and occupational needs among these patients over time. However, our sample was highly treated at baseline, as those from the MSAD and CLPS

studies, which entails the generalization of findings particularly to treatment-seeking populations (Zanarini et al., 2001; Bender et al., 2001).

Apart from mental resources, our results indicate that the use of health care services appears to be common among BPD patients in the long-term, particularly for those who have not achieved remission, in accordance with former studies (Frankenburg & Zanarini., 2004; Keuroghlian et al., 2013; Riihimäki et al., 2014). Our findings are in line with those from the MSAD, indicating that the persistence of BPD pathology appears to be associated with poorer physical health in the long-term, although this trend did not reach statistical significance in our study. Despite that, over two thirds of the overall sample reported some current medical illness at follow-up, mainly chronic conditions, which confirms that physical health problems are a relevant aspect to take into account in the assistance of these patients in the long-term (Doering, 2019).

According to previous evidence, our findings confirm that it is expected a functional improvement over time for BPD patients as a whole, in spite of particular variations in the level of psychosocial functioning achieved by individuals (Zanarini, 2012). Results of our meta-analysis suggest that this trend is generalizable to different populations, despite some heterogeneity between samples. In our follow-up study, there was a slight improvement in social functioning over time, although a part of the sample showed greater impairments in the occupational realm, in accordance with the MSAD (Zanarini et al., 2010b).

In terms of potential predictors of outcome, we explored the influence of the age of first BPD diagnosis on the course of BPD pathology and social functioning in our follow-up sample. Our results suggest that an earlier BPD diagnosis might be associated to a higher likelihood of BPD remission in the long-term and, perhaps, to greater improvements in the affective features of the disorder; no effects of the age of first BPD

diagnosis were found on the amount of improvement either in the impulsive, cognitive and interpersonal domains of the disorder or in social functioning over time. Differences observed in the course of affective features might be explained by the higher prevalence of lifetime mood disorders that was observed in those patients with a delayed BPD diagnosis, suggesting the presence of more persistent affective disturbances in these patients. On the other hand, these findings raise the question of whether an earlier diagnosis of BPD would benefit the clinical course, perhaps, by offering an adjusted understanding of symptoms and adequate treatments in earlier stages of life (Chanen & McCutcheon, 2013). In this sense, this predictor differs from the age of first symptoms and first treatment, previously considered by the MSAD, in studying the impact of receiving a full BPD diagnosis instead of the onset of general psychopathology (Zanarini et al., 2006; Zanarini et al., 2014). Notwithstanding, these findings are only tentative due to some methodological limitations, such as the small sample size for comparisons and the lack of control in the analyses over the confounding effects of other potential predictors (e.g., age, comorbidity with mood disorders, etc.).

In this line, findings from our meta-analysis indicate that a BPD diagnosis at a younger age seems to predict higher rates of remission from BPD in the long-term, consistently with findings in the MSAD study (Zanarini et al., 2006). Accordingly, cross-sectional research comparing BPD pathology by age also indicates a decline in BPD symptom severity from adolescence to mid-adulthood, particularly in impulsivity and suicidality (Blum et al., 2008; Stepp & Pilkonis, 2008; Morgan, Chelminski, Young, Dalrymple, & Zimmerman, 2013; Frías, Palma, Solves, Martínez, & Salvador, 2017). By contrast, in our meta-analysis there were not differences by age in the long-term course of depressive symptoms and functioning. This stands in contrast to evidence from cross-sectional research indicating greater functional impairments in older age, in terms of

poorer physical health and QOL, and higher use of assistance resources (Stepp & Pilkonis, 2008; Morgan et al., 2013; Frías et al., 2017). This might be due to the narrow range of ages in the studies' samples, mainly comprised into young adulthood. Previous reviews have pointed out the dearth of longitudinal studies following BPD samples into late life, which limits our knowledge of the course of BPD at older age (Beatson et al., 2016; Hutsebaut, Videler, Verheul, & Van Alphen, 2019). In this respect, there is growing interest in the literature to address various issues of PDs in light of a life course perspective, such as age-specific assessments and psychotherapeutic interventions, and the identification of particular course patterns of PDs, e.g., late-onset PDs (Oltmanns & Balsis, 2011; Beatson et al., 2016; Hutsebaut et al., 2019).

