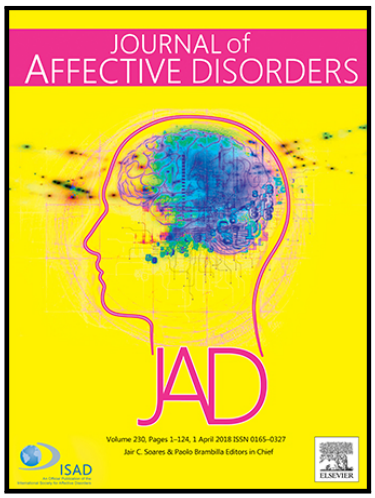

Violent criminal behavior in the context of bipolar disorder: Systematic review and meta-analysis

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Highlights

1. Even though one every fourteen patients suffering from bipolar disorder reported violent criminal behavior, the association with violent criminality was not significant in comparison with the general population.

2. The chance of committing violent criminal behavior was smaller in patients with bipolar disorder than in those suffering from psychotic disorders but higher in comparison with patients with depressive disorders.

3. In meta-regression analyses, no significant moderators emerged. The identification of potential moderators of the association between bipolar disorder and violence should be the focus of further research.

Violent criminal behavior in the context of bipolar disorder: Systematic review and meta-analysis

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Declaration of interest form

Dr. Norma Verdolini is funded by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through a "Río Hortega" contract (CM17/00258) and reports no competing interests.

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Prof. Alfonso Tortorella reports no competing interests.

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Abstract

Background: Despite the potential importance of understanding violent criminal behavior (VCB) in individuals suffering from bipolar disorder (BD), previous findings are conflicting. The aims of the present study are to clarify the association of VCB and BD in comparison to general population and other psychiatric conditions.

Methods: A systematic review of literature from January 1st, 1980 through January 16th, 2017 from 3 electronic databases (MEDLINE/PubMed, EMBASE and PsycInfo), following the PRISMA and the MOOSE statements. Original peer-reviewed studies reporting data on VCB in BD were included. A random-effects meta-analysis was performed. Potential sources of heterogeneity were examined through subgroup and meta-regression analyses. The protocol was registered in PROSPERO, CRD42017054070.

Results: Twelve studies providing data from 58,475 BD participants. The prevalence of VCB in BD was 7.1% (95%CI=3.0?16.5%; k=4). The association of BD and VCB compared to general population was not significant (OR=2.784; 95% CI, 0.687?11.287, P=.152). The association was significant only in cross-sectional studies, in studies in which VCB was assessed through self-reported measures, and in studies conducted in the USA. BD was more likely to be associated with VCB when BD patients were compared to controls with depressive disorders, whilst it was found to be less associated with VCB when BD was compared to psychotic disorders.

Limitations: 1. the methodological heterogeneity across the included studies. 2. causal inferences were precluded by the inclusion of cross-sectional studies.

Conclusions: These findings might provide a more balance portrait of the association between BD and VCB to clinicians, law enforcement and general public.

Key words: bipolar disorder, violence, systematic review, meta-analysis, moderators

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1. Introduction

Violence is an overt destructive behavior with the intention to inflict harm (Látalová, 2009) resulting in injury, death or psychological harm ("World Health Organization. Health topics-Violence," 2017). Violence is the basis of violent criminal behavior (VCB), with deleterious impact on individuals and societies (Krug et al., 2002; Látalová, 2009). Mass media often emphasized mental illness as the leading cause of violence in mass-shootings and terrorist attacks, and cinematographic depictions of the mentally ill are often sensationalized, contributing to stigma (Teplin, 1984; Varshney et al., 2016).

Risk factors for VCB include male sex, young age (Sher and Rice, 2015), parental criminality (Thapar, 2015), prior VCB (Johnson et al., 2016), childhood maltreatment (Jaffee et al., 2004) and victimization (Johnson et al., 2016). Psychiatric disorders have been studied as possible risk factors for VCB, with conflicting results (Johnson et al., 2016; Lysell et al., 2014; Rihmer et al., 2010).

Previous reviews (Fazel et al., 2010; Fovet et al., 2015; Látalová, 2009) attempted to summarize evidence on the association between violence and BD, but failed to include possible legal outcomes (Látalová, 2009), presented unstandardized methods or broader definitions of violence including aggressiveness (Fovet et al., 2015), provided a quantitative analysis limited to few studies (Fazel et al., 2010) or considered BD with other psychoses, providing mixed-samples results (Fazel et al., 2009; Witt et al., 2013).

Abbreviations: BD=bipolar disorder; BD-I=bipolar disorder, type I; CI=confidence interval; DSM=Diagnostic and Statistical Manual of Mental Disorders; ECA=Epidemiological Catchment Area study; ES=effect size; ICD=International Classification of Disease; MDD=major depressive disorder; MOOSE=Meta-analyses Of Observational Studies in Epidemiology; NCS=National Comorbidity Survey; NESARC=National Epidemiologic Survey on Alcohol and Related Conditions; NOS=Newcastle-Ottawa Scale; OR=odds ratio; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SUD= drug abuse/dependence disorders**;** UCR=Uniform Crime Reporting; USA=United States of America; VCB=violent criminal behavior

1.1 Aims of the study

The present systematic review and meta-analysis aimed at: 1. Assessing the prevalence of VCB in BD; 2. Establishing the relative risk for VCB in BD compared to the general population and other psychiatric conditions; 3. Evaluating possible risk or protective factors for increased VCB in patients with BD.

2. Methods

This systematic review and meta-analysis adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) and the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) (Stroup et al., 2000) statements. The protocol was prospectively registered in PROSPERO (CRD42017054070). Two investigators (NV and IP) independently performed the literature search, title/abstract screening, full-text review, data extraction and methodological quality assessment. A third investigator was consulted whenever a consensus could not be achieved (AM).

