

QUALITY OF LIFE IN EUTHYMIC BIPOLAR PATIENTS: A SYSTEMATIC REVIEW AND METAANALYSIS¹

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Abstract

Background: Patients with bipolar disorder, even euthymic, could suffer an impairment in their quality of life compared to healthy controls. Since no previous systematic review and meta-analysis has been conducted, the aim of the current study is to conduct a systematic review and meta-analysis of cross-sectional studies with matched cases and controls on quality of life in adult Euthymic Bipolar Disorder patients. Methods: A systematic review and meta-analysis that followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was conducted. Major electronic databases were searched on August 2018 to assess the variables associated with quality of life in euthymic bipolar disorder patients. After selecting the studies, data collection, quality assessment and subsequently statistical analysis were done. Results: Sixteen studies were finally selected for systematic review and meta-analysis. Four different quality of life instruments were used among the different studies. Effect size analysis showed that there were significant differences in quality of life outcomes between euthymic bipolar disorder patients and healthy controls ($d=0.997$; $SE=0.33$; $95\%CI=-1.64$ to -0.36), with lower quality of life in the euthymic patients. Furthermore, time since euthymia explained 15.62% of variability, and age of control group explained 28.39% of variability. No other moderators were statistically significant. Limitations: The instruments used were heterogeneous. Moreover, the role of other clinical moderators could not be included due to the lack of this information in most of the articles. Conclusions: Quality of life is lower in euthymic bipolar patients than in healthy controls. However, longer time in euthymia is associated with better outcomes.

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1. INTRODUCTION

Bipolar disorder (BD) is an affective disorder characterized by episodes of depression, mania or hypomania, alternating with periods of euthymia (APA, 2013; WHO, 1992). It affects more than 1% of the world's population (Grande et al., 2016). Given its severity and chronicity, patients with BD need to deal with different issues from its early onset. Such issues impose significant levels of burden to these patients. In fact, BD is one of the top 20 causes of disability and one of the top five mental disorders in terms of burden (Ferrari et al., 2016).

There is strong evidence that bipolar disorder patients could suffer a significant degree of functional impairment and low Quality of life (QoL) (Martín-Subero et al., 2014; Michalak et al., 2005a; Michalak et al., 2005b; Vojta et al., 2001). A large population-based study (Jansen et al., 2013) assessing the QoL of young adults across mood episodes found higher impairment in quality of life during mood episodes as compared to the general population. They also found more impact on quality of life among the young people who were experiencing a mixed episode, followed by depression. Nevertheless, some studies suggest that these outcomes may be experienced even when they are euthymic (Henry et al., 2013; Kuszniir et al., 2000). Quality of life (QoL) has been defined in existing literature as a multidimensional concept that includes physical, emotional, social, and spiritual well-being (WHOQOL Group). It refers to a person's individual perception of physical, emotional, and social status (Dickerson, et al. 2011; Jing et al., 2018). It is mostly a subjective experience, as achieving a good level of QoL depends on how the individual perceives that he or she has reached a good level of satisfaction in those different domains.

Studies have focused on a wide range of sociodemographic and clinical variables to explain the reduced QoL in euthymic bipolar disorder (EBD) patients. For instance, the number of previous episodes has a significant impact on functioning and wellbeing, with worse effects being associated to depressive episodes (MacQueen et al., 2000; Zhang et al., 2006). This effect could be even worse in women (Altshuler et al., 2010; Robb et al., 1998), since they tend to have longer depressive periods than men.

Cognitive deficits have also been found associated to poorer QoL outcomes in EBD patients (Sánchez-Morla et al., 2009). This effect is more significant when aging is taken into account (Weisenbach et al., 2014). In fact, cognitive reserve is positively associated with higher levels of functioning and quality of life in different domains (Anaya et al., 2016).

Physical comorbidity has also been studied. Illnesses such as viral infections can affect EBD patients at a cognitive level, with subsequent impairment in functioning

and QoL (Gerber et al., 2012). Pre-diabetes and type 2 diabetes have also been found in a third of EBD patients, which could also affect their QoL (Leopold et al., 2016). In addition, disruption in circadian rhythms could lead to worse quality of life in these patients (Cudney et al., 2016). In terms of psychopathological comorbidity, disorders such as anxiety (Albert et al., 2008; Maina et al., 2007; Simon et al., 2004), attention deficit hyperactivity disorder (Koc & Kesebir, 2014; Sentissi et al., 2008) have also been found associated with less time in euthymia and lower outcomes in functioning and QoL. Moreover, having a history of suicide attempts is also associated with worse QoL (de Abreu et al., 2012).

Other variables, such as high impulsivity (Kim et al., 2013) and early adverse experiences in childhood (Erten et al., 2014) have been shown to negatively affect the prognosis and QoL outcomes. In contrast, factors, such as religiosity, when used as a coping mechanism (Stroppa et al., 2018) are associated to better QoL and prognosis.

In terms of clinical practice, rather than focusing on symptoms as a target for treatments, QoL should be considered in the assessment and intervention in BD. In fact, there has been a strong interest in measuring QoL outcomes, and different scales have been developed to assess distress and QoL in EBD patients (Hayhurst et al., 2006; Michalak & Murray, 2010; Pascual-Sánchez et al., 2018), in order to achieve a better comprehension of how those patients perceive their life. EBD patients with high acceptance of the treatment, could have good life satisfaction, regardless the type of stabilizer used (Quante et al., 2010). Psychoeducation, as part of combined treatment in EBD patients can also improve QoL (Faridhosseini et al., 2017; Husain et al., 2017; Michalak et al., 2005b). Furthermore, cognitive remediation therapy can not only improve cognitive functions and even prevent mood symptoms but can also promote and improve QoL outcomes (Strawbridge et al., 2016). In sum, achieving a better understanding of predictors of QoL will allow them to be taken into account for facilitating treatment and improving prognosis (Robb et al., 1997).