Unexpectedly, female gender was associated in our meta-analysis to a lower improvement in functioning in the long-term, even though there were not significant differences in clinical course patterns between genders. This stands in contrast to results in the MSAD indicating that gender was not predictive of time-to-attainment of recovery, although it might be due to the fact that recovery comprises a mix of clinical and functional outcomes (Zanarini et al., 2014). Unfortunately, there is a lack of longitudinal studies that analyze gender differences in the functional course of BPD in the long-term. Several factors might hamper the improvement of functioning in females, which have been previously discussed in Article 2 (See section 4.3.1). On the one hand, some psychopathological particularities in females with BPD, reported in cross-sectional research on gender differences, might impact more negatively on functioning in the long-term, such as greater prevalence of comorbid affective disorders and PTSD, etc. (Bayes & Parker, 2017). On the other hand, the strains and benefits that are determined by gender roles might interfere more intensely the social adjustment in females (Leupp, 2017).

Contrary to our expectations, differences in treatment interventions during follow-up did not show relevant effects on the likelihood of remission in the long-term. Our findings stand in contrast to previous evidence indicating increasing effects of the specialized therapies over the usual treatment on BPD symptomatology at post-treatment (Stoffers et al., 2012; Cristea et al., 2017; Oud et al., 2018), which appear to be diluted in the long-term. Moreover, receiving an initial controlled treatment does not seem to improve the clinical outcome compared to results in naturalistic studies. This reinforces the concerns on the confounding effects of uncontrolled treatments, which may affect the long-term outcomes both in naturalistic and long-lasting post-treatment follow-ups. In the functional realm, it appears to be a beneficial effect of the controlled treatments, both specialized and usual interventions, on the functional adaptation over time, compared to the course described in naturalistic studies. Particularly, the length of these treatments appears to be a key factor to yield greater improvements in depressive symptoms and functioning in the long-term. However, none of these tendencies were statistically significant in our analyses, probably due to the scarcity of studies reporting data on these outcomes. These findings suggest that psychotherapeutic interventions, both specialized and usual ones, might interact positively with the natural course to enhance functional adjustment in treatment-seeking patients. One explanation might be that common aspects of psychotherapies may play a relevant role in improving the interpersonal functioning of these patients in the long-term (Sinnaeve, van den Bosch, & van Steenbergen-Weijenburg, 2015).

Apart from this, other potential predictors were studied in our meta-analysis as moderators of remission, depressive symptoms and functioning in the long-term. The length of follow-up was not relevant as moderator in our analyses, indicating that changes in the course of BPD diminish after five years. Contrary to our expectations, the

prevalence of comorbid mood disorders did not affect the rate of remission from BPD. This differs from findings in the CLPS study, indicating mutual interactions between these factors (Gunderson et al., 2014), probably due to methodological differences. Moreover, there were not relevant effects of the initial level of functioning on all outcomes.

Furthermore, we analyzed in our follow-up study the impact of several predictors on the QOL of BPD patients in the long-term. Among baseline predictors, the severity of childhood trauma was a significant predictor of a poorer QOL after 10 years of follow-up, even after controlling for the initial level of BPD symptomatology and social functioning, according to previous literature indicating a negative impact of these early traumatic experiences on the long-term outcome (Paris et al., 1987; Stone, 1990; McGlashan, 1985; Paris et al., 1988; Plakun, 1991; Zanarini et al., 2006; Zanarini et al., 2014). Higher initial level of social functioning was associated to a better long-term QOL only in bivariate analysis. A younger age showed no significant effects on the long-term QOL. Dimensional personality traits at baseline were also not predictive of long-term QOL in BPD patients, in contrast to findings in the general population (DeNeve & Cooper, 1998). On the other hand, our findings suggest that the persistence of BPD pathology over time might affect negatively the QOL in the long-term, consistently with previous studies indicating the positive effects of BPD remission on several clinical and functional aspects that may impact the QOL in the long-term, such as Axis I and II comorbidity, social functioning, and physical health (Zanarini, Frankenburg, Vujanovic et al., 2004; Zanarini, Frankenburg, Hennen, Reich et al., 2004; Gunderson et al., 2014; Zanarini et al., 2005b; Frankenburg & Zanarini., 2004). Moreover, physical health problems seem to worse more the QOL of those patients with persistent BPD symptoms than those who achieved remission. This finding indicates that attending medical

conditions is a relevant aspect for the assistance of the chronicity in BPD, in order to increase the subjective well-being of these patients (Doering, 2019).