2.1 Data Sources and Searches

The MEDLINE/PubMed, EMBASE and PsycInfo databases were searched from January 1st, 1980 through January 16th, 2017, augmented through the hand-searching of the reference lists of included articles. Detailed search strings are provided in the supplementary material that accompanies the online version of this article (Appendix S1).

2.2 Study Selection

The following inclusion criteria were applied: original peer-reviewed articles published in any language; observational studies; > 95.0% of sample participants aged ≥ 18 years; BD diagnosis established according to International Classification of Disease (World Health Organization, 1992) and/or Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association., 2013) criteria; studies had to provide data on the prevalence or the association between VCB and BD.

A crime is violent when a victim is harmed by or threatened with violence ("National Institute of Justice," 2017). Its definition may vary depending on national legal definitions according to: type of acts included (e.g. sexual crimes excluded in New Zealand) ("New Zealand Recorded Crime Tables," 2017), intensity of the VCB (e.g. minor violent acts excluded in France) ("European Sourcebook of Crime and Criminal Justice Statistics – 2010," 2010), age of the offender (overall in Europe, limiting comparison even between member Countries) (Aebi et al., 2014). In the United States of America (USA), two main crime databases report on VCB. In the Federal Bureau of Investigation's Uniform Crime Reporting (UCR) VCB are defined as those offenses involving force or threat of force, namely murder and nonnegligent manslaughter, legacy and revised rape, robbery and aggravated assault ("Uniform Crime Reporting Statistics," 2017). The Bureau of Justice Statistics's National Crime Victimization Survey (NCVS) provide measures for non-fatal violence reporting on rape and sexual assault, robbery, and aggravated and simple assault ("Bureau of Justice Statistics," 2017).

In the present study, the following working definition of VCB was used: Any record of conviction, involvement in the judicial system or charge for violent crime, namely homicide, attempted homicide, assault, robbery, arson, threat or intimidation, and all sexual offenses (Webb et al., 2014). Self-reported VCB assessed in large-scale

epidemiological surveys, namely the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Pulay et al., 2008), NCS (Corrigan and Watson, 2005), and the ECA (Swanson et al., 1990), were also deemed eligible.

The following exclusion criteria were applied: animal studies; meeting abstracts; case reports; letters to the editor; > 5.0% of the study population < 18 years; studies not providing the prevalence or association of VCB in BD; studies providing the prevalence or association in BD with non-VCB only; studies not providing comparison with general population; intervention studies.

2.3 Data extraction

A standardized extraction platform was developed in Microsoft Access 2010 ("Microsoft Access 2010, Microsoft Corporation, Redmond, Washington, USA," n.d.). For each study, we extracted the prevalence of VCB in participants with BD (see Appendix S2 for the complete list). The full contingency tables to estimate crude ORs were also extracted, considering the general population controls without psychiatric disorders and controls with any psychiatric disorder other than BD (including severe mental illness, depression, anxiety disorders, psychotic disorders, alcohol or drug abuse disorders, or personality disorders). The type of assessment (record-based vs. self-report) was also coded.

2.4 Methodological Quality Assessment

The methodological quality of included studies was rated through the Newcastle-Ottawa Scale [NOS] (Stang, 2010). An adapted version was used for cross-sectional studies (Herzog et al., 2013). For purposes of normalization, the % of criteria

met was considered as a proxy of the overall methodological quality. The inter-rater reliability of independent reviewers was high (92.8%).

2.5 Statistical Analysis

A random-effects meta-analysis estimated the prevalence of VCB in BD. The effect size (ES) measure used to estimate the prevalence of criminal behavior in BD was the proportion, but all analyses were conducted by converting proportions into logits. Simple proportions could underestimate the size of the 95% CI across the mean proportion, and could also overestimate the degree of heterogeneity across studies. Conversion into logits could circumvent these methodological shortcomings (Lipsey and Wilson, 2000).

The ES for the association measures were estimated as OR and 95% CI. Separate estimates were calculated considering the general population controls without psychiatric disorders or controls with any psychiatric disorder other than BD. Heterogeneity across studies was assessed with the Cochran's Q test (Bowden et al., 2011). Inconsistency across studies was estimated with the I^2 metric (Higgins et al., 2003). Evidence of publication bias was assessed with funnel plot graph and the Egger's regression test (Egger et al., 1997). When evidence of publication bias was observed, ES estimates were adjusted with the trim-and-fill procedure (Fazel et al., 2007).

Potential sources of heterogeneity were explored with subgroup and meta-regression analyses. The specific subgroup analyses considered a priori were reported in the Appendix S3. Meta-regression analyses were conducted when data from at least five independent datasets were available.

All analyses were conducted in Stata MP software version 14.0 ("Stata MP software version 14.0, Stata Corp, College Station, TX, USA," n.d.) using the metan package. Statistical significance was considered at an alpha level of .05.

3. Results

The database search generated 1,031 hits, 46 articles were identified after searching the references of included articles. After duplicates removal, the title/abstracts of 773 references were screened for eligibility; of those, 558 were excluded. Full-texts of 192 references were scrutinized in detail for eligibility, with 180 excluded (see Table S1 in the supplementary material for reasons), and 12 references included for systematic review and meta-analysis (see flowchart in Figure 1, characteristics in Table S2). Overall, data from 9,020,778 participants (58,475 patients with BD, 8,962,303 general population controls and 231,587 patients with any psychiatric disorder) were included. Participants presenting any VCB were 91,387. Studies have followed cross-sectional (k=4), case-control (k=3), or prospective (k = 5) designs. The mean % of criteria met in the NOS scale across studies was 82.1 (SD=17.3) (Table S3). A half of the included studies had a poor methodological quality. Nine out of twelve of the included studies used representative samples and only four specified in the methodology a diagnostic assessment with a structured interview.