Based on the aforementioned, there is evidence that euthymic patients with BD are influenced by different variables which may impact their quality of life. Yet, there is no systematic review and meta-analysis to clarify what variables are relevant, how its impact differs from general population, and what are the most utilized measures to assess QoL in this population.

Thus, the aim of the current study is to conduct a systematic review and meta-analysis of cross-sectional studies with matched cases and controls on QoL in EBD adult patients (EBD). Specifically, the aims are: (1) To examine differences in total scores of QoL outcomes between EBD adult patients and healthy controls (both screened individuals and individuals recruited from the general population); (2) To determine which QoL measures are included in the studies and how QoL is conceptualized; (3) To identify potential moderators of QoL in EBD patients, such as sociodemographic and clinical variables.

2. METHODS

The protocol of the current systematic review is available through International Prospective Register of Systematic Reviews (PROSPERO) (<https://www.crd.york.ac.uk/prospero/>); registration number: CRD42018108873.

2.1. Eligibility criteria

A modified version of the PICOS approach for observational cross-sectional studies with matched cases and controls, as defined in the PRISMA guidelines (Shamseer et al., 2015) was used. Criteria for inclusion of the studies were the following.

- a) *Characteristics of participants.* Studies were included if they were conducted on euthymic adult patients with a primary diagnosis of Bipolar disorder, and if the diagnosis was made through a semi-structured interview based on standardized diagnostic criteria, such as the Structured Clinical Interview for DSM-IV, or if the diagnosis method was detailed. Euthymia state assessment had to also be specified. Studies were included if they used adult samples, and if samples were over 10 subjects. Studies where all the patients have another comorbidity were excluded. However, studies where some of the patients have some comorbid disorders were included.
- b) *Characteristics of outcomes.* Studies were included if they used outcome measures of QOL with known psychometric properties, either self-report questionnaires or interviews.
- c) *Characteristics of comparators.* Studies were included if they used healthy control groups consisting of screened participants who have not reported any psychiatric disorder during a clinical interview or unscreened participants, such as undergraduates and individuals recruited from the general population.
- d) *Characteristics of design.* Studies were included if they used an observational cross-sectional research design with matched cases and controls, where groups of patients with a primary BD diagnosis and euthymic state were compared with healthy control groups on QoL outcomes. Studies without healthy control group were excluded from the meta-analysis.

2.2. Information sources and search strategy

Sources of information included the following databases: CIHAHL, MedLine, PsycINFO, PubMed, The Cochrane Central Register of Controlled Trials, Web of Science, and EMBASE. Neither date nor language restrictions were applied.

Searches were made using the following keywords or their combination in PubMed, accessed on 6 August 2018: ('bipolar disorder':ab,ti OR 'manic-depressive disorder':ab,ti OR 'bipolar affective disorder':ab,ti OR 'hypomania or mania':ab,ti) AND 'quality of life':ab,ti AND 'euthymic':ab,ti [Title/Abstract]

2.3. Data collection process

Two authors (AP and CJ) conducted a two-step literature search, in order to assess the articles on eligibility criteria. During the first stage, studies were examined with regard to inclusion criteria after the reading the title and the abstract. During this stage, studies were retained when there was no agreement on inclusion between the reviewers. During the second stage, the remaining studies were assessed on

eligibility criteria after reading the full-text. After data collection and extraction (during which the authors were blind to each other's results), the appointed authors compared their results to reach a final consensus based on consensual inclusion and exclusion criteria. Potential discrepancy in the judgement were addressed during meetings with another independent reviewer (JM) with the aim to obtain a shared pool of included studies for the meta-analysis.

After these stages, data were collected on the following characteristics: participants, outcomes and study design. Specifically, the recorded variables for each article included were: author(s), year of publication, study design, sample size, age and gender, diagnosis criteria, comorbidities, euthymic time required to be enroll in the study, QoL measure, QoL outcomes.

2.4. Risk of bias in individual studies

Potential major confounding biases in the studies were identified at the study level, focusing on the following: measurement/diagnostic bias, lack of accurate operational definitions or measures for "quality of life", confounding bias (e.g. lack of stratification and multivariate control for specific sociodemographic or clinical variables), information bias (e.g. role of funding sources that may lead to publication bias), unrepresentativeness or heterogeneity of the sample or lack of a healthy control group.

2.5. Quality assesment

Evaluated data were handled and compared by two independent authors (AP and CJ) using the checklist developed by Berra et al. (2008) It provides a 27-item checklist appraising a range of methodological features of the study, such as the objective definition, the sample size, the recruitment methods, the reliability of the methodological definitions, the comparability between groups, statistical analysis and results, and the implications and overall generalizability of the results. Disagreement between the independent raters was resolved by consensus among them.

2.6. Moderators coding

When inconsistency analyses indicated large and significant heterogeneity between the effect sizes, the role of moderators was investigated. Two independent reviewers (AP and CJ) coded the moderators, extracted the data from primary studies and inserted them in an excel worksheet. Each potential discrepancy was discussed and resolved with a third reviewer (JM). The following variables were coded as moderators: (1) mean age of the sample; (2) gender of the sample (coded as percentage of female participants); (3) time since euthymic to enroll the study.

2.7. Meta-analysis

The meta-analysis was performed using Jamovi software (jamovi, 2018) and Open-Meta (Wallace et al., 2012).

