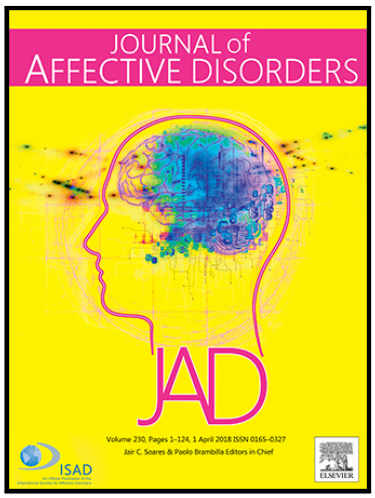

The prevalence, odds and predictors of lifespan comorbid eating disorder among people with a primary diagnosis of bipolar disorders, and vice-versa: systematic review and meta-analysis

Michele Fornaro , Federico Manuel Daray , Fernando Hunter , Annalisa Anastasia , Brendon Stubbs , Domenico De Berardis , Jae Il Shin , Muhammad Ishrat Husain , Elena Dragioti , Paolo Fusar-Poli , Marco Solmi , Michael Berk , Eduard Vieta , André Ferrer Carvalho

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The prevalence, odds and predictors of lifespan comorbid eating disorder among people with a primary diagnosis of bipolar disorders, and vice-versa: systematic review and meta-analysis

Running title: "BD⇌ED."

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Keywords
Bipolar disorder; Anorexia Nervosa; Bulimia Nervosa; binge eating disorder; prevalence; comorbidity; review; meta-analysis, psychiatry, mental health, neuroscience.

Highlights

- Bipolar and eating disorders often co-occur.
- Systematic and review and meta-analysis is warranted.
- Primary studies on pediatric populations are lacking.

- Bipolar and eating disorders span across a continuum.
- Diagnosis should follow a hierarchical approach.

Abstract

Background: There are scarce and discrepant data about the prevalence and correlates of co-occurring eating disorders (EDs) among people with a primary diagnosis of bipolar disorder (BD), and vice-versa, compelling a systematic review and meta-analysis on the matter.

Methods: MEDLINE/PsycINFO databases were systematically searched for original studies documenting BD⇌ED comorbidity across the lifespan, from inception up until April 20th, 2020. Random-effects meta-analysis and meta-regression analyses were conducted, accounting for multiple moderators.

Results: Thirty-six studies involved 15,084 primary BD patients. Eleven studies encompassed 15,146 people with primary EDs. Binge eating disorder (BED) occurred in 12.5% (95%C.I.=9.4-16.6%, I^2=93.48%) of BDs, while 9.1% (95%C.I.=3.3-22.6%) of BEDs endorsed BD. Bulimia Nervosa (BN) occurred in 7.4% (95%C.I.=6-10%) of people with BD, whereas 6.7% (95%C.I.=12-29.2%) of subjects with BN had a diagnosis of BD. Anorexia Nervosa (AN) occurred in 3.8% (95%C.I.=2-6%) of people with BDs; 2% (95%C.I.=1-2%) of BD patients had a diagnosis of AN. Overall, BD patients with EDs had higher odds of being female vs. non-ED controls. Several moderators yielded statistically significant differences both within- and between different types of BDs and EDs.

Limitations: Scant longitudinal studies, especially across different EDs and pediatric samples. High heterogeneity despite subgroup comparisons. Limited discrimination of the quality of the evidence.

Conclusions: The rates of BD⇌ED comorbidity vary across different diagnostic groups, more than they do according to the "direction" of BD⇌ED. Further primary studies should focus on the

risks, chronology, clinical impact, and management of the onset of intertwined BD⇌ED across different ages, promoting a continuum approach.

- PROSPERO protocol: CRD42020170343.

1. Introduction

Bipolar disorder (BD) is often comorbid with general medical (Kilbourne et al., 2004) and psychiatric conditions (McElroy, 2004), and a range of worse outcomes (Vieta et al., 2018). Recent interest has included the comorbidity with eating disorders (EDs), which are also leading psychiatric disorders and associated with an array of physical, psychiatric outcomes, and premature mortality (McElroy et al., 2016; McElroy, 2011).

In the general population, the estimated prevalence of anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) according to the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) (APA, 1994) are 0.9%, 1.5%, and 3.5% among women, and 0.3%, 0.5%, and 2.0% among men, respectively (Hudson et al., 2007), with slight variation across different investigations (Duncan et al., 2017), geographical regions or diagnostic criteria (Hay et al., 2015). The comparable DSM-IV lifetime prevalence of Type-I BD (BD-I) and Type-II BD (BD-II) in the general population is about 0.6% and 0.4%, respectively (Merikangas et al., 2011). The rates of comorbid ED among people with BD (hereafter, alternatively referred to as "BD⇌ED") have been reported between 2-33%, varying across different subtypes of BD (McDonald et al., 2019; Thiebaut et al., 2019a).

BD and EDs share multiple features related to eating behaviors and weight gain underpinned by emotional dysregulation and impulsivity (including attention-deficit hyperactivity disorder – ADHD), encompassing a broad range of manifestations, such as

affective lability, distractibility, irritability, frequent mood shifts, alcohol/substance use disorder (SUD), and suicidality (Jen et al., 2013; McDonald et al., 2019; McElroy et al., 2005).

Hypomania, mania, atypical, and melancholic depression associated with BD often present with increased or decreased appetite and weight loss, partially resembling the weight fluctuations seen among people with BN and AN, respectively (Fornaro et al., 2019; Lunde et al., 2009). However, it must be noted that people with AN often engage in severe feeding restriction, typically for reasons other than reduced appetite. In particular, bipolar depression with atypical features, and prominent cyclothymic affective disorder, is characterized by overeating and weight gain resulting in high body mass index (BMI), mimicking BED, and BN (Perugi and Akiskal, 2002; Perugi et al., 2006). Notably, people with BN often cycle between dietary restriction and binge eating (in addition to compensatory behaviors), and that weight change is not the unique feature of either BN or BED. Overall, "weight cycling" chaotic eating patterns (e.g., binge eating), overweight/obesity, weight fluctuations are common among people with BD (Reininghaus et al., 2015).

Chronic malnutrition in AN commonly results in moodiness and mixed features of depression (Fornaro et al., 2019), lack of focus, irritability, and distractibility, thus mimicking symptoms of BD and other related conditions such as ADHD since early adolescence (Moya et al., 2004).

However, while informative, the most recent reviews assessing the prevalence and clinical features associated with ED in BD provided only a qualitative synthesis of the evidence, or they offer limited stratification of the results across different subtypes of

either EDs or BDs (McDonald et al., 2019; Thiebaut et al., 2019a). Moreover, accurate rates of BDs among people with a primary diagnosis of ED, either among adult or pediatric samples, are yet to be elucidated. To the best of our knowledge, the present systematic review and meta-analysis is thus the first of its kind aiming at assessing the prevalence and clinical correlates of BD⇌ED across the lifespan.

2. Methods

The present systematic review and meta-analysis followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2010). The International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO/) protocol is CRD42020170343.

1.1 Information sources and search strategy

Four authors divided into two independent teams (MF, AA & FD, FH) searched PubMed, and PsycINFO databases for records indexed from inception until April the 20th, 2020. The following string was searched in PubMed: (((((((eating disorder[Title/Abstract]) OR bulimia[Title/Abstract]) OR anorexia[Title/Abstract]) OR binge eating[Title/Abstract])) OR ((((("Feeding and Eating Disorders"[Mesh] OR "Feeding and Eating Disorders of Childhood"[Mesh]) OR "Anorexia Nervosa"[Mesh]) OR "Bulimia Nervosa"[Mesh]) OR "Binge-Eating Disorder"[Mesh]))) AND ((((((bipolar disorder[Title/Abstract]) OR bipolar depression[Title/Abstract]) OR mania[Title/Abstract]) OR hypomania[Title/Abstract])) OR ("Bipolar Disorder"[Mesh])). Relevant cross-references,

textbooks and other material was likewise appraised (please see supplementary material number 1).

2.2 Inclusion criteria

We considered original peer-reviewed studies conducted in humans, both sexes, of any age, that included comorbid cases of BD (BD-I, BD-II, and NEC) and EDs, providing accurate diagnostic definitions based on either the DSM (any edition, or text revision) or the International Classification of Diseases (ICD), up to the tenth edition. Diagnoses had to be established by a validated (semi-)structured diagnostic interview, such as the Structured Clinical and Diagnostic Interview for Axis-I disorders (SCID-I) (First et al., 1997). Observational studies, including both cohort and cross-sectional studies, either population- or clinically based studies published in any language, were considered for inclusion if they provided a control group (namely, people without the BD⇌ED comorbidity).

Case reports/series (subjects, $n \leq 10$), opinion articles/letters to the Editor, conference proceedings, reviews, or controlled trials, or those studies reporting just the rates of schizoaffective disorder, cyclothymic disorder, affective temperaments, the avoidant-restrictive food intake, pica, and rumination disorders, or generic "eating behaviors or spectra" were excluded.

2.3 Outcome measures

Primary outcomes were (i) lifetime prevalence of comorbid EDs among people with BDs, and (ii) lifetime prevalence of comorbid BDs in EDs. Current prevalence rates (or other prevalence ranges, e.g., "12-month") were recorded whenever available. Additional

outcomes included the (iii) essential clinical features associated with BD⇌ED comorbidity. Those studies only assessing overweight/obese patients were excluded if not explicitly documenting cases of EDs.

2.4 Study selection and data extraction

Four authors divided into two teams (MF, AA & FD, FH) independently extracted data using a purpose-built data extraction spreadsheet. Relevant full-texts were retrieved upon the overall title and abstract screening. Contact with the authors was planned, as necessary. Disagreements by reviewers were solved by consensus at both stages, eventually seeking an independent senior investigator (AFC). Additional investigators with considerable expertise on the topic assisted in the critical interpretation of the results (MS, BS, JIS, ED, DDB, MIH, PFP, MB, and EV). Both auto- and hand-searches for "type-I" ("duplicates among/across different databases") and "type-II" ("duplicate publications in different Journals/issues") (Qi et al., 2013) were performed based on Thompson Endnote X9™ for Microsoft Windows™, as already appraised for a similar project (Fornaro et al., 2016b). The recorded variables included the followings: author(s), year of publication and data collection, study design, sample size (total, cases, controls), length of the eventual follow-up, age at the time of the assessment, sex, age at onset, sociodemographic status, major psychiatric and non-psychiatric comorbidities and features of specifiers, including – but not limited to – the proportion of overweight and obese cases, BMI, SUD, ADHD, measures of impulsivity, history of sexual abuse/physical harm, stressful/ traumatic events, suicidality, emotional dysregulation (author-based definition) and its correlates (namely rapid cycling course of BD and mixed features of either bipolar depression or mania), major rating scales, concurrent

therapy (any, including psychological, neuro-modulatory, psychotropic and non-psychotropic pharmacotherapy, e.g. lithium, anticonvulsant mood stabilizers, antidepressants, or the SGAs), geographical region, adopted diagnostic coding and structured interview, current mood polarity of BD, polarity of the index episode, predominant polarity, and setting (outpatients; inpatients; primary care; population-based study; other – e.g. treatment-resistant cases of BD).

2.5 Quality assessment

We assessed the quality of the included studies using the US National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NIH, 2014); lower scores indicated a lower quality of the included studies concerning the present research theme, using the interquartile range (IQR) method. Any disagreement was solved by consensus.