3.1 Violent criminal behavior in bipolar disorder

The prevalence of VCB in individuals with BD was 7.1% (95% CI, 3.0–16.5; k=4; Table 1). Heterogeneity was very large (I^2=96.9%) and significant (Q=97.00, P<.001). No evidence of publication bias was observed (P=.458; Egger's test) (funnel plot in Figure S1).

The association of BD and VCB compared to general population was significant (OR=5.206; 95% CI, 1.338–20.251; k=12; P<.001; Table 2, Figure 2A). The comparator group in the study by Fazel et al. (Fazel et al., 2007) did not have any VCB events, therefore the OR was large, possibly biasing further analysis. In sensitivity analyses, where this study was not included in main analysis, the association was no longer significant (OR=2.784; 95% CI, 0.687–11.287, P=.152; Table 2, Figure 2B). Between-study heterogeneity was very large (I^2=99.9%) and significant (Q=8,090.26, P<.001, df=11). No evidence of publication bias was verified (P=.759; Egger's test) (funnel plot in Figure S2). Main subgroup and meta-regression analyses were conducted without the aforementioned study by Fazel et al. (Fazel et al., 2007). The association between BD and VCB was significant only in cross-sectional (k=4) studies (Table 2, Figure 2B), in studies in which VCB was assessed through self-reported measures, and in studies conducted in the USA (Table 2). In meta-regression analyses, no significant moderators emerged (Table 2).

The association between BD and VCB compared to controls with any psychiatric disorder was not significant (OR=0.783; 95% CI, 0.438–1.398; k=9; P=.407; Table 3, Figure 3). Between-study heterogeneity was very large (I^2=98.1%) and significant (Q=429.35, P<.001, df=8). No evidence of publication bias was verified (P=.559; Egger's test) (funnel plot in Figure S4). The association between BD and VCB was significant only in cross-sectional (k=3) or case-control studies (k=3) (Table 3, Figure 3). The likelihood to present VCB was smaller for subjects with BD than for controls with any psychiatric disorder in case-control studies, (OR=0.493), whilst it was increased in cross-sectional studies (OR=1.285). The chance of VCB in BD was

significantly lower in studies where VCB was assessed from records or in studies conducted in European Countries (Table 3). Chance was increased in studies conducted in the USA or using self-report to assess VCB. In meta-regression analyses, no significant moderators emerged (Table 3).

Seven studies investigated VCB in BD patients compared to controls with major depressive disorder (MDD) (N=141,345), finding a significant association (OR=2.313; 95% CI, 1.721–3.110; k=7; P<.001; Figure S5 and Table S5). Heterogeneity was large (I^2=59.3%) and significant (Q=14.76, P=.022, df=6). Egger's test (P=.035) and funnel plot suggest publication bias (Figure S6). In subgroup analyses, the association was significant and without heterogeneity in studies that used a self-report for VCB, cross-sectional design or were conducted in the USA (Table S5). No moderators were significant in meta-regression analyses (Table S6).

Eight studies investigated VCB in BD patients compared to controls with psychotic disorders (N=55,285). Individuals suffering from BD had a smaller chance of VCB (OR=0.498; 95% CI, 0.329–0.751; k=8; P=.001; Figure S7, Table S5). Heterogeneity was very large (I^2=79.4%) and significant (Q=33.93, P<.001, df=7). No evidence of publication bias was observed (P =.802; Egger's test) (funnel plot in Figure S8). Subgroup analyses showed that the association was maintained in studies using a record-based assessment for VCB, case-control design or conducted in the USA (Table S5). No moderators were significant in meta-regression analyses (Table S6).

Five studies investigated VCB in BD patients compared to controls with anxiety (N=11,391). The association was not significant (OR=1.771; 95% CI,

0.978–3.207; k=5; P =.059; Figure S9 and Table S5). Heterogeneity was large (I^2=4.7%) and significant (Q=15.78, P=.003, df=4). No evidence of publication bias was observed (P=.290; Egger's test) (funnel plot in Figure S10). Subgroup analyses showed a significant association (OR=2.628) for 3 studies that used cross-sectional design, a self-report instrument and were conducted in the USA. No moderators emerged in meta-regression analyses.

Five studies investigated VCB in BD patients compared to controls with alcohol abuse/dependence disorders (N=13,572). The association was not significant (OR=0.454; 95% CI, 0.093–2.213; k=5; P=.328; Figure S11, Table S5). Heterogeneity was very large (I^2=97.1%) and significant (Q=138.17, P<.001, df=4). No evidence of publication bias was observed (P =.139; Egger's test) (funnel plot in Figure S12).

Six studies investigated VCB in BD patients compared to controls with drug abuse/dependence disorders (SUD) (N=12,668). The association was not significant (OR=0.980; 95% CI, 0.609–1.576; k=6; P=.933; Figure S13, Table S5). Heterogeneity was very large (I^2=87.7%) and significant (Q=40.741, P<.001, df=5). No evidence of publication bias was observed (P =.516; Egger's test) (funnel plot in Figure S14).

Only two studies investigated VCB in BD patients compared to controls with personality disorders (N=5,764). The association was not significant (OR=0.388; 95% CI, 0.022–6.742; k=2; P=.516), and heterogeneity was very large (I^2=98.0%) and significant (Q=50.68, P< .001, df=1).

4. Discussion

To the best of our knowledge, this is the first meta-analysis providing a comprehensive quantitative assessment of VCB and its components in individuals with BD.

The prevalence of VCB in BD individuals was lower than previous epidemiological studies, reporting estimates from 11% (Swanson et al., 1990) up to 25.34% (Pulay et al., 2008).