2.7.1. Data extraction and summary measures

As we expected heterogeneity across the included studies, effect sizes were calculated using random-effect models. Data requested for the calculation of the effect sizes were extracted independently by two meta-analysts (AP and CJ). Effect sizes were estimated using a 95%-confidence interval and interpreted according to criteria suggested by Cohen (1988). Thus, effect sizes of 0.80 or more were assumed to be large, 0.50 moderate, and 0.20 small.

A global effect size was calculated as a mean effect size obtained by combining effect sizes related to different QoL measures. For those studies using QoL measures related to different QoL domains (e.g., social functioning and subjective well-being), a mean effect size was calculated for each study as a global QoL outcome. Subsequently, effect sizes were calculated separately for specific domains related to QoL.

2.7.2. Inconsistency analysis

In order to assess between-studies heterogeneity, two complementary indices: the I^2 index (Higgins et al., 2003), and the Q statistic (Lipsey & Wilson, 2001), respectively, were used. A value of approximating to zero suggests homogeneity, whereas values of 25–50%, 50–75% and 75–100% represent low, medium and large heterogeneity, respectively (Higgins et al., 2003).

2.7.3. Analysis of moderators

Given that inconsistency analysis suggested large heterogeneity, an analysis of the above-mentioned moderators was conducted using mixed model-ANOVA and weighted least squares meta regressions.

2.7.4. Publication bias

In order to investigate likelihood that effect sizes are subjected to a publication bias, the Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000), and the visual inspection of the funnel plot were used.

3. RESULTS

3.1 Selection and descriptive characteristics of the studies

The electronic search produced 137 records after duplicates were removed. Of those studies, 83 were excluded at title or at abstract, as they were focused on constructs not related to the aims of the current study. Thus, 66 studies were screened at full-text for inclusion. Of those studies, 11 studies were excluded as they did not use measures of QoL, and 33 were excluded as they did not use a cross-sectional research design with matched cases and controls. Therefore, 23

studies remained for the systematic review and meta-analysis. Next, another 6 studies were excluded as they did not report enough data to calculate effect sizes (e.g., mean or standard deviations of QoL), and the authors did not reply when they were contacted to request the necessary data. An overview of the study procedure is provided in a flow chart in Figure 1.

All the included studies had been published in peer-reviewed journals. Twelve studies compared EBD patients QoL outcomes with screened healthy participants as controls, while five studies used unscreened control participants recruited from the general population. Four studies were conducted in India, three studies in Portugal, three studies in China, two studies in Spain, one study in the United States, one study in Germany and the Netherlands, one study in Brazil, one in Denmark and one study in Korea. Total sample sizes ranged from 20 to 1250 participants. Publication date of the studies ranged from 2005 to 2018. Regarding instruments used for QoL outcome, eleven studies (Brissos et al., 2008a; Brissos et al., 2008b; Chand et al., 2004; Dias et al., 2008; Goossens et al., 2008; Lee et al., 2017; Miskowiak et al., 2016; Pattanayak et al., 2012; Singh et al., 2005; Studart et al., 2017; Xiang et al., 2014) used WHOQOL-BREF, three studies (Ng & Johnson, 2013; Xiao et al., 2016a; Xiao et al., 2016b) used QoL BD-SF, two studies (Costa et al., 2018; Sierra et al., 2005) used SF-36, and one study (Chand et al., 2004) used Q-LES-Q. For further details, the characteristics of the included studies in the meta-analysis are reported in Table 1.

Not only were QoL instruments different regarding their names, but they were also different concerning their factorial structure. In other words, despite having a common definition on the whole, QoL was conceptualized in different ways depending on the instrument used. Regarding the most common instruments used in analysed studies, while WHOQOL-BREF assesses four different domains (physical, psychological, social relationships and environment) (WHOQOL Group, 1998), the QoL.BD-SF assesses 12 domains (physical health, sleep, mood, cognitive, leisure, social, spirituality, finances, household, self-esteem, independence, and identity) (Michalak et al., 2010). The SF-36 assesses eight different domains (physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health, as well as two different indexes: physical component and mental component (Ware & Sherbourne, 1992; Ware, 2000). This measure is more focused on health-related quality of life, so it stresses physical issues rather than mental issues. Finally, the measure least utilized in selected studies, the Q-LES-Q, assesses eight dimensions (physical health, subjective feeling of well-being, leisure activity, work, household duties, school/course, social relationship, and general activity (Endicott et al., 1993). Although each measure is composed by different subscales, all of them assess physical, psychological and social issues.

3.2. Comparison on global QoL between EBD patients and healthy controls

The analysis included 17 studies. Results showed a large effect size ($d=-0.922$; $SE=0.316$; $95\%CI=-1.541$ to -0.303 ; $p=.004$), suggesting that EBD patients had significantly lower scores on perceived QoL compared with healthy controls. Evidence for large heterogeneity was found ($I^2=98$, $Q_{(16)}=608.831$, $p<.001$). The largest effect sizes were identified in studies with unscreened controls (Costa et al., 2018; Xiao et al., 2016a), although studies with screened controls also obtained

large effect size (Brissos et al., 2008a). These previously mentioned studies utilized different measures of QoL.

When it comes to compare these results by instruments, three subgroups were done: WHOQOL-BREF, SF-36 and QoL.BD-SF. Results showed a large effect size in all of them: 1) WHOQOL-BREF: $d=-0.510$; $SE=0.186$; $95\%CI=-0.875$ to -0.146 ; $p=.006$; 2) SF-36: $d=-2.187$; $SE=1.197$; $95\%CI=-4.533$ to 0.159 ; $p=.068$; 3. QoL.BD-SF: $d=-2.164$; $SE=1.091$; $95\%CI=-4.302$ to -0.027 ; $p=0.047$. The overall effect size taking together the three subgroups was also large ($d=-1.067$; $SE=0.303$; $95\%CI=-1.661$ to -0.473 ; $p<.001$), These results suggest that EBD patients had significantly lower scores on perceived QoL compared with healthy controls, regardless of the instrument used to assess it.