2.6 Meta-analysis

We pooled individual study data using the DerSimonian-Laird proportion method (DerSimonian and Laird, 1986) using Comprehensive Meta-Analysis® software (version 2) (Borenstein et al., 2005), carrying random-effects meta-analyses. First, we calculated the prevalence of ED comorbidity in BD participants and the odd ratios (ORs) associated with BD⇌ED vs. non-comorbid controls. Second, we replicated the same analyses for people with a primary diagnosis of ED, with or without comorbid BDs. When three or more studies were available, and high heterogeneity detected ($I^2 \geq 75\%$, $p \leq .05$) (Higgins et al., 2003), we conducted subgroup meta-analyses accounting for multiple moderators. Publication biases were not assessed because studies included in proportion meta-

analyses are non-comparative; thus, there are no "negative" or "undesirable" results or study characteristics like significant levels that may have biased publications (Maulik et al., 2011). Finally, we conducted several meta-regression analyses to investigate further potential moderators.

3. Results

Seven hundred and eighty records were identified by inquiring about the selected sources, yielding 675 items. Further screening fetched 95 original full texts checked against the pre-determined inclusion and exclusion criteria (please refer to figure n.1, study flow-chart).

Forty-seven articles (Angst et al., 2018; Azorin, 2013; Baek et al., 2011; Baek, 2014; Baldassano, 2005; Balzafiore, 2017; Belizario et al., 2019; Berkol et al., 2016; Bobo, 2018; Boulanger, 2018; Brietzke et al., 2011; Dell'Osso et al., 2011; Faravelli, 2006; Fornaro, 2010; Goffin et al., 2016; Halmi et al., 1991; Hudson et al., 2007; Ivarsson et al., 2000; Javaras, 2008; Jen et al., 2013; Krüger, 1996; Lilenfeld et al., 2008; Liu et al., 2016; Loftus et al., 2020; McElroy et al., 2001; McElroy et al., 2016; McElroy, 2013; McElroy, 2002, 2011; Nery et al., 2014; Pashinian et al., 2006; Perugi et al., 2013a; Perugi et al., 2013b; Ramacciotti, 2005; Schoofs, 2011; Schreck-Del Bello, 2017; Seixas, 2012; Swanson et al., 2011; Thiebaut et al., 2019c; Toner et al., 1988; Torrent et al., 2008; Tseng et al., 2017; Tseng et al., 2016; Welch, 2016; Wildes et al., 2007; Winham, 2014) yielding 77 comparisons (“k”) were included in the present meta-analytic review. Tables 1 and its subsets outline 36 (Angst et al., 2018; Azorin, 2013; Baek et al., 2011; Baek, 2014; Baldassano, 2005; Balzafiore, 2017; Belizario et al., 2019; Berkol et al.,

2016; Bobo, 2018; Boulanger, 2018; Brietzke et al., 2011; Dell'Osso et al., 2011; Faravelli, 2006; Fornaro, 2010; Goffin et al., 2016; Jen et al., 2013; Krüger, 1996; Liu et al., 2016; Loftus et al., 2020; McElroy et al., 2001; McElroy et al., 2016; McElroy, 2013; McElroy, 2002, 2011; Nery et al., 2014; Pashinian et al., 2006; Perugi et al., 2013a; Perugi et al., 2013b; Ramacciotti, 2005; Schoofs, 2011; Schreck-Del Bello, 2017; Seixas, 2012; Torrent, 2008; Wildes et al., 2007; Winham, 2014) (k=58) studies investigating EDs among 15,084 univocal patients with a primary diagnosis of BD. Table 2 and its subsets documents eleven studies: (Halmi et al., 1991; Hudson et al., 2007; Ivarsson et al., 2000; Javaras, 2008; Lilenfeld et al., 2008; Swanson et al., 2011; Thiebaut et al., 2019c; Toner et al., 1988; Tseng et al., 2017; Tseng et al., 2016; Welch, 2016), fetching 19 comparisons about BD among 15,146 univocal patients with a primary diagnosis of ED.

No study concurrently assessed BD⇌ED, while the supplementary material n.2 references 48 studies excluded full-texts, with the reason(s).

3a *Comorbid ED in BD: AN in BD*

3.1.1 Study characteristics: AN in BD

Fifteen studies (Azorin, 2013; Baek, 2014; Balzafiore, 2017; Dell'Osso et al., 2011; Faravelli, 2006; Fornaro, 2010; McElroy et al., 2001; McElroy et al., 2016; McElroy, 2011; Nery et al., 2014; Pashinian et al., 2006; Perugi et al., 2013b; Schreck-Del Bello, 2017; Seixas, 2012; Torrent et al., 2008) investigated the prevalence and the clinical features associated with AN comorbidity among people with BD, of which 13 were cross-sectional (Azorin, 2013; Baek, 2014; Balzafiore, 2017; Faravelli, 2006; Fornaro,

2010; McElroy et al., 2016; McElroy, 2011; Nery et al., 2014; Pashinian et al., 2006; Perugi et al., 2013b; Schreck-Del Bello, 2017; Seixas, 2012; Torrent et al., 2008), and two prospective cohort studies (Dell'Osso et al., 2011; McElroy et al., 2001). A total of 6,207 patients were represented among the 15 hospital-based included studies; 166 BD patients had comorbid AN. The mean age of BD patients with comorbid AN was 41.11±12.91 years (documenting studies, N=15), and 3,416 out of 5,539 (61.67%) were females (N=11). Please refer to table n.1a for details and ratings.

3.1.2 Meta-analysis of the pooled prevalence of AN in BD, and odds

The pooled prevalence of AN comorbidity among 6,207 people with BD over 15 studies was 2.5%, (95%C.I.=1.5-3%, I^2=87.22%), supplementary material n.3. The trim and fill analysis adjusted for five studies, calculated an adjusted prevalence rate of AN in BD of 3.8% (95%C.I.=2-6%).

People with AN in BD comorbidity had a higher odd of being female compared to BD controls without AN comorbidity: OR=6.25 (95%C.I.=2.9-13.44, p<.01, N=4).

3.1.3 Sub-group meta-analysis of AN in BD

All the sub-group analyses investigating ED comorbidity in BD, including AN in BD, are presented in table n.3. Briefly, the adopted diagnostic criteria (and structured interview) affected the prevalence estimates of AN in BD, although heterogeneity was high across different subgroups.

3.1.4 Meta-regression of AN in BD

Meta-regression analysis demonstrated that the older the mean age of BD patients at the time of the interview, the higher the rates of lifetime AN comorbidity (β=.07178,

95%C.I.=.02501-.11854, p<.01, R^2=.84, N=10), supplementary material n.4. Younger age at onset of BD was associated with higher rates of comorbid AN. However, data rely on small numbers (β=-.32756, 95%C.I.=-.49974 to -.15538, p<.01, R^2=.27, N=3), supplementary material n.5, in line with the predictor "percentage of females among BDs" (β=3.53333, 95%C.I.=2.42212-4.64454, p<.01, R^2=.55, N=12), supplementary material n.6, as well as higher rates of rapid-cycling BDs (β=-.02981, 95%C.I.=-.04455 to -.01508, p=<.01, R^2=.21, N=3), supplementary material n.7. Concerning BD Types, a higher number of BD-I participants strongly predicted lower rates of AN-BD comorbidity (β=-1.25266, 95%C.I.=-1.83945 to -.66588, p<.01, R^2=.83%, N=13), supplementary material n.8.

Conversely, higher rates of BD-II strongly predicted a higher prevalence of AN comorbidity in BD, overall (β=1.16714, 95%C.I.=.53104-1.80323, p<.01, R^2=.91%, N=12), supplementary material n.9.

Finally, the length of bipolar illness and the proportion of SUD cases among BDs was not associated with the rate of comorbid AN in BD in a statistically significant way.

3b Comorbid ED in BD: BN in BD

3.2.1 Study characteristics: BN in BD

Seventeen hospital-based studies documented the rates of BN among BD patients (Azorin, 2013; Baek, 2014; Baldassano, 2005; Balzafiore, 2017; Bobo, 2018; Faravelli, 2006; Fornaro, 2010; McElroy et al., 2016; McElroy, 2011; Nery et al., 2014; Pashinian et al., 2006; Perugi et al., 2013a; Ramacciotti, 2005; Schreck-Del Bello, 2017; Seixas,

2012; Torrent et al., 2008), including 15 cross-sectional (Azorin, 2013; Baek, 2014; Baldassano, 2005; Balzafiore, 2017; Bobo, 2018; Faravelli, 2006; Fornaro, 2010; McElroy et al., 2001; McElroy et al., 2016; McElroy, 2011; Nery et al., 2014; Pashinian et al., 2006; Perugi et al., 2013a; Schreck-Del Bello, 2017; Seixas, 2012; Torrent et al., 2008), one retrospective (Ramacciotti, 2005), and one prospective cohort study (McElroy et al., 2001). A total of 7,399 participants were represented, of whom 720 were BDs with comorbid BN. The mean age of BD patients with comorbid BN was 34.5±9.7 years (N=17), and 4,328 out of 7,399 (58.49%) were females (N=17). Please refer to n.1b for details and ratings.

3.2.2 Meta-analysis of the pooled prevalence of BN in BD, and odds

The pooled prevalence of BN comorbidity among 7,399 people with BD over 17 studies was 6.6% (95%C.I.=4.8-8.8%, I^2=91.27%), supplementary material n.10. The trim and fill analysis adjusted for four studies and recalculated a prevalence rate of BN in BD of 7.4% (95%C.I.=6-10%).

People with BD and BN comorbidity had a higher odd of being female compared to BDs without BN: OR=4.02 (95%C.I.=1.72-9.39, p<.01, N=5).

3.2.3 Sub-group meta-analysis of BN in BD

All the sub-group analyses results investigating BN comorbidity in BD are presented in table n.3b. Briefly, the adopted diagnostic criteria (and structured interview), the type of the assessed prevalence rate (lifetime vs. current), setting of the study, and ethnicity affected the prevalence estimates; heterogeneity hold high across different subgroup analyses.

3.2.4 Meta-regression of BN in BD

Meta-regression analysis demonstrated that the older the mean age of the BD participants, the higher the rates of comorbid BN (β=.08412, 95%C.I.=.04381-.12444, p<.01, R^2=.26, N=11), supplementary material n.11. However, a longer duration of bipolar illness predicted lower rates of comorbid BN, although the model had little to no explanatory value (β=-.25783, 95%C.I.=-.41614 to -.09951, p<.01, R^2=.0, N=3), supplementary material n.12. Higher rates of female participants among BDs predicted higher rates of comorbid BN (β=1.48612, 95%C.I.=.75463-2.21760, p<.01, R^2=.30, N=17), supplementary material n.13. Higher numbers of BD-I participants predicted higher rates of comorbid BN (β=.72094, 95%C.I.=.32607 to 1.11582, p<.01, R^2=.34, N=17), supplementary material n.14. Obesity among BD patients strongly predicted higher rates of comorbid BN (β=.66322, 95%C.I.=.28433-1.04210, p<.01, R^2=.93, N=3), supplementary material n.15. The higher the proportion of bipolar patients with lifetime exposure to antidepressant drugs, the lower the rates of comorbid BN (β=-1.23797, 95%C.I.=-1.95634 to -.51960, p<.01, R^2=.08, N=3), supplementary material n.16. Bipolar patients endorsing lifetime suicidal behaviors had lower rates of comorbid BN (β=-9.25187, 95%C.I.=-16.14699 to -2.35675, p<.01, R^2=.20, N=3), supplementary material n.17.