BD was not significantly associated with VCB compared to general population controls or to patients with any psychiatric disorder. In both cases, a significant association between BD and VCB emerged when VCB was not based on criminal records but assessed from self-report and in cross-sectional surveys or conducted in the USA. This could be explained with the quite broad definition of self-reported VCB provided in the three USA surveys (Corrigan and Watson, 2005; Pulay et al., 2008; Swanson et al., 1990) deemed acceptable for inclusion in the present meta-analysis. However, the estimated prevalence of VCB in the general population in these surveys (from 0.66% (Pulay et al., 2008) to 2.05% (Swanson et al., 1990)) is lower than the prevalence reported in the included record-based studies (from 0.8% (Webb et al., 2014) to 8.9% (Daff and Thomas, 2014)). Self-reported and official records of VCB are highly correlated but the concordance between them varies, as individual traits and characteristics might influence the relative accuracy of records (Forrest et al., 2014).

In this meta-analysis, BD was significantly associated with VCB in cross-sectional surveys. This is not surprising as cross sectional studies are generally used to determine prevalence, although they cannot help assessing a possible causal relationship.

As for the significant association in the USA samples, speculative reasons derived from official reports about the geographic distribution of crimes may be

provided. Crime rates across Countries are complicated as crime recordings vary heavily. Yet, rates of VCB are generally higher in the USA than in Oceania and Europe (Dubow et al., 2014). USA have a homicide rate higher than Canada, Australia and UK ("United Nations Office on Drugs and Crime Statistics Online, Homicide counts and rates (2000-2015)," 2017), especially for homicides committed by firearms ("International firearm injury prevention and policy," 2017). Additional correlates to VCB explaining these different rates should also be addressed, such as Countries differences in accessing firearms (Appelbaum, 2006).

No moderators were identified to explain the associations. Neither comorbid SUD nor socio-demographic factors significantly moderated the risk of BD individuals to commit VCB. This is conflicting with previous findings in BD (Daff and Thomas, 2014; McCabe et al., 2013; Webb et al., 2014) or in the general population (Corrigan and Watson, 2005). A strong relation between SUD and violence is often assumed (Fazel et al., 2009). Nonetheless, genetic influences unrelated to SUD partially explained the correlation between VCB and BD (Sariaslan et al., 2015). Interestingly, sex did not significantly moderate the association between BD and VCB, despite male sex is a well-known risk factor for VCB in the general population (Sher and Rice, 2015) and in psychotic samples (Fazel et al., 2009).

In this meta-analysis, increased OR for the association of VCB in BD emerged when BD patients were compared to controls with depressive disorders, in USA cross-sectional studies assessing self-reported VCB. On the contrary, BD was less associated with VCB when BD was compared to psychotic disorders. The association was significant mainly in the USA, in case-control studies, or in studies reporting a record-

based assessment of VCB.

The OR for incarceration was as high as 1.34 in BD patients compared with MDD patients in an USA sample (Hawthorne et al., 2012) whilst in a Swedish case-control study, schizophrenia was a stronger predictor of violence than BD (Sariaslan et al., 2015). In a study analyzing cross-sectionally the first NESARC wave (2001-2002) (Pulay et al., 2008), the risk for VCB was as high as 3.72 in BD-I whilst it was 1.73 in MDD. With some discrepancy, similar results are observed in European studies. In Swedish population studies, the OR for VCB was 3.0 for MDD (Fazel et al., 2015), 2.6 for BD (Fazel et al., 2010), and 6.3 for schizophrenia (Fazel and Grann, 2006). In the Dunebin cohort study (Arseneault et al., 2000) the risks for court-convictions and/or self-reported violence were 2.1 in MDD, 3.5 in BD and 5.4 schizophrenia.

The risk for re-offending VCB seems to keep the previous progression among diagnoses (2.06 in schizophrenia, 1.96 in BD and 1.41 in MDD) (Chang et al., 2015).

4.1 Clinical implications

Despite specific manic symptoms (e.g. social indiscretions, reckless driving) predicted criminal involvement in previous studies (Christopher et al., 2012; McCabe et al., 2013), in the present meta-analysis mania was not a significant moderator of the association between VCB and BD. Yet, past affective episodes have strong implications on the course of life of BD patients, due to an increased risk for social drift (e.g. worse educational and working achievement, family and relational problems) compared to the general population and positively associated to VCB in BD (Elbogen and Johnson, 2009). Ensuring an early diagnosis, establishing a proper treatment and providing the appropriate management and follow-up in mental health outpatients units could represent important steps to reduce the risk of VCB in BD (Goodwin et al., 2016).

Treatments for BD exert an overall control over all symptoms dimensions, encompassing aggressive symptoms (Fazel et al., 2014). Psychiatric patients with a criminal history would benefit the most from treatment programs, that often exclude them (Appelbaum, 2006). Criminal history should be an indicator of an increased need for more integrated approaches, rather than a reason for treatment exclusion (Matejkowski et al., 2014). Recent clinical guidelines provide assistance, both in inpatient and outpatient units, for the identification of triggers and treatment strategies for violence (NICE, 2015; Stahl et al., 2014).

Patients already tracked in the justice system might benefit from an integrated case-management model within both criminal and mental health systems. The implementation of court liaison and diversion programs aims at reducing the clinical severity and the likelihood of VCB in such populations (McNiel and Binder, 2007). Specific treatment algorithms for the treatment of BD in the correctional setting should be improved and their efficacy tested (Kamath et al., 2013).

The association between BD and VCB should also be considered on the likelihood of BD patients to be victims of crimes. Unluckily in the present meta-analysis the study of victimization as a possible moderator of VCB was not possible due to scant evidence justifying a meta-regression. In the past, violent victimization among psychiatric patients was observed more frequently than VCB (Choe et al., 2008), yet this raised less attention by media than violent offending (Varshney et al., 2016). As patients victims of violence are more likely to engage in VCB (Latalova et al., 2014), avoidance of this potential, dangerous loop is warranted. Victimization is a serious medical and social problem that should be included in the clinical assessment and care for BD patients (Latalova et al., 2014).