Taking together all the included studies, the forest plot with study difference means and confidence intervals comparing QoL outcomes with EBD patients and healthy controls is provided in Figure 2. An additional forest plot with the selected studies for the three subgroups of measures is provided in Figure 3.

Significant factors associated with QoL in EBD patients were reported in the selected studies. For example, both impaired objective and subjective cognitive function were associated to poorer QoL outcomes in EBD patients (Brissos et al., 2008b; Xiao et al., 2016b). Regarding illness awareness, although some differences in QoL, depending on the degree of insight, have been found, these differences were not statistically significant (Dias et al., 2008). However, one of the studies suggests that patients stabilized on lithium could have comparable levels of QoL to healthy controls (Chand et al., 2004). Regarding affective temperaments, anxious and cyclothymic temperaments seem to be associated with lower QoL, while hyperthymic temperament is associated with better outcomes (Costa et al., 2018). On the other hand, resilience has also been found as a predictor of QoL: the more resilient the person, the better the QoL (Lee et al., 2017). Other variables, such as daily stress (Chand et al., 2004) and rejection sensitivity (Ng et al., 2013), are associated with less QoL and could explain significant percentages of variance in terms of different QoL domains.

3.3. Quality of the results

Funnel plots did not present significant asymmetry. In addition, regression and rank correlation tests for funnel plot asymmetry were not significant either. In sum, the results obtained did not seem to be attributable to publication bias. Funnel plot of publication bias for comparison between EBD patients and healthy controls QoL outcomes is presented in Figure 4.

3.4. Analysis of moderators

Since significant heterogeneity was found across effect sizes of the studies on global QoL, age, gender and time since euthymic for BD patients were assessed as moderators. Neither age nor gender were significantly correlated to effect sizes. Time euthymic helps explain 15.62% of variability.

What is more, time since euthymia was correlated with effect sizes ($\beta=0.142$, $SE=0.077$, $95\% CI: -0.011$ to 0.294 , $p=0.049$), suggesting that participants with longer time since euthymia, have higher QoL scores. Meta-regression of this finding is provided in Figure 5.

Concerning control group, age and gender were also included as covariables. Only the age of control group was significant and explained 29.6% of variability. Age of control group was correlated with effect sizes ($\beta=-0.104$, $SE=0.0390$, 95% CI: -0.181 to -0.028, $p=0.008$), suggesting that older control group participants, have lower QoL scores.

4. DISCUSSION

Findings in this study suggest that, as expected, EBD patients have lower QoL than healthy controls. These findings are consistent with several matched case-control studies, in which lower scores in QoL were reported in EBD patients compared to healthy controls studies (Brissos et al., 2008a; Brissos et al., 2008b; Chand et al., 2004; Dias et al., 2008; Goossens et al., 2008; Lee et al., 2017; Ng et al., 2013; Pattanayak et al., Sierra et al., 2005; Studart et al., 2016; Xiao et al., 2016a; Xiao et al., 2016b) Nevertheless, some studies have found inconsistent results (Chand et al., 2004; Singh et al., 2005; Xiand et al., 2014), by showing no differences between both groups. Different explanations are given for these inconsistencies. Chand et al. (2004) explained that patients in their sample have achieved a relevant degree of stabilization, which would also be consistent with our results: the longer the euthymia period, the better the QoL. In turn, Singh et al. (2005) reported no differences between both groups in psychological and social domains, while worse QoL in physical domain and global QoL were obtained. The study by Goossens et al. (2008) reported no differences between both groups, as the global score showed that EBD patients and healthy controls could be comparable in terms of QoL. Yet, it is important to note that although they reported similar QoL in the psychological domain, the overall QoL, as well as the scores in physical and social domains, were lower. The authors claim that despite being euthymic, BD patients may present subthreshold symptoms that could have a negative impact on their QoL, and that could explain differences across the sample. Finally, Xiang et al. (2014) argued that there might be a consequence of sociocultural factors. In this sense, this study could overcome that limitation, as different cultures have been included in the meta-analysis.

Several measures have been utilized to assess QoL outcomes. Although more than a decade ago, different literature reviews (Leidy et al., 1998; Michalak et al., 2005a) showed that the MOS in its different versions: MOS-20 (Cooke et al., 1996), SF-36 (Ware, 2000), SF-12 (Rebollo, 2008; Pickard et al., 2005) was the most used instrument to assess QoL. We have identified that, in recent years, the WHOQOL-BREF (WHOQOL Group, 1998) has been the most used instrument to measure QoL in EBD patients, as it has been used in 11 out of the 17 selected studies. Only three studies (Ng et al., 2013; Xiao et al., 2016a; Xiao et al., 2016b) utilized an instrument specifically designed for BD patients, namely the QoL.BD-SF. Regarding differences in effect sizes in the studies, the results showed that the three aforementioned studies were part of the eight studies which reported more differences between both groups. This could be explained as an easier differentiation between groups while using a specific measure for BD. However, the WHOQOL-BREF, which was used in the majority of the studies, showed results in different directions, for the previously explanations given. Future research will clarify if recent developed

instruments (Michalak et al., 2010; Pascual-Sánchez et al., 2018; Xiao et al., 2016b) that assess QoL and related outcomes in BD, are more useful than general purpose QoL scales.