6. STRENGTHS & LIMITATIONS

OF THE THESIS

The present thesis makes a substantial contribution to our knowledge about the long-term prognosis of BPD in adulthood. Firstly, our prospective study offers empirical data on a variety of clinical and functional outcomes, using validated instruments in the Spanish population, from a well-defined Spanish BPD sample. In this study, the follow-up period extends up to 10 years, presenting a reduced drop-out rate of the sample, which supports the validity of findings. Secondly, our meta-analysis synthesizes prospective data from different populations on relevant outcomes in the long-term. Moreover, combining naturalistic and follow-up clinical studies in the meta-analyses represents an innovative methodology that has allowed us to study the predictive effects of various treatment factors on the long-term outcome. Lastly, the present thesis offers new evidence about the impact of other potential predictors on the long-term course, both from the empirical research and the meta-analytic review.

However, there are some methodological limitations to take into account when interpreting the findings that are comprised in this thesis. Our follow-up study and those that were also included in the meta-analysis are observational in nature, reporting descriptive data and correlational relationships between variables, which impedes drawing causal conclusions. The limited sample size in our prospective study and the scarcity of selected studies in the meta-analisis affected the statistical power of some analyses and, therefore, the robustness of some findings. This limitation was particularly relevant when comparing subgroups in the follow-up study and exploring the predictive effects of moderators in the meta-analysis. In addition, the comparison with a control group was not considered neither in our follow-up study nor in the meta-analysis, which prevents us to compare the long-term course of BPD patients with those of other clinical

populations, and with the normal trajectories over the lifespan in the general population. It is also relevant to note that findings of our follow-up study on potential predictors of long-term course (i.e., age of first BPD diagnosis and predictors of QOL) have only been reported in posters and communications up until now, which implies that this part of our research work is due for an in-depth methodological review. These results should therefore be considered as tentative and interpreted with caution.

7. CONCLUSIONS &

IMPLICATIONS

To sum up, BPD seems not to look like a fixed picture that is invariable over time. Our findings confirm a favorable course of BPD in the long-term, which suggests that BPD might be considered as a remitting disorder, in contrast to early conceptualizations describing it as chronic by nature. However, we should be cautious about jumping to over-optimistic conclusions on the long-term prognosis for all BPD patients, since there is also solid evidence indicating persistent disturbances in some patients over time, both in the clinical and functional realms. In this respect, our findings suggest that treatment interventions for patients with chronic BPD should address other aspects apart from persistent BPD features, such as comorbid medical problems, to improve their general well-being in the long-term.

These variations in the long-term prognosis among BPD patients emphasizes the need to deepen in the knowledge of significant predictors of outcome, in order to take account of them not only in the clinical practice but also in research. In this respect, our findings indicate that age and gender modulate the long-term course of the disorder. In the clinical practice, this suggests that it would be recommended to adapt therapeutic interventions to be applied differently by gender and the specific stages of the lifespan. In this line, our findings suggest that strategies for an early detection of BPD diagnosis might improve the long-term prognosis. On the other hand, it is necessary to conduct further longitudinal research on BPD in adolescence and later life, and addressing gender differences over time. It is worth noting that including a gender perspective might represent an improvement for the overall research in the field, reviewing methodological issues such as the definition of relevant outcomes, recruitment strategies, etc.

In terms of treatment efficacy, our findings put into question the increasing efficacy of specialized therapies over usual treatments in light of the long-term course,

suggesting that some common factors of treatments might play a relevant role on the long-term outcome. However, further evidence on the long-term outcome of treatment interventions are needed to draw solid conclusions. In order to study the long-term efficacy of treatments, assessing other outcome measures apart from the most acute symptomatic ones and controlling for other moderators of change over time would be strongly recommended.

On the other hand, longitudinal research on the long-term course of BPD has mainly focused on following treatment-seeking samples, probably due to the convenience of recruiting samples with a well-defined diagnosis in clinical settings rather than in the community. However, our findings indicate that uncontrolled treatments might also exercise some impact on the long-term course of the disorder, introducing confounding effects in naturalistic follow-ups. Therefore, conducting longitudinal studies in community samples would be also recommended.