Finally, the mean age at onset of BD, the percentage of BD-II cases, the rate of BD patients with lifetime comorbid SUD, and the percentage of rapid-cycling BDs, failed to affect the proportion of cases with comorbid BN statistically significantly.

3.3.1 Study characteristics: BED in BD

Fifteen cross-sectional, hospital-based studies documented the rates of BED among BD patients (Bobo, 2018; Boulanger, 2018; Fornaro, 2010; Krüger, 1996; McElroy et al., 2016; McElroy, 2013; McElroy, 2002, 2011; Nery et al., 2014; Pashinian et al., 2006; Ramacciotti, 2005; Schoofs, 2011; Schreck-Del Bello, 2017; Seixas, 2012; Winham, 2014). A total of 7,098 people with BD were represented, of whom 845 had comorbid BED. The mean age of BD patients with comorbid BED was 40.56±12.19 years (N=11), and 3,253 out of 6,027 (54%) were females (N=12). Please refer to table n.1c for details and ratings.

3.3.2 Meta-analysis of the pooled prevalence of BED in BD, and odds

The pooled prevalence of BED comorbidity among 7,098 people with BD over 15 studies was 12.5% (95%C.I.=9.4-16.6%, I^2=93.48%), supplementary material n.18. The trim and fill analysis was not significant, and the pooled prevalence was unadjusted.

BDs with BED had higher odds of being female: OR=1.83 (95%C.I.=1.41-2.37, p=<.01, N=6).

3.3.3 Sub-group meta-analysis of BED in BD

All the sub-group analyses' results investigating BED comorbidity in BD are presented in table n.3c.

Briefly, the setting, geographical region, design of the study, the adopted (semi-)structured interview, and the ethnicity of study participants affected the prevalence estimates of BED in BD. However, heterogeneity was high across different subgroup analyses.

3.3.4 Meta-regression of BED in BD

Meta-regression analysis demonstrated an older mean age at onset of BD strongly predicted higher rates of comorbid BED, although relying on only three studies (β=.20811, 95%C.I.=.0546-.36161, p<.01, R^2=94.34%, N=3), supplementary material n.19. Higher BMI scores across the 25-30 range – overweight - predicted lower rates of comorbid BED (β=-.3152, 95%C.I.=-.43004 to -.20037, p<.01, R^2=13.4%, N=3), supplementary material n.20, higher rates of obesity (BMI>30) predicted higher prevalence of BED (β=4.31405, 95%C.I.=3.02607-5.6024, p<.01, R^2=32.7%, N=4), supplementary material n.21. The higher the proportion of female BDs, the higher the rate of comorbid BED cases (β=.9682, 95%C.I.=.12299-1.81342, p<.02, R^2=33%, N=12), supplementary material n.22. The higher the proportion of BD-I participants, the lower the prevalence of comorbid BED (β=-1.75055, 95%C.I.=-2.46685 to -1.03424, p<.01, R^2=29%, N=12), supplementary material 23. Conversely, higher numbers of BD-II participants predicted higher rates of comorbid BED (β=2.28578, 95%C.I.=1.49457 - 3.07698, p<.01, R^2=27%, N=12), supplementary material 24. A rapid-cycling course of BD predicted lower rates of comorbid BED (β=-1.0326, 95%C.I.=-1.49959 to -.56561, p<.01, R^2=39%, N=3), supplementary material 25. The meta-regression of the current mood phase and current prevalence of BED was not clinically informative since the few corresponding studies involved only cases of currently euthymic people with BD. Finally, the mean age of BD, and the average duration of BD illness, and lifetime SUD, failed to affect the proportion of cases with comorbid BED significantly.

3d Comorbid ED in BD: Any ED in BD

3.4.1 Study characteristics: Any ED in BD

Seven studies documented the occurrence of any ED among people with BD. The latter studies included five hospital-based studies, including three prospective (Ivarsson et al., 2000; Thiebaut et al., 2019c; Toner et al., 1988), one case-control (Tseng et al., 2016), and one cross-sectional (Halmi et al., 1991) report; and two cross-sectional, population studies (Hudson et al., 2007; Swanson et al., 2011). A total of 4,856 participants encompassed 521 people with BD and any comorbid ED. The mean age of BD with any ED comorbidity was 40.25±9.65 years (N=2). Please refer to table n.1d.

3.4.2 Meta-analysis of the pooled prevalence of any ED in BD

The pooled prevalence of any ED comorbidity among 4,856 people with BD over ten studies was 12.7% (95%C.I.=9.5-16.8%, I^2=90.56%), supplementary material n.26. The trim and fill analysis adjusted for three studies and calculated an adjusted prevalence rate of 9.5% (95%C.I.=7-13%).

3.4.3 Sub-group meta-analysis of any ED in BD

All the sub-group analyses investigating the comorbidity of any ED in BD are presented in table n.3d. Briefly, just the diagnostic criteria affected the prevalence estimates of any ED in BD, and heterogeneity holds high across different subgroup analyses.

3.4.4 Meta-regression of any ED in BD

Meta-regression analysis demonstrated that higher proportions of females among BD patients predicted higher rates of any comorbid ED (β=1.69205, 95%C.I.=.53561-2.8485, p<.01, R^2=.46, N=6),

supplementary material n.27. The higher the proportion of BD-I participants, the lower the prevalence of any comorbid ED (β=-.96649, 95%C.I.=-1.6317 to -.30127, p<.01, R^2=.25, N=9), supplementary material 28. A similar trend was documented for BD-II patients (β=.66981, 95%C.I.=.00807 to 1.33154, p=.05, R^2=.32, N=8), supplementary material n.29. Finally, the mean age of BD failed to affect the proportion of cases with any comorbid ED significantly.

3e Comorbid BD in ED: BD in AN

Meta-regression analyses could not be performed for any of the" BD in primary ED" conditions due to the shortage of corresponding data. Corresponding ORs could not be reliably pooled either. Qualitative syntheses and subgroup analyses are nonetheless outlined below.

3.5.1 Study characteristics: BD in AN

Seven reports explored the prevalence and clinical features associated with BD in AN. These studies comprised four hospital-based studies, in turn including three prospective (Toner et al., 1988) (Ivarsson et al., 2000), one case-control (Tseng et al., 2016), and one cross-sectional study (Halmi et al., 1991). The remaining two population-based studies featured a cross-sectional design (Hudson et al., 2007; Swanson et al., 2011). A total of 13,456 patients were represented overall, of whom 146 people with AN had comorbid BD. The mean age of AN patients with comorbid BD was 16.1±0 years (N=1, n=51). Please refer to table n.2a for details and rating of the included studies.

3.5.2 Meta-analysis of the pooled prevalence of BD in AN

The pooled prevalence of BD comorbidity among 13,456 people with AN over seven studies was 3.8% (95%C.I.=1.2-11.2%, I^2=96.75%), supplementary material n.30. The trim and fill analysis was adjusted for two studies and calculated a new prevalence rate of BD in AN of 2% (95%C.I.=1-2%).

3.5.3 Sub-group meta-analysis of BD in AN

All the sub-group analyses investigating BD comorbidity in EDs, including BD in AN, are presented in table n.4.

Briefly, the study design and the geographical region affected the prevalence estimates of BD in AN, although heterogeneity was high across different subgroup analyses.

3f Comorbid BD in ED: BD in BN

3.6.1 Study characteristics: BD in BN

Four reports explored the prevalence and clinical features associated with BD in BN. These studies comprised two hospital-based studies, in turn, including one prospective cohort (Thiebaut et al., 2019c) and one case-control study (Tseng et al., 2016). Two additional population-based studies employed a cross-sectional design(Hudson et al., 2007; Swanson et al., 2011). A total of 13,295 patients were represented overall, of whom 674 people with BNs had comorbid BD. However, the mean age of BN patients with comorbid BD could not be computed (N=0). Please refer to table n.2b for details and rating of the included studies.

3.6.2 Meta-analysis of the pooled prevalence of BD in BN

The pooled prevalence of BD comorbidity among 13,295 people with BN over four studies was 10.8% (95%C.I.=1.7-45.3%, I^2=99.63%), supplementary material n.31. The trim and fill analysis, adjusted for one study, set a new prevalence rate of 6.7% (95%C.I.=1.2-29.2%).

3.6.3 Sub-group meta-analysis of BD in BN

All the sub-group analyses investigating the comorbidity of BD in BN are presented in table n.4b. Briefly, the geographical region and the adopted structured interview affected the prevalence estimates of any BD in BN, although heterogeneity was high across different subgroup analyses.

3g Comorbid BD in ED: BD in BED

3.7.1 Study characteristics: BD in BED

Seven reports explored the prevalence and clinical features associated with BD in BED. These studies comprised five hospital-based studies, in turn including three cross-sectional (Javaras, 2008; Lilenfeld et al., 2008; Welch, 2016), one case-control (Tseng et al., 2016), and one prospective report (Thiebaut et al., 2019c). Two additional population-based studies adopted a cross-sectional design (Hudson et al., 2007; Swanson et al., 2011). A total of 14,374 patients were represented overall, including 643 people with BED and comorbid BD. However, the mean age of BED patients with comorbid BD could not be computed (N=0). Please refer to table n.2c.

3.7.2 Meta-analysis of the pooled prevalence of BD in BED

The pooled prevalence of BD comorbidity among 14,374 people with BED over seven studies was 9.1% (95%C.I.=3.3-22.6%, I^2=99.1%), supplementary material n.32. The prevalence estimates of BD in BED were held after the trim and fill analysis.

3.7.3 Sub-group meta-analysis of any BD in BED

All the sub-group analyses investigating the comorbidity of BD in BED are presented in table n.4c. Briefly, the geographical region and the study design affected the prevalence estimates of any BD in BN, although heterogeneity was high across different subgroup analyses.

3h Comorbid BD in ED: BD in any ED

Only one study (Tseng et al., 2017) documented a prevalence of either BD-I or BD-II among ED as a whole diagnostic category approximating 41.4% (table n.2d).

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to assess the prevalence, odds, and predictors of ED among people with a primary diagnosis of BD, and BD among people with a primary diagnosis of ED.

4.1 Main findings

Side-by-side comparisons of the prevalence rate of a given ED in BD against the corresponding rate of BD in ED varied against each other, and both between and within different subgroups. However, the point-prevalence rates of given comorbidity, e.g., AN in BD, were within the confidence intervals of the prevalence rates of the same comorbidity, yet following the opposite direction (e.g., BD in AN).

Specifically, the rates of AN in BD were 3.8% (range, 2-6%), whereas the rates of BD in AN were 2% (range, 1-2%). Comparably, BN in BD occurred in 7.4% of patients (range, 6-10%), whereas BD in BN occurred in 6.7% of the cases (range, 1.2-29%). Also, the presence of a limited number of studies focusing on BD comorbidities among people with a primary diagnosis of ED precluded any reliable OR comparison across the complementary BD⇌ED relationship.