4.2 Research implications and unmet needs

The comparison between existing studies in this meta-analysis was difficult because of differences in the VCB classification systems with consequent high heterogeneity. Methodological quality of included studies was varied. Better quality, multicenter, longitudinal studies are required to disentangle the timing of the association between BD and VCB.

The identification of a worldwide accepted operational definition of VCB might help achieving generalizable and reliable results. A wide range of structured tools assessing violence is present, often with poor-to-moderate accuracy, scant external validations, especially in women or ethnic minorities (Douglas et al., 2017). Well-defined and generalized risk-assessment indicators and outcomes of VCB, early identification of potential offenders and effectiveness of interventions are still lacking and represent possible subjects of future research.

In terms of public health perspective, research focus should be switched from relative to absolute risk measured, i.e. population-attributable risk. Identifying the percentage of VCB that can be ascribed to BD would help reducing stigmatization (Varshney et al., 2016). Possible confounders, i.e. social and cultural variables or comorbidity-related factors, should be controlled. In this meta-analysis SUD did not represent a moderator for the association between BD and VCB. This was probably related to the heterogeneity in the assessment of SUD across the included studies, with only few of them (Abram and Teplin, 1991; Alnıak et al., 2015; Shaffer et al., 2007) separated recent from past SUD.

VCB should be considered in randomized controlled trials and adequately researched as a specific treatment outcome of antipsychotics and mood stabilizers. The

tendency towards manic relapses should be properly addressed (Samalin et al., 2016) as well as the depressive polarity to avoid self-injuries representing predictors of both criminality and suicide in BD (Sahlin et al., 2017; Verdolini et al., 2017; Webb et al., 2014).

Future studies should examine the possible underlying genetic risk for VCB in BD. The significant heterogeneity of the association between VCB and BD could be explained with the phenotypic variability of BD (ALDA, 2004) that should be studied at a genetic level, possibly through a mendelian randomization experiment (Burgess et al., 2015). Recently, genetic influences unrelated to SUD were found to explain a fifth of the correlation with VCB in BD (Sariaslan et al., 2015), but implications for these findings are still to be ascertained.

4.3 Limitations

This meta-analysis presents limitations. First, the considerable methodological heterogeneity across the included studies. Second, the exploratory nature of the meta-analysis has to be taken into account and negative findings should be carefully considered. Also, the generalizability of the findings should be limited due to the absence of studies proceeding from Asia, Africa and South America. Furthermore, a third of the included studies were cross-sectional, precluding causal inferences and limiting the deduction of the directionality between BD and VCB. Finally, excluding the risk of publication bias is not possible.

4.4 Conclusions

One every fourteen patients suffering from bipolar disorder reported violent criminal behavior. Overall, the association with violent criminality was not significant when bipolar disorder was compared with the general population. Despite this, the association between bipolar disorder and violent criminal behavior was significantly higher than in depressive disorders whilst the chance was smaller in comparison with psychoses. Since the associations varies depending on the comparison group and the type of methodology, predictors of violent behavior should be further investigated in bipolar disorder, differentiating between those properly related to the illness and those possibly biased by confounders. The limitations in the included articles do not allow for definitive conclusions regarding the prevalence or causes of violent criminal behavior in bipolar disorder. Nonetheless, clinicians should promote awareness in order to minimize stigmatization. From a clinical perspective, increasing the efforts in providing to patients suffering from bipolar disorder, with or without a criminal history, appropriate and integrated treatment strategies is strongly warranted.

Figure Legends:

FIGURE 1. PRISMA flowchart of study selection for systematic review and meta-analysis.