Even though current instruments are composed of different domains (Endicott et al., 1993; Michalak et al., 2010; Ware et al., 1992; WHOQOL Group, 1998), all of them claim to share a common conception of QoL, and to assess physical, psychological and social domains. It would be interesting to assess the adequacy of their content from clinicians' and patients' perspective, to plan interventions and to promote better adjustment and quality of life.

Regarding the analysis of potential moderators of QoL, previous studies have found inconsistent results in terms of the impact of gender and age. Some studies find that being female and older is associated to worse QoL outcome (Thomas et al., 2016), while other studies do not find differences in QoL based on age and gender (Sierra et al., 2005). In this study, findings suggest that neither age nor gender seem to be related to QoL outcomes in EBD patients. Yet, age was significantly associated with poorer QoL outcomes in control group. The pervasive impact of EBD patients could be overshadowing the impact of age in QoL. Further studies will help shed light on these results.

This study has some practical implications. The fact that EBD patients have lower QoL than healthy controls deserves strong attention from a clinical practice standpoint. First, it underscores the need to assess this multidimensional concept in BD, even when they are euthymic. Second, and in line with this, is the importance of helping these patients to reach the euthymic state and to keep it as long as possible. That is, EBD patients might reach a comparable level of QoL if a maintained state of euthymia is achieved, as the more time euthymic, the better the QoL. Third, multidimensional measures with a solid psychometric and conceptual foundation should be utilized when assessing QoL outcomes, for both clinical and research purposes.

4.1. Limitations

Even though this is the first systematic review and meta-analysis study analyzing quality of life in EBD patients, it has several limitations that should be noted. Firstly, although the main data bases which are more focused in the topic under study have been searched, the current study did not include documents from conference proceedings, and doctoral dissertations, so it is possible that some relevant studies could be missing. Second, the instruments included in the study were heterogeneous. Even though this limitation was overcome by using the global score means and effect sizes, as well as by performing separate analyses of effect sizes for the most common utilized measures, some separate analyses could not be performed due to the lack of enough studies with a specific measure (e.g. study by Gerber et al. 2012). Thirdly, as explained before, some studies included unselected controls, and it is not clear how they guaranteed that healthy controls were not psychiatric patients. This finding calls for better description of the

samples included in the studies, and also should be taken into account when interpreting the current findings. Finally, the role of other clinical moderators, such as occurrence of comorbid disorders, severity of the symptoms, predominant polarity, could not be included in the current study due to the lack of this information in most of the articles. It is advisable to include these variables in further studies to determine their impact on prognosis and QoL outcomes.

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Table 1. Descriptive characteristics of the cross-sectional studies with matched cases and controls included in the meta-analysis (n=17).

Study name	Publication date	Country	Sample age and gender*	Recruitment strategies for EBD patients	Recruitment strategies of controls	Design	Screening of controls	n	Instruments used to make BD diagnoses	QoL outcomes
Brissos et al._1	2008	Portugal	Adults (17-63 years) Gender: BD=60; Controls=68	Patients were consecutively recruited from the Department of Psychiatry of Santarém's Hospital, and the Association of Bipolar and Depressive	Controls were recruited from patients' acquaintances and hospital personnel	Cross-sectional case-control	Screened controls	EBD patients (n=55) Controls (n=50)	DSM-IV	WHOQOL-BREF

				Patients						
Brissos et al._2	2008	Portugal	Adults (18-63 years) Gender: BD=50; Controls=82.60	Patients were consecutively recruited from the Department of Psychiatry of Santarém's Hospital, and from private practice.	Controls were recruited from patient's spouses or hospital personnel.	Cross-sectional case-control	Screened controls	EBD patients (n=30) Controls (n=23)	DSM-IV	WHOQOL-BREF
Chand et al._1	2004	India	Adults (20-50 years)	Patients were consecutively recruited from the	The healthy controls were taken from among the employees of the Panjab	Cross-sectional case-control	Screened controls	EBD patients (n=50) Controls	ICD-10	WHOQOL-BREF

				outpatient services of the Department of Psychiatry, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.	University located near PGIMER.			(n=20)		
Chand et al._2	2004	India	Adults (20-50 years)	Patients were consecutively recruited from the outpatient services of the	The healthy controls were taken from among the employees of the Panjab University located near	Cross-section al case-control	Screened controls	EBD patients (n=50)	ICD-10	Q-LES-Q
								Controls (n=20)		

				Department of Psychiatry, Postgraduate	PGIMER.					
				Institute of Medical Education and Research						
				(PGIMER), Chandigarh, India.						
Costa et al.	2018	Spain	Adults (Mean age: BD=46.3±12.4; Controls: 44.5±11.3) Gender: BD=65; Controls=54.7	Patients were consecutively recruited from Outpatient Mental Health Centres at four participating Spanish	Group of healthy volunteers. No more details reported.	Cross-sectional case-control	Unscreened controls (they did not clarify how they confirmed that the controls did not have a psychiatric disorder)	EBD patients (n=180)	DSM-IV-TR (SCID-I)	SF-36
								Control s (n=95)		

				hospitals.						
Dias et al.	2008	Portugal	Adults (17-63) Gender: BD=62.86; Controls=68	Patients were recruited from the Department of Psychiatry of Santarém's Hospital, Júlio de Matos' Psychiatric Hospital, and from the Association of Bipolar and Depressive Patients	Controls were recruited from patients' acquaintances and hospital Personnel.	Cross-sectional case-control	Screened controls	EBD patients (n=70) Controls (n=50)	DSM-IV	WHOQOL-BREF
Goossen	2008	Deutschland &	Adults	Patients were	Controls were	Cross-section	Unscreened controls	EBD patient	DSM-IV-	WHOQOL

s et al.	Netherlands	(Mean age BD=50.06)	recruited from the outpatient clinic where they were being treated.	recruited from individuals visiting their general practitioner in the Netherlands and general Dutch population who determined the validity of the SCL-90. Dutch version in the general population.	al case-control	(data were collected from the WHOQOL-Bref data of 630 adults from a general population in the Netherlands).	s (n=108)	Control s (n=630)	TR	L-BREF
Lee et al. 2017	Korea	Adults (Mean age: BD=44.2±38.12;	Patients were	Controls were	Cross-section	Screened	EBD patient	DSM-IV-	WHOQO	