BED in BD occurred in 12.5% of patients (range, 9.4%-16.6%), whereas lower rates of BD were documented among people with a primary diagnosis of BED (9.1%, range=3-22.6%). However, we could not assess the impact of weight gaining medications among people with BD⇌BED. The pooled prevalence rates of BED in BD and those of BD in BED seem not to be affected by the diagnostic shift introduced by the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) (APA, 2013) vs. the DSM-IV category of BED, a finding contrasting with the previous qualitative synthesis

of the on the matter (Thiebaut et al., 2019b). On the other hand, the pooled prevalence of AN in BD based on 15 indicated a higher prevalence rate (3%) with the DSM-IV criteria (based on 14 studies) than with the DSM-5 codes (<1%), which is an unexpected result possibly due to the publication bias in the DSM-5 studies (n=1) considering that the AN diagnosis according to the DSM-5 criteria is less stringent than the one allowed by the previous edition of the manual, as documented elsewhere (Mustelin et al., 2016).

Overall, EDs were more prevalent among people with a primary diagnosis of BD than the general population documented elsewhere (Duncan et al., 2017; Hay et al., 2015; Hudson et al., 2007).

The rates of "any" ED in BD (9.5%, range 7-13%) could not be compared to the rates of any BD in ED (lack of quantitative information).

BDs with either AN (highest odds), BN (intermediate), or BED (lower) comorbidity had higher odds of being female compared to BD controls without any ED. A similar pattern was documented for BD type, with BD-II being more common than BD-I among people with a primary diagnosis of BDs with different EDs.

4.2 Clinical and research implications

Despite the broad range of clinical correlates we sought to extract about BD⇌ED, a considerable number of clinical moderators could not be reliably pooled, especially concerning the comorbidity and treatment of BDs among people with EDs. Such publication bias was particularly evident for pediatric samples; hence forthcoming primary research studies should focus on those clinical populations.

This is a crucial issue, considering that BD and ED span a common "emotional dysregulation" gradient, and may be viewed as part of the same neurodevelopmental

process (McDonald et al., 2019). Common pathophysiology for BD and several manifestations of EDs seems to hold true based on several findings. This includes the notion that the menstrual cycle affects BED frequency and intensity before and during menstruation and that these changes occur in patients with BD, with BED, or both (Ruiz and Gutiérrez-Rojas, 2015; Schoofs, 2011; Wildes et al., 2008). Abnormalities in brain-derived neurotrophic factor, which is involved in the regulation of mood and appetite in persons with BD and EDs, have been likewise documented (Lin, 2009; McElroy et al., 2011). A series of studies comparing levels of various neurotransmitters, hormones – the hypothalamic-pituitary-adrenal axis in AN patient with comorbid BD, in particular, further support the notion of related conditions rather than distinct entities (McElroy et al., 2005; Millischer, 2020). Similarly, variants of the neurotrophic tyrosine kinase receptor 3 gene have been associated with early onset of BD and EDs (Feng et al., 2008; McElroy et al., 2011; Mercader et al., 2008). Genome-wide association studies of BD with comorbid ED documenting the association of specific regions as PRR5-ARHGAP8 (McElroy et al., 2018) and SOX2-OT(Liu et al., 2016) broadly support the involvement of neurodevelopmental and neuroprotective mechanisms involved in the pathophysiology of both disorders.

In particular, primary research about the chronology and timing of the onset of each condition across the lifespan and sexes should provide a better understanding of some of the features related to emotional dysregulation, e.g., personality comorbidity, trait impulsivity, rapid-cycling course of BD, and suicidality – which we did not pool altogether due to the significant discrepancy of the author-based definitions appraised in the screened literature (Loftus et al., 2020; McDonald et al., 2019). Additionally, most of

the subgroup analyses we performed across different BD⇌ED configurations failed to reduce the level of heterogeneity for several comparisons. This latter outcome may indicate that additional, non-controlled moderators could contribute to the explanation of the variance between and within different diagnostic groups.

Finally, although we strived to extract such information, the original studies at review failed to provide sufficient quantitative information about affective temperaments or other hints relevant to the understanding of the proposed continuum existing between BDs and EDs, including the relevant shared genetic and environmental factors, which deserve ad-hoc quantitative reports.

4.3 A critical perspective about BD⇌ED comorbidity

The term "comorbidity" was initially introduced to refer to the coexistence of two mostly independent and distinct disorders (Maj, 2005). According to this early concept, there exists an "index" or "primary" disorder and a comorbid separate second disorder, which potentially affects the selection of treatment and the prognosis of the index one (Feinstein, 1970). In Feinstein's formulation, the implication was that a completely different and independent disease occurred at the same time as another disease. These two diseases co-occur, more often than not, randomly over the lifespan, often intertwined with each other (e.g., BN and bipolar depression with atypical features), as exemplified by previous meta-analytic comparison of borderline personality disorder (BPD) comorbidity among people with a primary diagnosis of BD, and the comorbidity of BD among people with a primary diagnosis of BPD (Fornaro et al., 2016b). Sub-threshold and spectrum manifestations may likewise occur or anticipate a full-blown mood episode of BD or behavioral disturbance seen in different people with EDs.

In reality, diagnostic entities are categorical constructs built on top of dimensional disturbances of mental functions, and the current classifications fail to address the complexity of overlapping symptoms across psychiatric conditions (Stein et al., 2020; Vieta, 2016). Dimensional and quantitative assessments of symptoms related to eating behavior in patients with mood disorders lack in most of the studies, and the same can be said for mood dimensions in ED patients (Torrent et al., 2008). The borders between mood and eating disorders might be mediated by biological rhythms disruption (Giglio et al., 2009). Moreover, certain eating disturbances are not included in the official classifications or unofficially classified in other chapters, like "food addiction" (Nunes-Neto et al., 2018), as part of behavioral addictions, a controversial group of compulsive behaviors that could belong either to addictions, obsessive-compulsive disorders, or under the umbrella of eating, sleep, sex, or other disorders (Varo et al., 2019).

The DSM explicitly produces overlapping clinical criteria for many diagnoses, allowing comorbidity in quite a different sense than in the medical meaning of the term as the co-occurrence of independent diseases (Maj, 2005). Using a DSM definition, it is unclear whether concomitant diagnoses reflect the presence of distinct clinical entities or refer to multiple manifestations of a single clinical entity (Maj, 2005). However, a common clinical suspicion is that the "comorbidity" construct poorly fits most real-world patients, including BD⇌ED cases, further reinforcing the need for primary research adopting a longitudinal approach accounting for the progression of the illness, history of treatment resistance of BD (Fornaro et al., 2020), age at onset, and sex distribution, among other pivotal hallmarks (Nemeroff et al., 2013). Concerning BD⇌ED, we propose that the concept of "diagnostic hierarchy," rather than boundary comorbidity, would

better fit the complexity of EDs in the presence of an underlying BD. “All diagnoses are not created equal” (Surtees and Kendell, 1979), and specific diagnoses (namely EDs) will be lower on the hierarchical approach, with major implications for clinical psychopharmacology and overall care of the patients presenting with complex and heterogenous BD (Ghaemi, 2008). Such a” diagnostic hierarchy” is essential for a “management hierarchy,” where clinicians typically must focus attention on the most pressing presenting issue.

As an alternative to the DSM approach, the hierarchical taxonomy of psychopathology (HiTOP) proposes a dimensional approach to the traditional classification (Kotov et al., 2017). In this system, comorbidity is incorporated into the classification with the assignment of syndromes to spectra. Comorbidity conveys important information about shared risk factors, pathological processes, and illness course. A quantitative nosology formalizes this information, making it explicitly available to researchers and clinicians. Hence, if a question concerns a clinical feature common to multiple syndromes, the clinician or researcher may focus on the higher-order dimension. Alternatively, if a specific syndrome is of interest, the higher-order dimension can be controlled statistically to elucidate information unique to this syndrome. This hierarchical organization is an important feature of a quantitative nosology; the multilevel approach (including individual symptoms, components/traits, syndromes, subfactors, and spectra) allows for a more flexible description of a patient depending on the desired degree of specificity (Forrest et al., 2017; Jones et al., 2019; Kotov et al., 2017).

However, in the clinical setting, clinicians often tend to prioritize the disorder they know best or rank as clinically to the foreground, meaning that those primarily involved in mood disorders patients will promote BD over ED in this context. In contrast, the specialists of EDs will argue that AN – for example – should be the primary diagnosis to look at, as one should not expect any mood regulation and pharmacological efficiency

without restoration of weight, suggesting a case-by-case approach to the most complex scenarios.

Avoiding fragmentation of the diagnosis and artificial comorbidities – "nosologomania" - (Van Praag, 2000) would, ideally, reduce the risk for overexposure to psychotropic polypharmacy (Fornaro et al., 2016a), resource utilization (Hirschfeld and Vornik, 2005), stigma, misdiagnosis overall (McElroy, 2004), and enhance the quality of life of patients with BD⇌ED (Merikangas et al., 2007). In particular, several mood stabilizers and second-generation antipsychotics needed in the treatment of BD may further inflate cardiovascular risk (Correll et al., 2017), as well as the appetite and weight imbalance (McElroy, 2011; Wildes et al., 2008) often leading either to metabolic syndrome, diabetes mellitus, fibromyalgia, osteoporosis – a critical issue in AN – especially in the presence of unhealthy habits such as cigarette smoking (Solmi et al., 2016), poor diet and physical activity (McAulay et al., 2019; Vancampfort et al., 2013). Such weight gain may drive compensatory dysfunctional eating behaviors in vulnerable individuals. Conversely, serotonergic antidepressants often prescribed to ED patients may inflate the risk for treatment-emergent mania in BD, even when bipolar depression is managed with established mood stabilizers (Fornaro et al., 2018). This is compelling considering that psychiatric comorbidities – including BD - are common among people with a primary diagnosis of ED (>70%) (Keski-Rahkonen and Mustelin, 2016; Udo and Grilo, 2019), as further detailed and stratified by the present work. Both BN and BED are often accompanied by, or they lead to, obesity (up to 30-45% of the cases), diabetes, and related metabolic disorders, hampering the management of BD⇌ED (Hay et al., 2015; Kessler et al., 2013; Mcintyre et al., 2005). Together with anxiety disorders and SUD,

EDs may precede the onset of BD in up to 41.4% of the BD⇌ED cases (Serra et al., 2015), particularly among females (Loftus et al., 2020).

Moreover, mixed states may underly many of the associations between eating and mood symptoms (Petri et al., 2017).

Therefore, establishing a sensible, "Hippocratic" diagnosis and treatment plan is crucial to avoid harm (Ghaemi, 2008).

4.4 Study limitations and strengths

As mentioned, the main limitations of the present study are mainly related to the DSM "pragmatic approach" towards the diagnosis of BDs and EDs and the elusive definition of "mental disorder" as a whole diagnostic entity by either the ICD, DSM-IV, or the DSM-5 (Stein et al., 2010). Most studies are observational and based on retrospective assessments. Also, the diagnostic instability of EDs complicates the interpretation of prevalence, especially since studies are most often cross-sectional (Milos et al., 2005); this latter issue also precludes the opportunity to analyze those subjects with lifetime ED types. Many otherwise clinically relevant moderators (including, but not limited to, treatment variables, mixed features of BD, affective instability, emotional disturbances, measures of personality, impulsivity, and suicidality) were often unavailable for data extraction. The dearth of information is critical in pediatric samples, and even when documented, a linear gradient of age (rather than distinct age groups) is unavailable. Also, the adopted rating of the quality of the appraised studies allowed only for marginal discrimination of the quality of the evidence at synthesis: IQR=5-4=1.