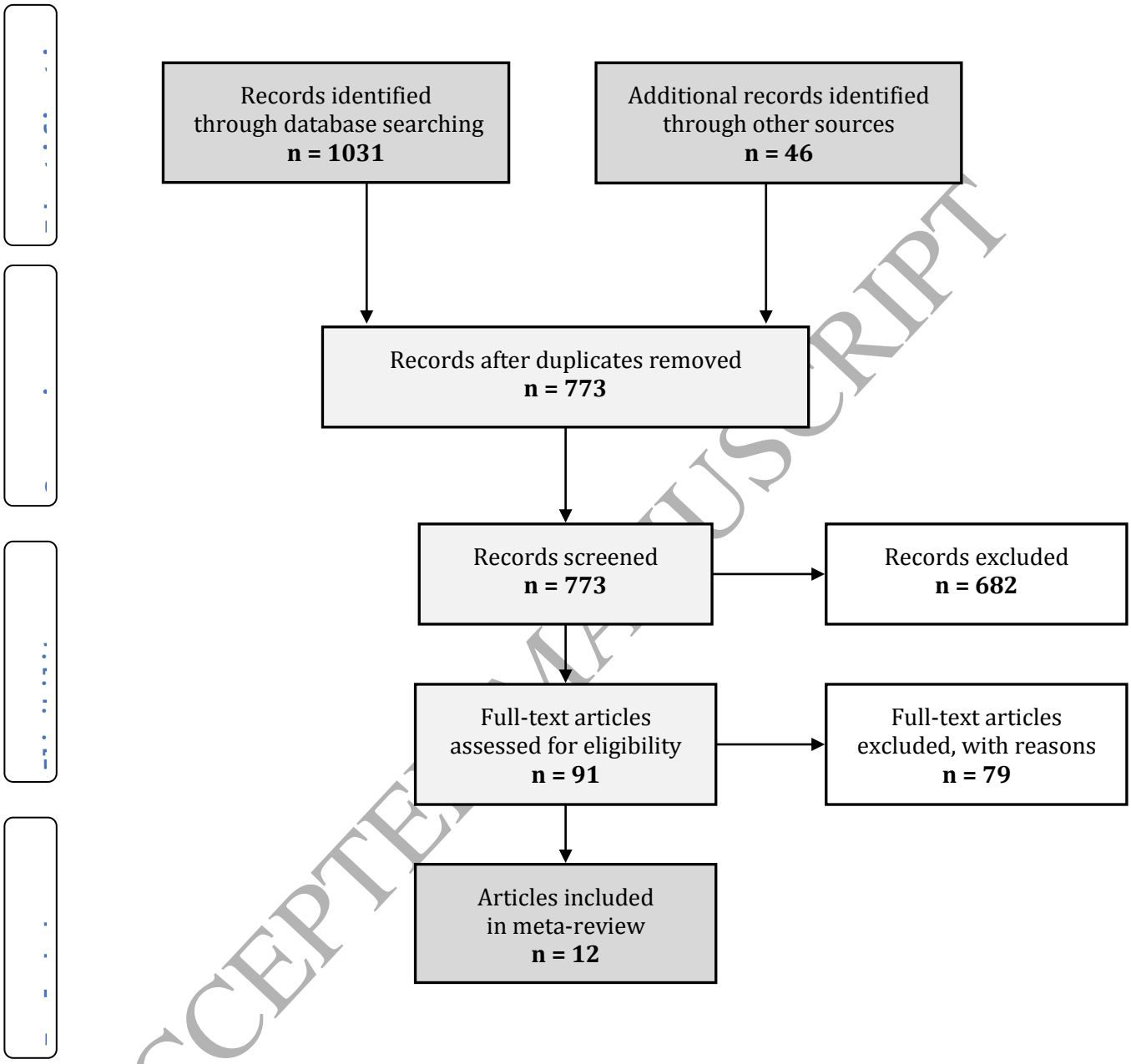
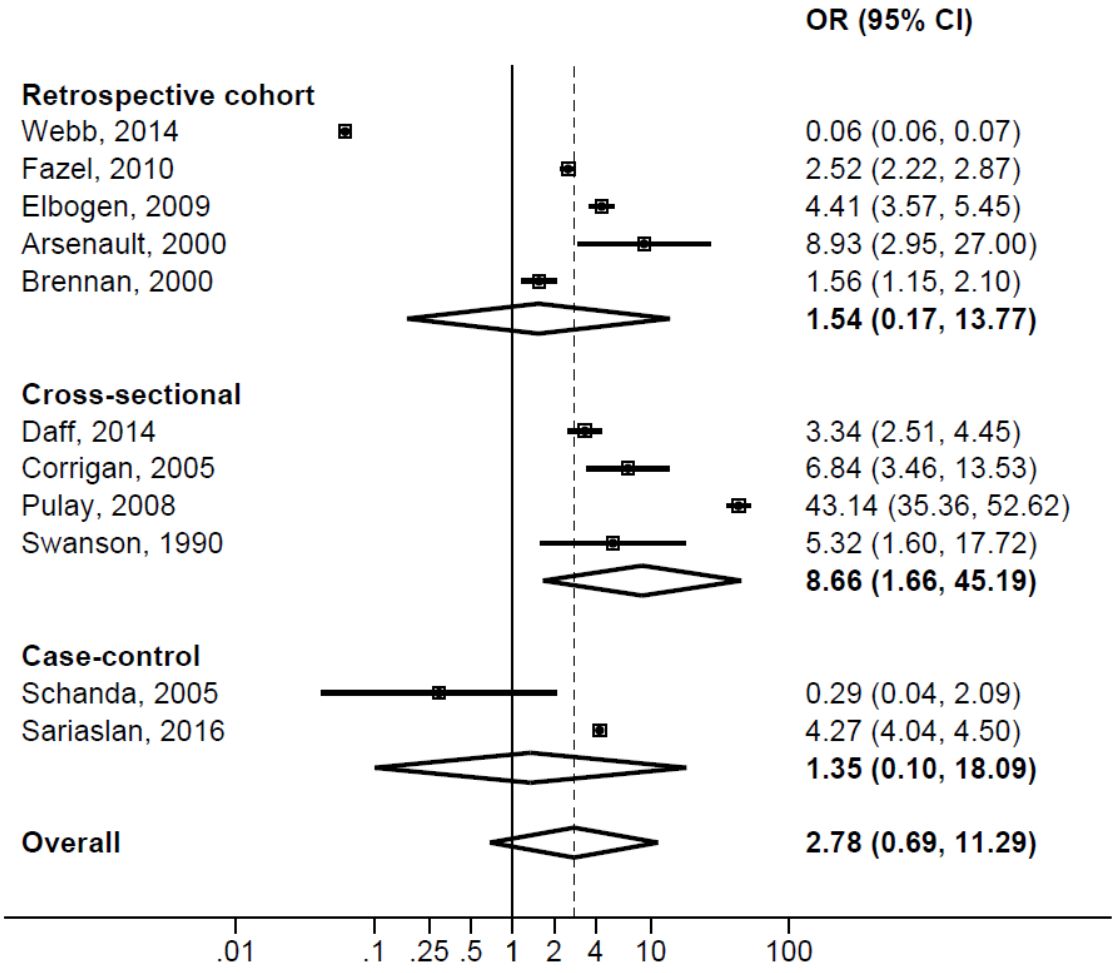


FIGURE 2. Forest plot of the association of violent criminal behavior in BD subjects in comparison to the general population. Subgroup estimates are provided in accordance to study design. Effect sizes are reported as OR and 95% CIs. The sizes of the squares are proportional to sample sizes, and diamonds depict pooled effect size estimates through random-effects modeling. Panel A shows the meta-analysis of all 12 included studies, whilst panel B shows the meta-analysis excluding the study by Fazel et al. 2007.