Controls=47.06±38.38)	recruited from an ongoing long-term follow-up project investigating the psychological characteristics of mood disorder patients	recruited from the Health Promotion Center at the Gyeongsang National University Medical Center, where they went for a regular health check-up.	al case-control	controls	s (n=68)	TR	L-BREF
Gender: BD=38.12; Controls=38.38					Controls (n=68)		
	in the psychiatric outpatient clinic at Gyeongsang National University Hospital (GNUH) in South Korea.						

Miskowiak et al.	2016	Denmark	Adults (18-65 years) Gender: BD=40; Controls=43	Participants were recruited from the outpatient clinic Copenhagen Clinic for Affective Disorders, Psychiatric Centre Copenhagen	Controls were recruited consecutively from the blood bank at Copenhagen University Hospital, Rigshospitalet.	Cross-sectional case-control	Screened controls	EBD patients (n=109) Controls (n=110)	ICD-10	WHOQOL-BREF
Ng et al.	2013	USA	Adults (18-60 years) Gender: BD=35.21; Controls=32.07	Participants were recruited from the San Francisco Bay Area via online advertisement	Control participants were recruited through community flyers and web-based	Cross-sectional case-control	Screened controls	EBD patients (n=53) Controls (n=44)	DSM-IV (SCID)	QoL.BD-SF

				nts, flyers forwarded to local mental health practitioners, and referrals from treatment centers in the communit							
Pattanayak et al.	2012	India	Adults (18-55 years) Gender: BD=36.7; Controls=40	Patients were consecutively recruited from Outpatient Clinic, Department of Psychiatry, All India Institute of	Controls were recruited after proper screening from amongst the non-related attendants of patients, consenting staff	Cross-section al case-control	Screened controls	EBD patients (n=30) Controls (n=20)	DSM-IV (SCID-CV)	WHOQOL-BREF	

				Medical Sciences (AIIMS), New Delhi, India.	members, hospital employees and persons from the community.					
Sierra et al.	2005	Spain	Adults (Mean age: BD=45.14±40; Controls=40±33.25) Gender: BD=40; Controls=33.25	Patients were consecutively recruited from a hospital unit specifically for bipolar patients in the city of Valencia.	Control data came from the validation of the Spanish version of SF-36 which used a representative stratified random sample of 1250 subjects (623 males and 627females) aged 18–64 years drawn from a city's	Cross-sectional case-control	Unscreened controls (Data were collected from mean values in SF-36 Spanish validation. The subjects there were drawn from a city's voting registry).	EBD patients (n=50)	DSM-IV	SF-36

Singh et al.	2005	India	Adults (20-60 years) Gender: BD=37.5; Controls=50	Patients were recruited from the Department of Psychiatry and the Drug De-addiction and Treatment Centre, Nehru Hospital, PGIMER, Chandigarh, India.	voting registry. No details reported.	Cross-sectional case-control	Unscreened controls (they did not clarify how they confirmed that the controls did not have a psychiatric disorder)	EBD patients (n=40) Controls (n=40)	ICD-10	WHOQOL-BREF
Stuart et al.	2016	Brazil	Adults (Mean age: BD=47.5±75.5;	Participants were	The healthy control group	Cross-sectional case-	Screened controls.	EBD patients	DSM-IV (SCID-I)	WHOQOL-BREF

			Controls=40±71) Gender: BD=75.5; Controls=71	recruited from an outpatient clinic, which also has a research center, the Mood and Anxiety Program, located at a teaching hospital at Federal University of Bahia-Brazil.	comprised volunteers who were from the same community and were being treated for other medical conditions at the outpatient center.	control		(n=119) Controls (n=63)		
Xiang et al.	2014	China	Adults (16-50 years)	Patients were consecutively recruited from the Outpatient Department	Controls were recruited from the community by advertise	Cross-sectional case-control	Screened controls.	EBD patients (n=47) Controls (n=47)	DSM-IV	WHOQOL-BREF

				of a	nts.					
				university-affiliated psychiatric hospital in Beijing, China.						
Xiao et al._1	2016	China	Adults (16-60 years) Gender: BD=52; Controls=55.7	Patients were consecutively recruited from the psychiatric service of the Second Xiangya Hospital, Changsha	Controls were recruited from staff members (nurses, care workers, cleaner) of the Second Xiangya Hospital and nearby residents.	Cross-sectional case-control	Screened controls.	EBD patients (n=100) Controls (n=115)	DSM-5	QoL.BD-SF
Xiao et al._2	2016	China	Adults (Mean age: BD=51.5±26.4;	Patients were	Controls were recruited	Cross-sectional case-	Unscreened controls (healthy	EBD patients	DSM-5	QoL.BD-SF

<p>Controls=52.3±28)</p> <p>Gender: BD=26.4; Controls=28</p>	<p>consecutively recruited from the psychiatric service of the Second Xiangya Hospital, Changsha</p>	<p>from the general population within the catchment area of the Second Xiangya hospital</p>	<p>control</p>	<p>controls were recruited from the general population and they had no first-degree relatives with BD or other psychiatric disorders and were without physical problems. However, they did not clarify how they did it, if it was by self-report or in other systematic</p>	<p>(n=101)</p> <p>Controls (n=130)</p>
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ways).