Nevertheless, allowing for these caveats, our study is a first and contains numerous strengths. First, the strength of the selected studies is that the diagnosis of BD and ED were consistently based on the DSM or ICD criteria and were established by trained investigators using validated assessment scales mainly with interrater reliability. The main strength of this review is that it is systematic, and it included the core peer-reviewed evidence published so far on two main medical and psychological databases. ED and BD were also compared against each other and tested for a considerable number of moderators.

5. Conclusions

In this meta-analysis, we established that i) BD and ED and ii) ED and BD comorbidity affect a considerable number of patients, documented both by hospital-based and population-based studies. Further higher rates of BD⇌ED comorbidity would be expected in clinical practice beyond the boundary of the ICD, DSM-IV (and DSM-5) approach, ultimately influencing therapeutic choices and patient outcomes as well as the accuracy and homogeneity of the diagnostic samples when studying endophenotypes and other genetic investigations.

Above all, BD⇌ED comorbidity is common and necessitates appropriate diagnosis and treatment in clinical practice, ideally using a "diagnostic hierarchy" approach. Future longitudinal prospective studies are required to understand better the common risk pathways, diagnostic boundaries between these two conditions, and, more importantly, "management hierarchies" to overcome them.

Comprehensive quantitative assessment of the overlapping and differential clinical mediators and moderators across the lifespan is also warranted to better understand the actual diagnostic and neurobiological boundaries of BD and ED. This can lead to the delivery of more accurate therapeutic interventions and better insight on potential underlying biomarkers and genetics validators, allowing a more precise distinction between these two prevalent and disabling mental disorders.

Declaration of Competing Interest

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Contributors

Drs: MF, FH and AFC conceived the study. FH and AN assisted across different analytical procedures of the report. The remaining authors either served as senior reviewers or they did critically appraise the results of the study.

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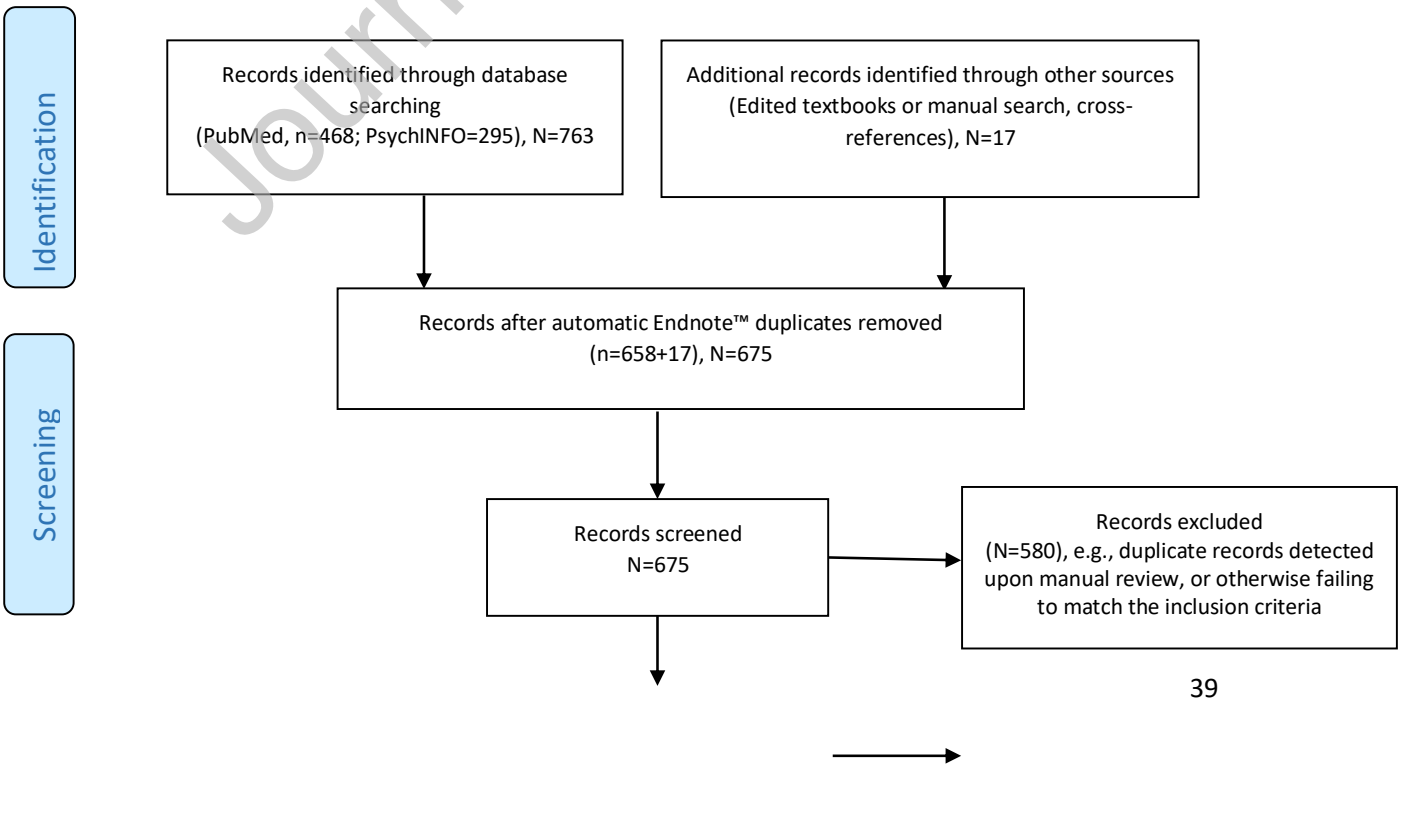
Figure 1: PRISMA 2009 Flow Diagram, adapted



Eligibility

Included

Full-text articles assessed for eligibility
N=95

Full-text articles excluded, with reasons, N=48 (7% of the screened records). Please refer to supplementary material n.2 for details)

Records included in the *qualitative* synthesis, N=47 (7% of the screened records)

Records included in the *quantitative* synthesis: N=47 original studies yielding **77 comparisons**, of which:

- AN in BD=15 (19% of comparisons)
- BN in BD=17 (22% of comparisons)
- BED in BD=16 (21% of comparisons)
- BD in AN=7 (9% of comparisons)
- BD in BED=7 (9% of comparisons)
- BD in BN=4 (5% of comparisons)
- Whole ED in BD=10 (13% of comparisons)
- Whole BD in ED=1 (1% of comparisons)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

Table 1a: Studies assessing AN comorbidity in BD samples according to our inclusion/exclusion criteria for systematic review, N=15.

Reference	Study design	Country	Study population	Sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations/ biases	NIH Quality
Hospital-based studies: AN comorbidity in BD samples							
(Baek, 2014)	Cross-sectional	Korea	417 BDs inpatients and outpatients recruited in four medical centers in Korea from November 2004 to July 2011	4 (1%)	DIGS (DSM-IV)	Recall bias, selection bias	5/14
(Balzafiore, 2017)	Cross-sectional	USA	503 BDs outpatients referred to Stanford University B.D. Clinic within the years 2000-2011	27 (5%)	SCID-I, M.I.N.I. (DSM-IV)	Recall bias, limited stratification of EDs	4/14
(Azorin, 2013)	Cross-sectional	France	1,090 manic BD-I inpatients recruited between December 2000 and April 2002	53 (5%)	SCID (DSM-IV)	Recall bias, over-representation of BD-I cases	5/14

(Schreck-Del Bello, 2017)	Cross-sectional	France	80 BDs (BD-I, BD-II, and cyclothymia) recruited between March and November 2002, multicentric study	4 (5%)	SCID-I (DSM-IV)	Small sample size, selection and recall biases	5/14
(Fornaro, 2010)	Cross-sectional	Italy	148 females with BDs (BD-I, BD-II, and cyclothymia)	23 (15%)	SCID-I (DSM-IV-TR)	Recall bias, high rate of inpatients may have led to an overrepresentation of most severe cases. Females only sample	5/14
(Seixas, 2012)	Cross-sectional	Brazil	356 BD patients seeking specialized service treatment recruited from March 2005 to March 2009	8 (2%)	SCID-I (DSM-IV)	Recall and selection biases	5/14
(Faravelli, 2006)	Cross-sectional	Italy	Representative sample of a general Italian population aged 14 years or older	1 (7%)	M.I.N.I. (DSM-IV)	Recall bias	4/14
(Torrent, 2008)	Cross-sectional	Spain	90 BDs inpatients and outpatients	1 (1%)	M.I.N.I. (DSM-IV)	Small sample size, inclusion of B.D. patients of varying current	5/14

						mood state	
(McElroy, 2011)	Cross-sectional	USA	875 BD-I and BD-II outpatients aged 18 years or older	12 (1%)	SCID-P (DSM-IV)	Potential interviewer/Berkson's biases due to non-blind interview may have led to inflated rates of E.D. comorbidity	5/14
(Perugi et al., 2013b)	Cross-sectional	Italy	202 BD-I inpatients referred for electroconvulsive therapy.	3 (1%)	M.I.N.I. (DSM-IV)	Treatment-seeking, severe, patients may have resulted in selection bias. Potential confounding effects of medication on E.D. symptom presentation and evolution	5/15
(McElroy et al., 2016)	Cross-sectional	USA	1,092 BD patients (BD-I=699, BD-II=393)	BD-I=0 BD-II=2 (2 out 393)	SCID-I (DSM-IV), and EDDS (DSM-5, adopted for the definition of BED)	Recall bias. The subset of B.D. without any E.D. included only 33 patients.	5/16
(Dell'Osso et al., 2011)	Baseline data of a prospective cohort study	Italy	508 consecutive BD outpatients (treatment-seeking patients)	9 (2%)	SCID-I (DSM-IV)	Recall bias due to the cross-sectional record of baseline info. Selection bias	3/14
(McElroy et al., 2001)	Baseline data of a prospect	The U.S.A. and the	288 BD outpatients with BD-I (n=	6 (2%)	SCID-P (DSM-IV)	Berkson's/interviewer, recall biases	3/14

	ive cohort study	Netherlands	239) and BD-II (n=49) recruited from private, academic, and community mental health clinic outpatient settings				
(Nery et al., 2014)	Cross-sectional study	Brazil	483 consecutive BD outpatients from three research centres participating in the Brazilian Bipolar Research Network BD-I (n= 434), BD-II (n=36) and BD-NOS (n=13)	12 (2%)	SCID-P (DSM-IV)	Recall bias. Selection bias: patients attending tertiary level of care	3/14
(Pashinian et al., 2006)	Cross-sectional study	Israel	56 BD-I patients consecutively admitted with acute mania	1 (2%)	SCID-I/P (DSM-IV)	Recall bias, small sample size	3/14

Legend of table 1a: ED=eating disorder; AN=Anorexia Nervosa; BD=bipolar disorder; NOS=Not otherwise specified; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); DIGS= Diagnostic Interview for Genetic Studies; SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; M.I.N.I.=Mini-International Neuropsychiatric Interview; DIGS= Diagnostic Interview for Genetic Studies; EDDS=Eating Disorders Diagnostic Scale; NIH=(U.S.) National Institute

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Note: Higher scores of the NIH quality assessment tool indicate lower quality of the study concerning our research theme.

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Table 1b: Studies assessing BN comorbidity in BD samples according to our inclusion/exclusion criteria for systematic review, N=17.