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9. ANNEX

TABLE I. Systematic Assessment of Quality in Observational Research (SAQOR): <u>Sample Summary</u>

Country	Reference	Sample					Summary
		Representative	Clear Source	Sampling method described	Sample Size Calculation	Inclusion Exclusion Criteria	Sample (≥ 3 of 5)
Australia	Stevenson et al., 2005 Stevenson, J. & Meares, R., 1992	No	Yes	Yes	No	Yes	A
UK	Bateman & Fonagy, 1999, 2008	No	Yes	Yes	No	Yes	A
	Davidson et al., 2006, 2010 Davidson, Tyrer, et al., 2006	Yes	Yes	Yes	*Yes*	Yes	A
Norway	Antonsen et al., 2015 Arnevik et al., 2009	No	Yes	Yes	No	Yes	A
Sweden	Sahin et al., 2017	No	Yes	Yes	Yes	Yes	A
Canada	Links et al., 1995, 1998	No	Yes	Yes	No	Yes	A
US	Zanarini et al., 2003 Zanarini et al., 2006	No	Yes	Yes	No	Yes	A
	Gunderson et al., 2011 Gunderson et al., 2014	No	Yes	Yes	Yes	Yes	A
Finland	Riihimäki et al., 2014	Yes	Yes	Yes	No	Yes	A
Spain	Alvarez-Tomas et al., 2017	No	Yes	Yes	No	Yes	A
Germany	Zeitler et al., 2018	No	Yes	Yes	No	Yes	A

Ratings that needed consensus between raters are written in italics in the table.

TABLE II. Systematic Assessment of Quality in Observational Research (SAQOR): <u>Measures and Follow-Up</u>

Country	Reference	Quality of exposure/outcome measures		Summary	Follow-up		Summary
		Exposure	Outcomes	Measures (2 of 2)	Lost to follow-up stated	Loss explained	Follow-up (2 of 2)
Australia	Stevenson et al., 2005 Stevenson, J. & Meares, R., 1992	Yes	Yes	A	Yes	Yes	A
UK	Bateman & Fonagy, 1999, 2008	Yes	Yes	A	Yes	Yes	A
	Davidson et al., 2006, 2010 Davidson, Tyrer, et al., 2006	Yes	Yes	A	Yes	Yes	A
Norway	Antonsen et al., 2015 Arnevik et al., 2009	Yes	Yes	A	Yes	No	I
Sweden	Sahin et al., 2017	Yes	Yes	A	*Yes*	No	I
Canada	Links et al., 1995, 1998	Yes	Yes	A	Yes	No	I
US	Zanarini et al., 2003 Zanarini et al., 2006	Yes	Yes	A	Yes	Yes	A
	Gunderson et al., 2011 Gunderson et al., 2014	Yes	Yes	A	Yes	*No*	*I*
Finland	Riihimäki et al., 2014	Yes	Yes	A	Yes	*No*	*I*
Spain	Alvarez-Tomas et al., 2017	Yes	Yes	A	Yes	Yes	A
Germany	Zeitler et al., 2018	Yes	Yes	A	Yes	Yes	A

Ratings that needed consensus between raters are written in italics in the table.

TABLE III. Systematic Assessment of Quality in Observational Research (SAQOR): <u>Influential variables and Reporting of data</u>

Country	Reference	Influential variables					Summary	Reporting of data		Summary
		Gender/ Age	Psychiatric comorbidity	Type of initial treatment	Treatment over follow-up	Other	Influential variables (≥ 3 of 5)	Missing data explained	Data clearly presented	Data (2 of 2)
Australia	**Stevenson et al., 2005** **Stevenson, J. & Meares, R., 1992**	No	No	*No*	No	No	**I**	**No**	**Yes**	**I**
UK	**Bateman & Fonagy, 1999, 2008**	No	No	Yes	No	No	**I**	*No*	**Yes**	*I*
	Davidson et al., 2006, 2010 **Davidson, Tyrer, et al., 2006**	*Yes* Only suicidal attempts	No	Yes	No	*Yes* Only suicidal attempts	*A*	**Yes**	**Yes**	**A**
Norway	**Antonsen et al., 2015** **Arnevik et al., 2009**	No	*Yes* AVPD for GAF	Yes	No	No	**I**	**No**	**No**	**I**
Sweden	**Sahin et al., 2017**	No	No	Yes	No	*Yes* Initial BPD severity	**I**	**Yes**	**Yes**	**A**
Canada	**Links et al., 1995, 1998**	*Yes*	*Yes*	No	No	*Yes* Initial BPD severity	*A*	**No**	*Yes*	**I**
US	**Zanarini et al., 2003** **Zanarini et al., 2006**	Yes	Yes	No	No	Yes Race	**A**	**No**	**Yes**	**I**
	Gunderson et al., 2011 **Gunderson et al., 2014**	Yes	Yes	No	No	Yes Education	**A**	**Yes**	**Yes**	**A**
Finland	**Riihimäki et al., 2014**	Yes Age	Yes	No	No	*No*	*I*	**No**	**Yes**	**I**
Spain	**Alvarez-Tomas et al., 2017**	No	No	No	No	No	**I**	**No**	**Yes**	**I**
Germany	**Zeitler et al., 2018**	No	No	No	No	No	**I**	**No**	**Yes**	**I**