*gender is expressed as the percentage of women in EBD patients and control groups

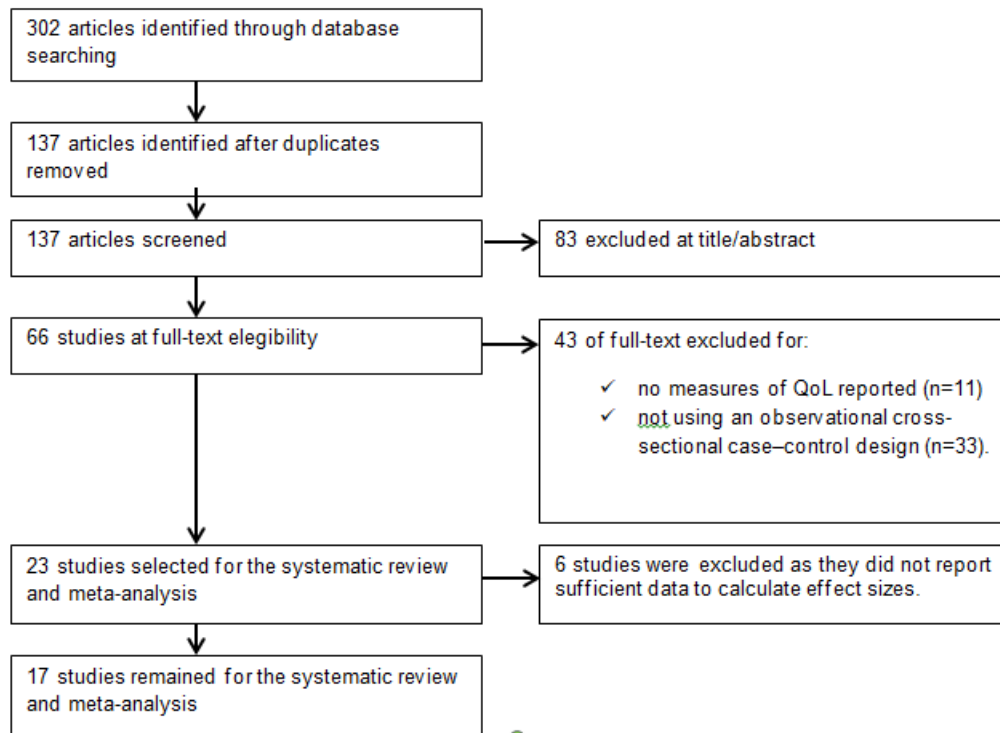


Figure 1. PRISMA flow chart of the study selection.

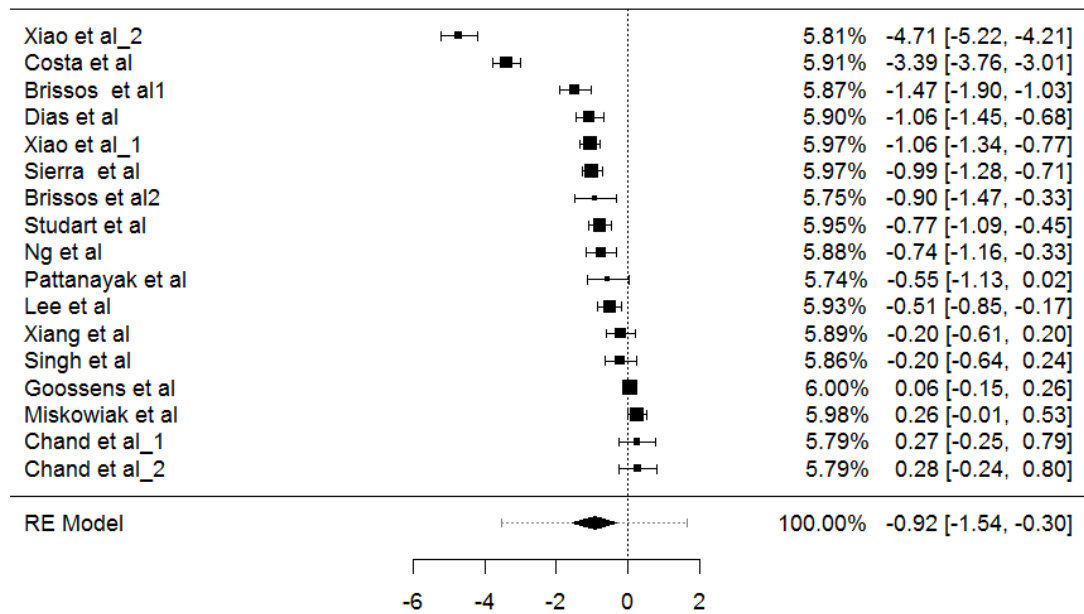


Figure 2. Forest plot of the comparison between EBD patients and healthy controls on QoL outcomes (studies sorted by observed effect sizes).