Reference	Study design	Country	Study population	Sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations/ biases	NIH Quality
Hospital-based studies: BN comorbidity in BD samples							
(Ramacciotti,	Retrospec	Italy	51 adult outpatient	5	SCID-I (DSM-	Recall bias, broad	5/14

2005)	tive		s with BDs, of whom 9 BED and 5 BN	(10%)	IV)	definitions of some diagnostic categories	
(Baek, 2014)	Cross-sectional	Korea	417 inpatients and outpatients BDs recruited in four medical centers in Korea from November 2004 to July 2011	25 (6%)	DIGS (DSM-IV)	Recall bias, selection bias	5/14
(Baldassano, 2005)	Cross-sectional	USA	482 BD-I and BD-II patients obtained by the population included in the STEP-BD study	36 (7%)	M.I.N.I. and ADE (DSM-IV)	Recall bias; failure to record the number of past mood episodes of BD	6/14
(Balzafiore, 2017)	Cross-sectional	USA	503 BDs outpatients referred to Stanford University BD Clinic within the years 2000-2011	43 (8%)	SCID-I, M.I.N.I. –(DSM-IV)	Recall bias, limited stratification of EDs	4/14
(Bobo, 2018)	Cross-sectional	USA	1,465 BDs referred to specialty clinics - Bipolar	210 (14%)	SCID-I (DSM-IV)	Recall bias, selection bias, the potential confounding effect of	5/14

			Biobank database			medications on eating behavior not controlled	
(Azorin, 2013)	Cross-sectional	France	1,090 manic BD-I inpatients recruited between December 2000 and April 2002	149 (14%)	SCID-I (DSM-IV)	Recall bias, the overrepresentation of BD-I cases	5/14
(Schreck-Del Bello, 2017)	Cross-sectional	France	80 BDs (BD-I, BD-II, and cyclothymia) recruited between March and November 2002, multicentric study	11 (14%)	SCID-I (DSM-IV)	Small sample size, selection and recall biases	5/14
(Fornaro, 2010)	Cross-sectional	Italy	148 females with BDs (BD-I, BD-II, and cyclothymia)	8 (5%)	SCID-I (DSM-IV-TR)	Recall bias, high rate of inpatients may have led to over-representation of most severe cases. Females only sample	5/14
(Seixas, 2012)	Cross-sectional	Brazil	356 BD patients seeking specialized service treatment recruited from March 2005 to	8 (2%)	SCID-I (DSM-IV)	Recall and selection biases	5/14

			March 2009				
(Faravelli, 2006)	Cross-sectional	Italy	A representative sample of an Italian general population aged >14 years old	0	M.I.N.I. (DSM-IV)	Recall bias	4/14
(Torrent, 2008)	Cross-sectional	Spain	90 BDs in- and outpatients	2 (2%)	M.I.N.I. (DSM-IV)	Small sample size, inclusion of B.D. patients of varying current mood state	5/14
(McElroy et al., 2011)	Cross-sectional	USA	875 BD-I and BD-II outpatients aged 18 years or older	27 (3%)	SCID-P (DSM-IV)	Potential interviewer/Berkson's biases due to non-blind interview may have led to inflated rates of E.D. comorbidity	5/14
(McElroy et al., 2016)	Cross-sectional	USA	1,092 BD patients (BD-I=699, BD-II=393)	98 BD-I (13%) and BD-II=62 (16%)	SCID-I (DSM-IV), and EDDS (DSM-5, adopted for the definition of BED)	Recall bias. The subset of B.D. without any E.D. included only 33 patients.	5/14
(Perugi et al., 2013a)	Cross-sectional	Italy	192 BD outpatients with or without lifetime comorbid ADHD	1 BD-II patient (5 out 1000 BDs)	DCTC (DSM-IV)	Recall bias	4/14

(McElroy et al., 2001)	Baseline data of a prospective cohort study	The U.S.A. and The Netherlands	288 BD outpatients with BD-I (n= 239) and BD-II (n=49) recruited from private, academic, and community mental health clinic outpatient settings	11 (4% among BD, overall)	SCID-I/P (DSM-IV)	Berkson's/interviewer, recall biases	3/14
(Nery et al., 2014)	Cross-sectional study	Brazil	483 consecutive BD outpatients from three research centres participating in the Brazilian Bipolar Research Network BD-I (n= 434), BD-II (n=36) and BD-NOS (n=13)	23 (5%)	SCID-I/P (DSM-IV)	Recall bias. Selection bias: patients attending tertiary level of care	3/14
(Pashinian et al., 2006)	Cross-sectional study	Israel	56 BD-I patients consecutively admitted with acute	1 (2%)	SCID-I/P (DSM-IV)	Recall bias, small sample size	3/14

			mania				

Legend of table 1b: ED=eating disorder; BN=Bulimia Nervosa; BD=bipolar disorder; NOS=Not otherwise specified; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); DIGS= Diagnostic Interview for Genetic Studies; DCTC=Diagnostic, Clinical and Therapeutic Checklist; SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; M.I.N.I.=Mini-International Neuropsychiatric Interview; ADE=Affective Disorder Evaluation; NIH=(U.S.) National Institute of Health (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies).

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Table 1c Studies assessing BED comorbidity in BD samples according to our inclusion/exclusion criteria for systematic review, N=15 (*one study documented also the current prevalence rate besides the sole standard lifetime one accounted for subsequent meta-analytic pooling, overall comparisons n=16).

Reference	Study design	Country	Study population	Sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations/ biases	NIH Quality
Hospital-based studies: BED comorbidity in BD samples							
(Boulanger, 2018)	Cross-sectional	France	145 adult BDs referred to a specialty clinic, of whom 86 BD-I and BD-II=59	27 people, overall (19%)	SCID-I (DSM-IV)	Small sample size, recall and selection biases	5/14
(Schoofs, 2011)	Case-control	Germany	52 women across different phases of the menstrual cycle, of whom BD-I=23 and BD-II=29	15 (29%)	SCID-I (DSM-IV)	Small sample size recall bias. Selection bias (unmediated BD only)	4/14
(Winham, 2014)	Cross-sectional	USA	929 (out of 1,001 European-American) BDs underwent assessment for comorbid BED	206 (22%)	DIGS (DSM-III and DSM-IV)	Recall bias	5/14

(McElroy et al., 2016)	Cross-sectional	USA	1,092 BD patients (BD-I=699, BD-II=393). Note, shown data refer to cases with a definitive diagnosis of BED rather than "BED spectrum"	129, or 12% (BD-I=75 or 18%; BD-II=54, or 14%)	SCID-I (DSM-IV), and EDDS (DSM-5, adopted for the definition of BED)	Recall bias. The subset of BD without any ED included only 33 patients	5/14
(Ramaccio tti, 2005)	Cross-Sectional	Italy	51 adult outpatients with BD, of whom 9 BED and 5 BN	9 (18%)	SCID-I (DSM-IV)	Recall bias, broad definitions of some diagnostic categories	5/14
(Bobo, 2018)	Cross-sectional	USA	1,465 BDs referred to specialty clinics - Bipolar Biobank database	210 (14%)	SCID-I (DSM-IV)	Recall bias, selection bias, the potential confounding effect of medications on eating behavior could not be controlled	5/14
(McElroy, 2013)	Cross-Sectional	USA	717 BDs from the Bipolar Biobank	68 (9%)	SCID-I (DSM-IV)	Recall bias, especially for those diagnoses just partially vouched by the means of the structured interview	5/14
(Krüger, 1996)	Cross-Sectional	Canada	61 Euthymic outpatient	8 (13%)	SADS (DSM-III-R/DSM-	Small sample size, selection and recall biases	5/14

			s with BD		IV)		
(McElroy, 2002)*	Cross-Sectional	USA	409 BDs underwent *LIFETIME and* • Current prevalence of BED in BD=21/409, or 5.1% vs. lifetime prevalence of 33/409 =8.1%	33 (8%)	SCID-I/P (DSM-IV)	Berkson's bias (treatment-seeking patients only), obesity was self-reported	5/14
(Schreck-Del Bello, 2017)	Cross-Sectional	France	80 BDs (BD-I, BD-II, and cyclothymia) recruited between March and Nov 2002, multicentric study	22 (27%)	SCID-I (DSM-IV)	Small sample size, selection and recall biases	5/14
(Fornaro, 2010)	Cross-Sectional	Italy	148 females with BDs (BD-I, BD-II, and cyclothymia)	21 (14%)	DSM-IV-TR	Recall bias, high rate of inpatients may have led to overrepresentation of most severe cases. Females only sample.	5/14
(Seixas, 2012)	Cross-sectional	Brazil	356 BD patients seeking specialized service treatment recruited from March	8 (2%)	SCID-I (DSM-IV)	Recall and selection biases	5/14

			2005 to March 2009				
(McElroy et al., 2011)	Cross-Sectional	USA	875 BD-I and BD-II outpatients with age 18 years or older	77 (9%)	DSM-IV	Potential interviewer/Berkson's biases due to non-blind interview may have led to inflated rates of ED comorbidity	5/14
(Nery et al., 2014)	Cross-sectional study	Brazil	483 consecutive BD outpatients from three research centres participating in the Brazilian Bipolar Research Network BD-I (n= 434), BD-II (n=36) and BD-NOS (n=13)	11 (2%)	SCID-P (DSM-IV)	Recall bias. Selection bias: patients attending tertiary level of care	3/14
(Pashinian et al., 2006)	Cross-sectional study	Israel	56 BD-I patients consecutively admitted with acute mania	1 (2%)	SCID-I/P (DSM-IV)	Recall bias, small sample size	3/14

Legend of table 1c: ED=eating disorder; BED=binge eating disorder; BN=bulimia nervosa; BD=bipolar disorder; NOS=Not otherwise specified; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician

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Table 1d. Studies documenting ED, any, among BDs according to our inclusion/exclusion criteria for a systematic review, N=10.

Reference	Study design	Country	Study population	A sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations / biases	NIH Quality
Hospital-based studies: ED comorbidity in BD samples							
(Brietzke et al., 2011)	Cross-sectional	Brazil	137 BD-I female patients	BD-I with any ED=20	SCID-I (DSM-IV)	Selection bias: female	5/14

			consecutively admitted to the Bipolar Disorder Program at the University of Sao Paulo	(15%)		sample only	
(Belizario et al., 2019)	Cross-sectional	Brazil	147 BD-I and BD-II outpatients from the Bipolar Disorder Research Program ("PROMAN") at the University of Sao Paulo	BD with any ED=20 (14%)	SCID-CV - "customized version" (DSM-IV)	Berkson's bias: treatment-seeking patients	5/14
(Berkol et al., 2016)	Cross-sectional	Turkey	208 BD-I and 10 BD-II outpatients treated between 2013 and 2014	BD with any ED=5 (2%)	SCID-I (DSM-IV)	Recall bias	5/14
(Baek et al., 2011)	Cross-sectional	South Korea	105 BD-I and BD-II out- and inpatients recruited from 2007 to 2010	15 BDs (15%), of whom, BD-I with any ED=6 out of 71 BD-I (8%); BD-II with any	DIGS (DSM-IV)	Recall bias, relatively small sample size	5/14

				ED=9 out of 34 BD-II (26%)			
(Loftus et al., 2020)	Cross-sectional	France	707 BD patients assessed for comorbid ED	70 patients endorsed at least one comorbid ED (10%)	DIGS (DSM-IV)	Recall bias	5/14
(Wildes et al., 2007)	Cross-sectional	USA	69 adult outpatients with BD with or without comorbid ED	25 BDs had comorbid ED (36%), including 19 out of 54 diagnosed as BD-I (35%); and 6 out 15 diagnosed as BD-II (4%)	SCID-I (DSM-IV-TR)	Recall bias, small sample size	5/14
(Goffin et al., 2016)	Cross-sectional	USA	494 adult outpatients with BD assessed comparing those with- or without suicidal attempts	A total of 76 BDs (15%) included 34 BD-I (48%), and 42 BD-II (55%)	SCID-I (DSM-IV-TR)	Recall bias	4/14
(Liu et al., 2016)	Cross-sectional	USA	Data from the Bipolar Genome Studies,	A total of 184 patients endorse	DIGS (DSM-III-R and DSM-	Sub-optimal stratification of the	5/14

			2,190 adults with BD	d at least one comorbid ED (8%)	IV)	results due to the post-hoc nature of the report	
(Jen et al., 2013)	Cross-sectional	USA	356 Outpatients with BD-I, BD-II, and BD-NOS	A total of 63 patients endorsed at least one comorbid ED (18%)	DIGS (DSM-IV)	Recall bias	5/14
Population-based studies: ED comorbidity in BD samples							
(Angst et al., 2018)	Cross-sectional	International multicentric study	432 BD-I patients, of whom 109 with unipolar mania, recruited among the general population	BD-I with any ED=43 (10%)	M.I.N.I. (DSM-IV)	Recall bias, lack of further stratification	5/14

Legend of table 1d: ED=eating disorder; BD=bipolar disorder; NOS=Not otherwise specified; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); DIGS= Diagnostic Interview for Genetic Studies; SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; M.I.N.I.= Mini-International Neuropsychiatric Interview; NCS=National Comorbidity Survey-(project edition); NIH=(U.S.) National Institute of Health (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies).