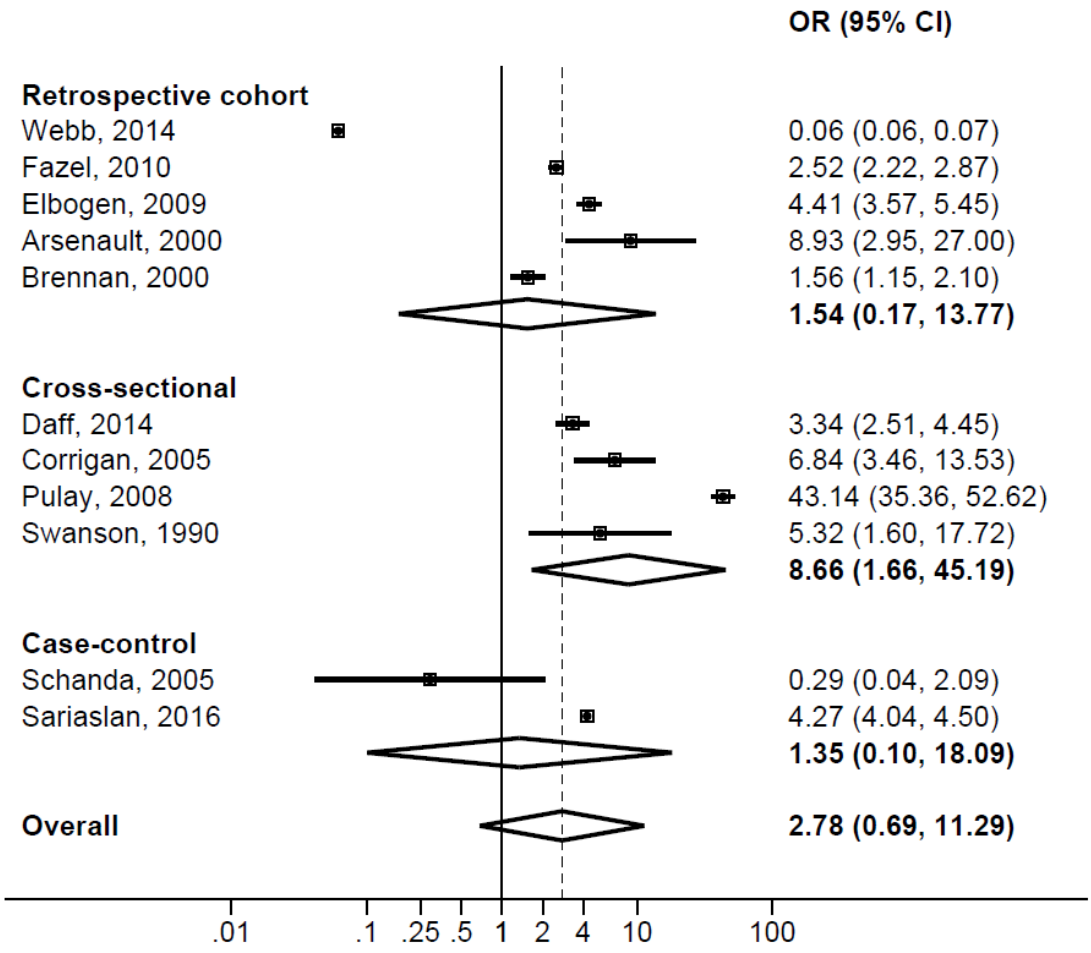
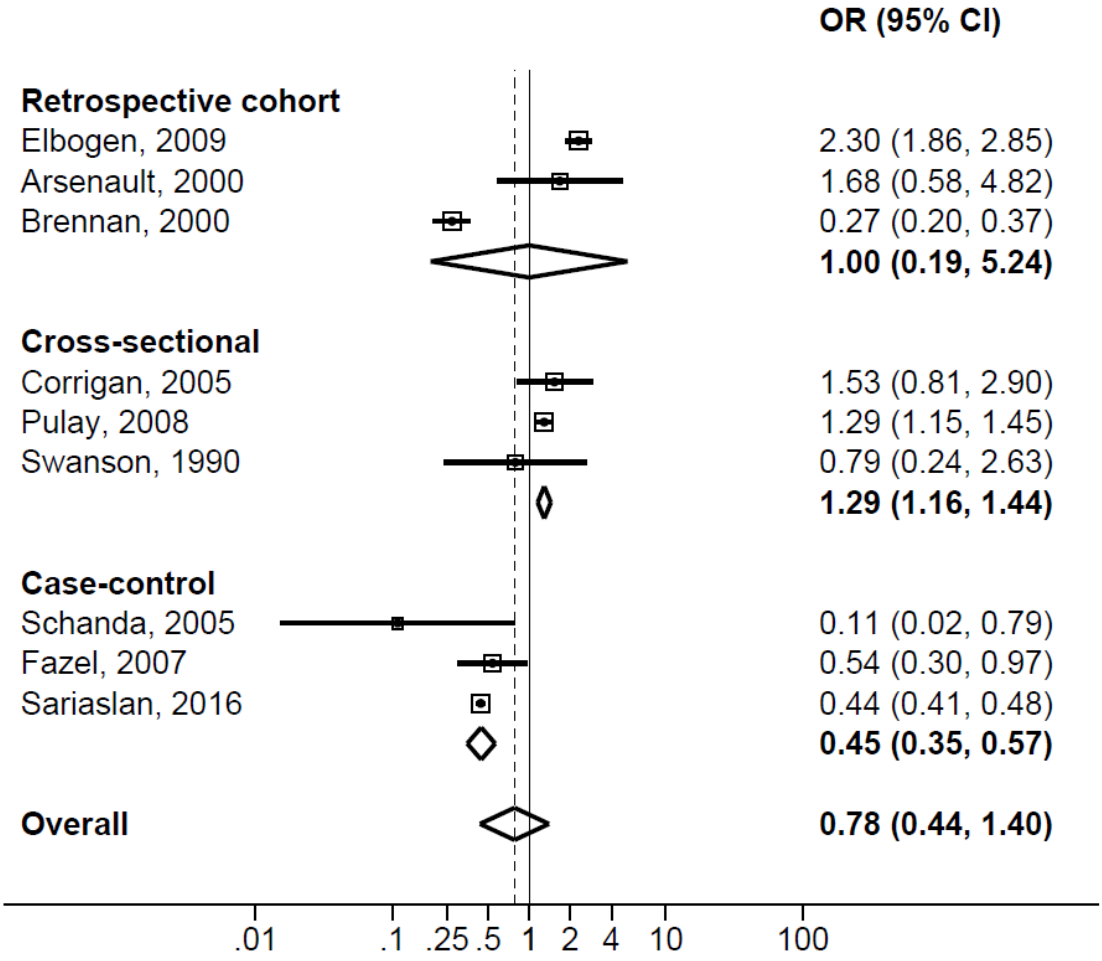