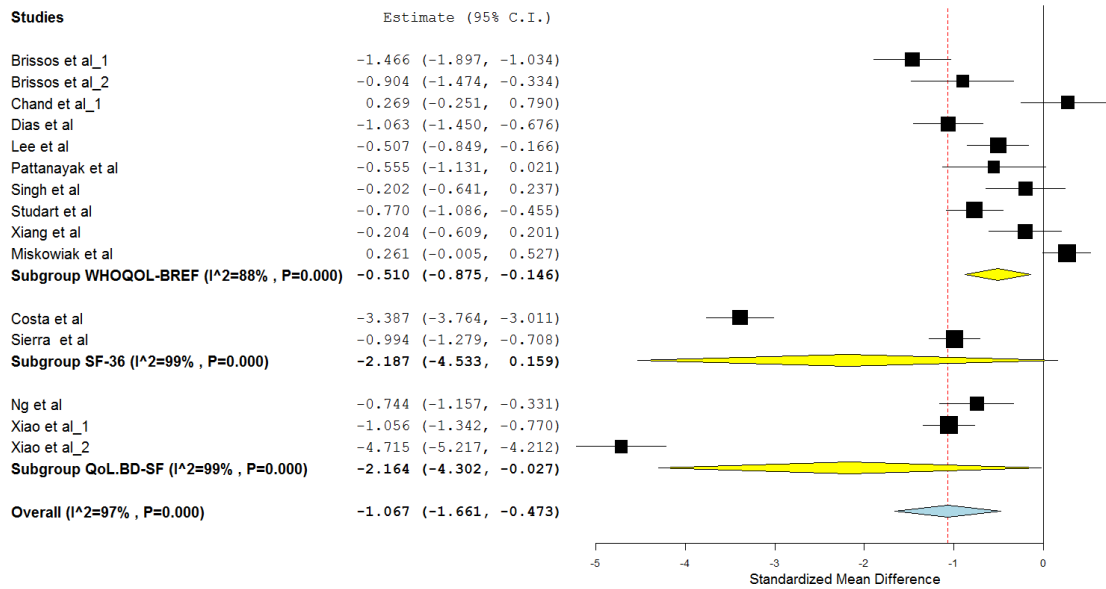


Figure 3. Forest plot of the comparison, by instrument to measure QoL subgroups, between EBD patients and healthy controls on QoL outcomes.

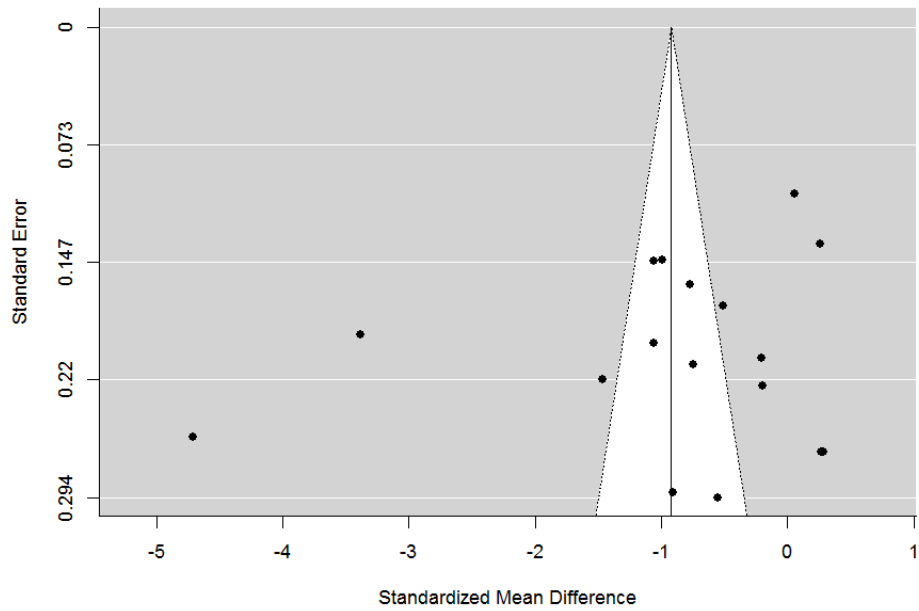


Figure 4. Funnel plot of publication bias for the comparison between EBD patients and healthy controls on QoL outcomes

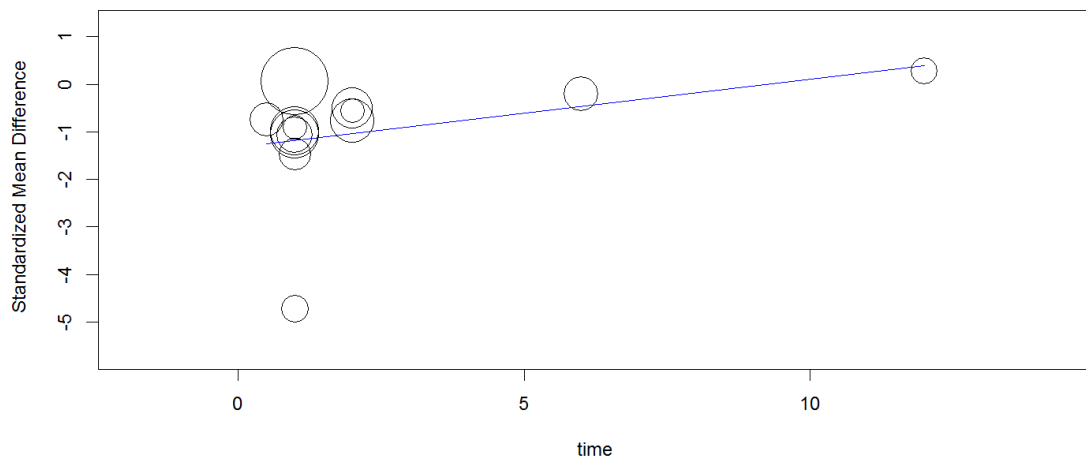


Figure 5. Meta-regression of QoL outcome based on time (in months) since euthymia