Note: Higher scores of the NIH quality assessment tool indicate lower quality of the study concerning our research theme.

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Table 2a: Studies assessing BD comorbidity in samples with a primary diagnosis of AN according to our inclusion/exclusion criteria for systematic review, N=7.

Reference	Study design	Country	Study population	Sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations / biases	NIH Quality
Hospital-based studies: BD comorbidity in sample with a primary diagnosis of AN							
(Ivarsson et al., 2000)	Prospective cohort	Sweden	51 AN adult patient who developed anorexia at a young age	3 (6%)	SCID-I/P (DSM-III)	Small sample size, selection bias	8/14
(Halmi et al., 1991)	Cross-sectional	USA	62 patients who received the AN diagnosed ten years earlier than the BD one, on average	2 (3%)	DIS, version III (DSM-III-R)	Small sample size; some clinical data documented by proxy only (parents)	5/14
(Tseng et al., 2016)	Case-control	Taiwan	288 consecutively EDs outpatients from the general outpatient clinics of the Department of Psychiatry of a Teaching Hospital (AN=54)	9 (3%)	SCID-I, M.I.N.I. (DSM-IV)	Selection bias, limited stratification of the results	4/14
(Thiebaut et al., 2019)	Ancillary study to a larger prospective project	France	The study included 139 outpatients with AN	9 (6%)	M.I.N.I. (DSM-5)	The small sample size precluded further stratification of the	3/14

						diagnostic groups	
(Toner et al., 1988)	Prospective cohort	USA	47 women	3 (6.4%)	DIS (DSM-III)	Small sample size	2/14
Population-based studies: BD comorbidity in samples with comorbid AN							
(Swanson et al., 2011)	Cross-sectional	USA	10,123 adolescents (13-18 years old) asked to participate to a survey (NCS-A)	30 (0.3%)	CIDI (DSM-IV)	Recall bias; the small subset of comorbid cases precluded further stratification of the results	5/14
(Hudson et al., 2007)	Cross-sectional	USA	2,980 adults recruited for an interview survey (NCS-R)	90 (3%)	CIDI (DSM-IV)	Lack of stratification of the results across different subtypes of BDs	5/14

Legend of table 2a : AN=Anorexia Nervosa; BD=bipolar disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); DIS=Diagnostic Interview Schedule; M.I.N.I.=Mini-International Neuropsychiatric Interview; CIDI=Composite International Diagnostic Interview; NCS=National Comorbidity Survey-(project edition); NIH=(U.S.) National Institute of Health (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies); OR=odd ratio; C.I.=confidence interval.

Note: Higher scores of the NIH quality assessment tool indicate lower quality of the study concerning our research theme.

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Table 2b: Studies assessing BD comorbidity in BN samples according to our inclusion/exclusion criteria for systematic review, N=4.

Reference	Study design	Country	Study population	A sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations / biases	NIH Quality
Hospital-based studies: BD comorbidity in BN samples							
(Tseng et al., 2016)	Case-Control Study	Taiwan	288 consecutively EDs outpatients from the general outpatient clinics of the Department of Psychiatry of a Teaching Hospital (BN=125)	45 (16%)	SCID-I, M.I.N.I. (DSM-IV)	Selection bias, limited stratification of the results	4/14
(Thiebaut et al., 2019)	Ancillary study to a larger prospective project	France	The study included 67 BN outpatients	11 (16%)	M.I.N.I. (DSM-5)	The small sample size precluded further stratification of the diagnostic groups	3/14
Population-based studies: BD comorbidity in BN samples							
(Swanson et al., 2011)	Cross-sectional	USA	10,123 adolescents (13-18 years old) asked to	91 (0.9%)	CIDI (DSM-IV)	Recall bias; the small subset of comorbid cases	5/14

			participate to a survey (NCS-A)			precluded further stratification of the results	
(Hudson et al., 2007)	Cross-sectional	USA	2,980 adults recruited for an interview survey (NCS-R)	527 (17.7%)	CIDI (DSM-IV)	Lack of stratification of the results across different subtypes of BDs	5/14

Legend of table 2b: BN=Bulimia Nervosa; BD=bipolar disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); CIDI=Composite International Diagnostic Interview; M.I.N.I.=Mini-International Neuropsychiatric Interview; NCS=National Comorbidity Survey-(project edition); NIH=(U.S.) National Institute of Health (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies); OR=odd ratio; C.I.=confidence interval.

Note: Higher scores of the NIH quality assessment tool indicate lower quality of the study concerning our research theme.

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Table 2c: Studies assessing BD comorbidity among people with a primary diagnosis of BED samples, any type, according to our inclusion/exclusion criteria for systematic review, N=7.

Reference	Study design	Country	Study population	Sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations/ biases	NIH Quality
Hospital-based studies: BD comorbidity in BED samples							
(Javaras, 2008)	Cross-Sectional	USA	285 BED (probands and their relatives) from October 2002 to July 2004	31 (11%)	SCID-I (DSM-IV)	The over-representation of obese cases limits the generalizability of the results in the absence of further stratification	5/14
(Welch, 2016)	Cross-Sectional	Sweden	Data extracted during the year 2009 from the Swedish population register, 850 BEDs	35 (4%)	SCID-I (DSM-IV)	Recall bias	5/14
(Lilenfeld et al., 2008)	Cross-sectional study	USA	31 female BED patients and 32 female	1 (3%)	SCID-I (DSM-IV)	Recall bias, small sample size, selection bias (Caucasian	4/31

			controls with difficulty controlling weight but no BED			females only)	
(Tseng et al., 2016)	Case-Control Study	Taiwan	288 consecutively EDs outpatients from the general outpatient clinics of the Department of Psychiatry of a Teaching Hospital (BED=75)	37 (13%)	SCID-I/P (DSM-IV)	Recall bias, small sample size, selection bias	4/14
(Thiebaut et al., 2019)	Ancillary study to a larger prospective project	France	The study included 30 BED outpatients	5 (17%)	M.I.N.I. (DSM-5)	The small sample size precluded further stratification of the diagnostic groups	3/14
Population-based studies: BD comorbidity in BED samples							
(Swanson et al., 2011)	Cross-sectional	USA	10,123 adolescents (13-18 years old) asked to participate to a survey (NCS-A)	162 (1.6%)	CIDI (DSM-IV)	Recall bias; the relatively small subset of comorbid cases precluded further stratification of the results	5/14
(Hudson	Cross-	USA	2,980 adults	372	CIDI	Lack of	5/14

et al., 2007)	sectional		recruited for a interview survey (NCS-R)	(12.5%**)**	(DMS-IV)	stratification of the results across different subtypes of BDs	

Legend of table 2d: BED=binge eating disorder; BD=bipolar disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); CIDI=Composite International Diagnostic Interview; M.I.N.I.=Mini-International Neuropsychiatric Interview; NCS=National Comorbidity Survey-(project edition); NIH=(U.S.) National Institute of Health (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies); OR=odd ratio; C.I.=confidence interval.

Note: Higher scores of the NIH quality assessment tool indicate lower quality of the study concerning our research theme.

Table 2d references:

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Table 2d. Studies documenting BD, any, among EDs according to our inclusion/exclusion criteria for a systematic review, N=1.

Reference	Study design	Country	Study population	Sample size of comorbid BD-ED cases	Diagnostic assessment	Limitations/ biases	NIH Quality
Hospital-based studies: ED comorbidity in BD samples							
(Tseng et al., 2017)	Cross-sectional	USA	227 outpatients with any ED with comorbid BD (or major depressive disorder)	ED with BD-I=39 (17%); ED with BD-II=55 (24%)	SCID-I, M.I.N.I. (DSM-IV)	Selection bias, limited stratification of the results	5/14

Legend of table 2d: ED=eating disorder; BD=bipolar disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; M.I.N.I.=Mini-International Neuropsychiatric Interview; NIH=(U.S.) National Institute of Health (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies).

Note: Higher scores of the NIH quality assessment tool indicate lower quality of the study concerning our research theme.

Table 2d references:

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Table 3a: Sub-group analyses investigating AN comorbidity in BD

Analysis	Number of study estimate	Meta-analysis	Heterogeneity

	s					
		Prevalence of AN in BD	95%C.I.		Between-group p-value	I^2
Main analysis	15	2%	.02	.04		87.22%
Study design					.42	
Cross-sectional	13	3%	.01	.04		88.05**%**
Prospective cohort study	2	2%	.01	.03		0%
Geographical region					.24	
Europe	7	4%	.02	.08		87.19%
North America	3	1%	<.01	.06		93.92%
South America	2	2%	.02	.04		0%
Asia	2	1%	<.01	.03		0%
Various (North America + Europe)	1	2%	.01	.05		0%
Setting					0.11	
Inpatient	2	5%	.03	.07		2.83%
Outpatient	6	2%	.01	.04		76.25%
Mixed	6	2%	<.01	.08		92.88%
Population-based	1	5%	.01	.28		0%
Adopted Structured Interview					.03	
M.I.N.I.	2	2%	.01	.10		13.45%
SCID	12	2%	.01	.04		89.49%
M.I.N.I.+SCID	1	5%	.04	.08		0%
Diagnostic Criteria					<.01	
DSM-IV/DSM-IV-TR	14	3%	.02	.05		85.58%
DSM-5+DSM-IV/DSM-IV-TR	1	<1%	<.01	.01		0%
Prevalence type					.40	
Lifetime prevalence	14	3%	.02	.04		87.42%
Current prevalence	1	2%	.01	.03		0%
Ethnicity					.43	
Caucasian	2	5%	<.01	.39		93.77%
Asian	1	1%	<.01	.03		0%
Mixed	2	1%	<.01	.24		95.41%

Legend for table 3a: AN=Anorexia Nervosa; BD= bipolar disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; M.I.N.I.= Mini-International Neuropsychiatric Interview; C.I.=confidence interval.