Ratings that needed consensus between raters are written in italics in the table.

SAMPLE:

Representativeness: It was defined as met if the study made an effort to determine a base sample across multiple sources (i.e., varied health services or country areas) and used random sampling to arrive at the sample.

Clear Source: It was met if the region, population, or other context for study recruitment was described.

Method: This criterion was met if the method of study recruitment was defined, such as contact after discharge, etc.

Sample size: It was met if a power calculation was provided for sample size determination given a specific study hypothesis.

Inclusion/exclusion: It was met if the process of determining whether a participant met BPD criteria or not was described and if any other inclusion/exclusion criteria were included. Inclusion/exclusion criteria had to be clear and justified, i.e., explicitly described and applied consistently to all groups.

To achieve a score of 'Adequate' in this section, studies must have met 3 of 5 Sample criteria.

MEASURES AND FOLLOW-UP:

Exposure: Exposure (BPD diagnosis) was required to be assessed either by a gold standard method, or confirmed through two independent sources.

Outcome: Criteria were met if instruments used were either developed for the local population or went through a validation process.

To achieve a score of 'Adequate' in this category, studies must have met both criteria.

Follow-Up: They were met if the number lost and reason for the loss were described in the text.

To achieve a score of 'Adequate', studies must have met both criteria.

INFLUENTIAL VARIABLES:

Influential variables: Criteria were met when some of the defined influential variables were included in regression or covariance analyses.

To achieve a score of 'Adequate' in this category, studies must have met 3 or more criteria.

Missing data: It was met if the reason for missing data and the statistical technique used for accounting for missing data were discussed.

Data clearly presented: Data were clearly and accurately presented including confidence intervals where appropriate. Specifically, we noted whether sample sizes were included in figures or tables, and if so, whether the numbers in tables and figures added up as expected.

To achieve a score of 'Adequate' in this category, studies must have met both criteria.

TABLE IV. Systematic Assessment of Quality in Observational Research (SAQOR): <u>Final Quality Summary</u>

Country	Reference	Domains - Summary					Quality of evidence
		Sample	Exposure/Outcome Measures	Follow-up	Influential variables	Data	
Australia	Stevenson et al., 2005 Stevenson, J. & Meares, R., 1992	A	A	A	I	I	Moderate
UK	Bateman & Fonagy, 1999, 2008	A	A	A	I	I	Moderate
	Davidson et al., 2006, 2010 Davidson, Tyrer, et al., 2006	A	A	A	A	A	High
Norway	Antonsen et al., 2015 Arnevik et al., 2009	A	A	I	I	I	Moderate
Sweden	Sahin et al., 2017	A	A	I	I	A	Moderate
Canada	Links et al., 1995, 1998	A	A	I	A	I	Moderate
US	Zanarini et al., 2003 Zanarini et al., 2006	A	A	A	A	I	High
	Gunderson et al., 2011 Gunderson et al., 2014	A	A	I	A	A	High
Finland	Riihimäki et al., 2014	A	A	I	I	I	Moderate
Spain	Alvarez-Tomas et al., 2017	A	A	A	I	I	Moderate
Germany	Zeitler et al., 2018	A	A	A	I	I	Moderate

Ratings that needed consensus between raters are written in italics in the table.

Criteria for computing quality of evidence: High = 4-5 adequate; Moderate = 2-3 adequate; Low = 1 or less adequate.