FIGURE 3. Forest plot of the association of violent criminal behavior in BD subjects in comparison to a comparator group with any psychiatric disorder. Subgroup estimates are provided in accordance to study design. Effect sizes are reported as OR and 95% CIs. The sizes of the squares are proportional to sample sizes, and diamonds depict pooled effect size estimates through random-effects modeling.



Author Statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (evieta@clinic.cat).

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Table 1. Prevalence of criminal behavior in individuals with bipolar disorder. Data from four cross-sectional studies. Sources of heterogeneity were explored through subgroup and meta-regression analyses.

Subgroup	N studies	BD Prevalence			Heterogeneity		
		%	95% CI		I^2	Q	P-value
Overall	4	7.07	3.04	16.45	96.9	97	< **.001**
Crime report type							
Self-report	2	9.28	4.79	18.01	74.0	7.71	< **.001**
Geographic region							
US	2	9.28	4.79	18.01	74.0	7.71	< **.001**

Moderator	N studies	Meta-regression			Meta-regression		
		Slope	95% CI		P-value	Intercept	z	P-value
% Newcastle-Ottawa Scale score	4	0.026	-0.006	0.057	0.113	-3.955	-3.026	.002
Publication year	4	-0.002	-0.092	0.087	0.959	2.795	0.031	.976

Abbreviations: BD = bipolar disorder; **CI** = confidence interval;

Table 2. Association of bipolar disorder and criminal behavior in comparison to general population controls. Sources of heterogeneity were explored through subgroup and meta-regression analyses.

Subgroup	N studies	Meta-analysis				Heterogeneity		
		OR	95% CI		P-value	I^2	Q	P-value
Overall	12	5.206	1.338	20.251	**.017**	99.9	8090.26	**< .001**
Excluding Fazel et al. 2007	11	2.784	0.687	11.287	.152	99.9	8038.78	**< .001**
Crime-report type								
Self-report	4	9.339	2.06	42.333	**.004**	98.8	0.36	**< .001**
Record-based	7	1.395	0.233	8.35	.715	99.9	0.71	**< .001**
Study design								
Retrospective cohort	5	1.542	0.173	13.771	.698	99.9	0.05	**< .001**
Cross-sectional	4	8.663	1.66	45.194	**.010**	98.6	0.67	**< .001**
Case-control	2	1.35	0.101	18.093	.821	86	0.14	**.008**
Geographic region								
US	4	9.339	2.06	42.333	**.004**	98.8	0.36	**< .001**
EU	4	1.007	0.092	11.061	.996	100	0.09	**< .001**
Oceania	3	2.753	0.785	9.658	.114	77.6	0.92	**.012**

Moderator	N studies	Meta-regression			Meta-regression		
		Slope	95% CI	P-value	Intercept	z	P-value

% Newcastle-Ottawa Scale score	11	-0.007	-0.070	0.055	.817	1.642	0.612	.54
Publication year	11	-0.054	-0.200	0.092	.469	109.497	0.732	.464
% Female	4	-0.378	-1.991	1.235	.646	-0.082	-0.052	.958
% Any substance use disorder	4	0.127	-0.182	0.436	.421	-0.997	-0.616	.538

Abbreviations: BD = bipolar disorder; **CI** = confidence interval; **NOS** = not otherwise specified.

Table 3. Association of bipolar disorder and criminal behavior in comparison to controls with any psychiatric disorder. Sources of heterogeneity were explored through subgroup and meta-regression analyses.

Subgroup	N studies	Meta-analysis				Heterogeneity		
		OR	95% CI		P-value	I^2	Q	P-value
Overall	9	0.783	0.438	1.398	.407	98.1	429.35	**< .001**
Crime-report type								
Self-report	4	1.551	1.006	2.394	**.047**	87.0	23.04	**< .001**
Record-based	5	0.438	0.289	0.665	**< .001**	77.0	17.37	**.002**
Study design								
Retrospective cohort	3	1.000	0.191	5.236	1.000	98.4	121.58	**< .001**
Cross-sectional	3	1.291	1.155	1.444	**< .001**	0.0	0.92	.632
Case-control	3	0.447	0.353	0.565	**< .001**	16.0	2.38	.304
Geographic region								
US	4	1.551	1.006	2.394	**.047**	87.0	23.04	**< .001**
EU	3	0.392	0.272	0.564	**< .001**	78.3	9.22	**.010**

Moderator	N studies	Meta-regression				Meta-regression		
		Slope	95% CI		P-value	Intercept	z	P-value
% Newcastle-Ottawa Scale score	9	0.012	-0.021	0.045	.471	-1.252	-0.877	.381
Publication year	9	0.003	-0.087	0.093	.945	-6.593	-0.072	.943
% Female	3	-0.563	-7.895	6.769	.880	-1.124	-1.509	.131

Abbreviations: BD = bipolar disorder; **CI** = confidence interval; **NOS** = not otherwise specified