Table 3b: Sub-group analyses investigating BN comorbidity in BD.

Analysis	**Number of study estimates**	**Meta-analysis**			**Heterogeneity**
		Prevalence of BN in BD	95%C.I.	Between-group p-value	I^2
Main analysis	17	6.6%	.048 .088		91.27%
Setting				.05	
Inpatient	2	6%	.08 .35		78.11**%**
Outpatient	7	4.4%	.03 .07		80.53%
Mixed	7	9%	.07 .13		87.56%
Population-based	1	2.4%	.01 .29		0%
Geographical region				.07	
Europe	6	8.6%	.05 .01		69.29%
North America	6	7.6%	.05 .12		94.76%
South America	2	4.1%	.03 .06		31.76%
Asia	2	4.8%	.02 .12		32.65%
Various (North America + Europe)	1	3.8%	.02 .07		0%
Adopted Structured Interview				.03	
M.I.N.I.	2	2.3%	.01 .07		0%
SCID	13	6.6%	.05 .09		92.78%
M.I.N.I.+SCID	2	8%	.05 .10		0%
Diagnostic Criteria				<.01	
DSM-IV/DSM-IV-TR	16	6%	.04 .08		90.84%
DSM-5+DSM-IV/DSM-IV-TR	1	14.7%	.13 .17		0%
Prevalence type				<.01	
Lifetime prevalence	13	4.9%	.03 .08		87.42%
Current prevalence	3	11.8%	.09 .16		86.85%
Ethnicity				<.01	
Black	9	4.8%	.02 .09		92.34%
Caucasian	3	4.2%	.01 .13		73.43%
Asian	1	6%	.04 .09		0%
Mixed samples	2	10.7%	.05 .20		93.44%
Two or more races	2	11.3%	.07 .18		90.86%

Legend for table 3b: BN=Bulimia Nervosa; BD= bipolar disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; M.I.N.I.= Mini-International Neuropsychiatric Interview; C.I.=confidence interval.

Table 3c: Sub-group analyses investigating BED comorbidity in BD.

Analysis	**Number of study estimates**		**Meta-analysis**				**Heterogeneity**	**Publication bias**	
			Prevalence of BED in BD	95%C.I.		Between-group p-value	I^2	Egger test, p-value	Trim and fill (95% C.I.) [adjusted studies]
Main analysis	15		12.5%_ ___	.94	.166		93.%	-2.73256, p=.11	15.6% (.11-.21) [3]
Setting						.02			
Inpatient	1		1.8%	.003	.166		0%	-	-
Outpatient	8		9.9%	.058	.163		90.27%	-.32314, p=.90	Unadjusted
Mixed	6		16%	.12	.22		94.08%	-2.57473, p=.58	18% (.13-.25) [1]
Geographical region						<.01			
Europe	5		20.6%	.15	.27		53.87%	1.97929, p=.65	Unadjusted
North America	7		12.7%	.0.9	.18		95.56%	-7.0104, p=.12	17.8% (.13-.24) [3]
South America	2		0.8%	.001	.101		73.5%	-	-
Asia	1		1.8%	.003	.116		0%	-	-

Adopted Structured Interview						<.01			
SCID-I	13		11.7%	.08	.16		93.25%	-2.45870, p=.19	13.1% (.09-.18) [2]
SCID-I & SADS	1		13.1%	.07	.24		0%	-	-
DIGS	1		22.2%	.20	.25		0%	-	-
Diagnostic Criteria						.20			
DSM-III & DSM-IV/TR	2		18.8%	.11	.29		62.81%	-	-
DSM-IV/DSM-IV-TR	12		11.4%	.07	.17		93.57%	-2.69028, p=.16	16.2% (.09-.19) [2]
DSM-IV-TR/DSM-5	1		11.8%	.1	.14		0%	-	-
Prevalence type						<.01			
Lifetime prevalence	8		8.4%	.05	.13		90.34%	-2.12945, p=.33	10% (.06-.15) [2]
Current prevalence	6		17.9%	.13	.23		90.52%	-1.50135, p=.61	Unadjusted
Ethnicity						<.01			
Caucasian	3		18.6%	.13	.25		61.34%	-1.97277, p=.37	22.2% (.17-.29) [2]
Two or more races	1		20.5%	.19	.23		0%	-	-
Mixed	2		10%	.07	.14		76.64%	-	-
Study design						<.01			

Cross-sectional	14		11.8%	.09	.16		93.75%	-.3.30778. p=.07	15.8% (-.12-.21) [4]
Case-control	1		28.8%	.18	.42		0%	-	-

Legend for table 3c: BED=Binge eating disorder; BD=Bipolar Disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; DIGS=Diagnostic Interview for Genetic Studies; SADS=Schedule for Affective Disorders and Schizophrenia; C.I.=confidence interval.

Table 3d: Sub-group analyses investigating the comorbidity of any ED in BD.

Analysis	**Number of study estimates**	**Meta-analysis**				**Heterogeneity**
		Prevalence of any ED in BD	95%C.I.		Between-group p-value	I^2
Main analysis	10	12.7%	.09	.17		90.55%
Study Design					1	
Cross-sectional	10	12.7%	.09	.17		90.55%
Setting					.43	
Outpatient	5	14.5%	.09	.23		90.41%
Mixed	4	10.7%	.08	.14		69.66%
Population-based	1	10%	.07	.13		0%
Geographical region					.17	
Europe	2	5.1%	.01	.20		90.74%
North America	4	17.1%	.10	.28		96%
South America	2	14%	.10	.19		0%
Asia	1	14.3%	.09	.22		0%
Various (North America +South America + Europe)	1	10%	.07	.13		0%
Adopted Structured Interview					.55	
M.I.N.I.	1	10%	.07	.13		0%
SCID-I	5	13.6%	.08	.23		90.35%
DIGS	4	11.9%	.08	.17		90.25%
Diagnostic Criteria					<.01	
DSM-III & DSM-IV/IV-TR	1	8.4%	.07	.09		0%
DSM-IV/DSM-IV-TR	9	13.4%	.10	.18		87.39%
Prevalence type					.52	
Lifetime prevalence	8	12.4%	.29	.17		92.49%
Current prevalence	2	14%	.10	.19		0%
Ethnicity					.83	
Asian	1	14.3%	.09	.22		0%
Mixed samples	5	15.3%	.10	.23		94.76%

Legend for table 3d: ED=Eating Disorder; BD= bipolar disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; DIGS= Diagnostic Interview for Genetic Studies; M.I.N.I.= Mini-International Neuropsychiatric Interview; C.I.=confidence interval.

Table 4a: Sub-group analyses investigating BD comorbidity in AN.

Analysis	**Number of study estimates**	**Meta-analysis**			**Heterogeneity**
		Prevalence of BD in AN	95%C.I.	Between-group p-value	I^2
Main analysis	7	3.8%	.01 .11		96.75%
Study Design				.01	
Case-control	1	16.7%	.09 .29		0%
Cross-sectional	4	2%	.01 .09		97.84%
Prospective cohort	2	6.1%	.03 .13		0%
Setting				.25	
Outpatient	2	10.5%	.04 .25		77.59%
Inpatient	1	3.2%	.01 .12		0%
Mixed	1	6.4%	.02 .18		0%
Population-based	3	1.7%	<.01 .10		96.75%
Geographical region				.01	
Europe	2	6.3%	.04 .11		0%
North America	4	2%	<.01 .09		97.67%
Asia	1	16.7%	.09 .29		0%
Adopted Structured Interview				.24	
M.I.N.I.	1	6.5%	.03 .12		0%
SCID-I	2	10.9%	.04 .27		63.7%
DISv3	2	4.8%	.02 .11		0%
CIDI	2	1%	<.01 .09		99.19%
Diagnostic Criteria				.63	
DSM-III	3	5.2%	.03 .10		0%
DSM-IV/DSM-IV-TR	3	2.5%	<.01 .15		98.79%

DSM-5	1	6.5%	.03	.12		0%
Prevalence type						
Lifetime prevalence	6	3.6%	.01	.12		97.25%

Legend for table 4a: BD= bipolar disorder; AN=Anorexia Nervosa DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; M.I.N.I.= Mini-International Neuropsychiatric Interview; DIS=Diagnostic Interview Schedule; CIDI=Composite International Diagnostic Interview; C.I.=confidence interval.

Table 4b: Sub-group analyses investigating BD comorbidity in BN.

Analysis	**Number of study estimates**	**Meta-analysis**			**Heterogeneity**
		Prevalence of BD in BN	95%C.I.	Between-group p-value	I^2
Main analysis	4	10.8%	.02 .45		99.63%
Study Design				.10	
Case-control	1	36%	.28 .45		0%
Cross-sectional	3	6.7%	<.01 .45		99.73%
Setting				.21	
Outpatient	2	25.6%	.11 .49		87.03%
Population-based	2	4.2%	<.01 .50		99.86%
Geographical region				<.01	
Europe	1	16.4%	.09 .27		0%
North America	2	4.2%	<.01 .50		99.86%
Asia	1	36%	.28 .45		0%
Adopted Structured Interview				<.01	
M.I.N.I.	1	16.4%	.09 .27		0%
SCID-I	1	36%	.28 .45		0%
CIDI	2	4.2%	<.01 .50		99.86%
Diagnostic Criteria				.60	
DSM-IV/DSM-IV-TR	3	9%	.01 .51		99.75%
DSM-5	1	16.4%	.09 .27		0%
Prevalence type				1	
Lifetime prevalence	3	9.1%	<.01 .67		99.51%

Legend for table 4b: BD= bipolar disorder; BN=Bulimia Nervosa DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; CIDI=Composite International Diagnostic Interview; M.I.N.I.= Mini-International Neuropsychiatric Interview; C.I.=confidence interval.

Table 4c: Sub-group analyses investigating BD comorbidity in BED.

Analysis	**Number of study estimates**	**Meta-analysis**			**Heterogeneity**
		Prevalence of BD in BED	95%C.I.	Between-group p-value	I^2
Main analysis	7	9.1%	.03 .23		99.079%
Study Design				<.01	
Case-control	1	49.3%	.38 .60		0%
Cross-sectional	6	6.3%	.02 .17		99.05%
Setting				.17	
Outpatient	4	16.4%	.05 .43		94.32%
Population-based	3	4.4%	<.01 .18		99.61%
Geographical region				<.01	
Europe	2	8%	.02 .28		88.6%
North America	4	5.5%	.01 .20		99.41%
Asia	1	49.3%	.38 .60		0%
Adopted Structured Interview				.47	
M.I.N.I.	1	16.7%	.07 .34		0%
SCID-I	4	11.2%	.03 .37		97.47%
CIDI	2	4.6%	<.01 .29		99.8%
Diagnostic Criteria				.29	
DSM-IV/DSM-IV-TR	6	8.2%	.03 .22		99.22%
DSM-5	1	16.7%	.07 .34		0%
Prevalence type				1	
Lifetime prevalence	7	9.1%	.03 .23		99.079%

Legend for table 4c: BD= bipolar disorder; BED=Binge-Eating Disorder; DSM=Diagnostic Interview for Mental Disorders (…edition/revision); SCID-I (either the patient or clinician edition)=Structured Clinical Interview for DSM-IV Axis-I Disorders; CIDI=Composite International Diagnostic Interview; M.I.N.I.= Mini-International Neuropsychiatric Interview; C.I.=confidence interval.