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Do patients with bipolar disorders have an increased risk of myocardial infarction? A systematic review and meta-analysis

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Abstract. – OBJECTIVE: Research shows that patients with bipolar disorders (BD) may have an altered risk of cardiovascular diseases; however, the association between the two is not clear. In this study, we reviewed evidence on the association between BD and subsequent risk of myocardial infarction (MI).

MATERIALS AND METHODS: Studies published on PubMed, Embase, Scopus, CENTRAL, and Web of Science were identified up to 30th August 2023. Random-effects meta-analysis was done to calculate the pooled odds ratio (OR).

RESULTS: A total of six studies with 19,862,894 individuals were included. Of these, 46,627 were diagnosed with BD (0.23%). The median follow-up of the studies varied from 7.6 to 20 years. Meta-analysis of all six studies showed that BD patients do not have a higher risk of MI as compared to the general population (OR: 1.36, 95% CI: 0.99, 1.86). The overall analysis had substantial heterogeneity with I^2=86%. No publication bias was noted among the studies. Results did not change during sensitivity analysis.

CONCLUSIONS: Current evidence fails to show an association between BD and subsequent risk of MI. The high heterogeneity in the meta-analysis and lack of adjustment of all important confounders are significant limitations that need to be overcome by future studies.

Key Words:
Mental disorders, Cardiovascular disorders, Heart disease, Psychiatric disease.

Introduction

Bipolar disorder (BD) is a common chronic mental health condition characterized by unusual changes in the person's mood state, energy, activity levels and concentration[1]. BD remains a major public health concern affecting about 1-1.5% of the worldwide population, with most patients diagnosed very late after the onset of the disorder[2,3]. The disease does not have any predilection for sociodemographic factors and affects irrespective of gender, ethnicity, and socioeconomic status[2,3]. BD is known to be associated with cognitive decline and high mortality rates, mostly due to suicide. Also, patients have a high degree of relapse and recurrence even after treatment[2]. Research[4-6] has shown that BD patients have a two times increased risk of all-cause mortality and a 1.9-2.6 times increased risk of cardiovascular mortality.

Interestingly, patients with severe mental disorders like BD, schizophrenia, and major depression have all been associated with a higher risk of cardiovascular events. While no single contributor has been identified, it is postulated[7] that disparity in the care received by patients with severe mental illnesses, psychopharmacotherapy, modifiable cardiovascular risk factors, and the disease itself can increase the risk of cardiovascular events. A study[8] has shown that patients with BD have a two-fold increase in the number of cardiovascular risk factors as compared to the general population. Also, drug therapy for BD is associated with insulin resistance and weight gain, which are known risk factors for cardiovascular diseases[9]. In this context, it is necessary to evaluate if BD patients have a higher risk of specific cardiovascular events like myocardial infarction (MI) as compared to the general population. Such data can aid in formulating preventive strategies and reducing cardiovascular mortality in BD patients.

To the best of our knowledge, only one prior meta-analysis[10] published in 2014 has examined the risk of MI in BD patients and included a limited number of studies. Hence, this current study aims to perform an updated literature search and assess if BD patients have a higher risk of MI as compared to the general population.

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Materials and Methods

Inclusion Criteria

The review protocol registration was completed on PROSPERO and the review was allotted the number CRD42023453050. We included cohort or case-control studies that examined the association between the diagnosis of BD and subsequent risk of MI. Studies were included to compare BD patients with the general population and report the risk of MI in the follow-up period. There was no restriction on the method of assessment of BD or MI.

Cross-sectional studies, studies not reporting separately on MI, and studies on a population of other mental illnesses were excluded. Duplicate studies using the same database and non-pre-reviewed studies were also not eligible. In case articles reported overlapping data, the study with the maximum number of participants was eligible.

Search Source and Strategy

Studies for the review were identified by a literature search conducted on PubMed, Embase, Scopus, CENTRAL, and Web of Science. Two reviewers were involved in the selection process. The search was completed on 30th August 2023. Also, the bibliography of the final included studies was hand-searched for any missed articles.

Keywords used were "cardiovascular", "cardiac disease", "coronary artery disease", "myocardial infarction", AND "bipolar disorder". The search string was: ((((cardiovascular) OR (myocardial infarction)) OR (cardiac disease)) OR (coronary artery disease)) AND (bipolar disorder[Title/Abstract]). This was also replicated across the different databases.

Two investigators separately examined the titles and abstracts of searched studies after electronic deduplication. Studies relevant to the review were identified, while non-relevant articles were excluded. Selected studies underwent full-text analysis against the inclusion criteria. All discords between reviewers were solved by discussion.

Extracted Data and Risk of Bias Analysis

Two reviewers independently extracted relevant information from the studies, which included the name of the first author, publication year, location of the study, exposed cohort, non-exposed cohort, identification of MI, sample size, patients with BD, follow-up, adjusted covariates, and outcome data. Study details were then cross-matched, and any discrepancies were resolved in a discussion with the third author.

Two reviewers assessed the methodological quality of the observational studies by the Newcastle Ottawa Scale (NOS)[11]. Points were awarded for representativeness of the study cohort, comparability of groups, and measurement of outcomes.

Statistical Analysis

PRISMA reporting guidelines were followed[12]. The meta-analysis was done on "Review Manager" (RevMan, version 5.3, Cochrane Collaboration). Data on the association between BD and MI was reproduced from the studies and entered into the software to derive a pooled odds ratio (OR) with 95% confidence intervals (CI). A random-effects model was preferred. Outliners were assessed using a sensitivity analysis involving the removal of one study at a time. A funnel plot was used to check publication bias. The Chi-square-based Q statistics and I^2 statistics were used for inter-study heterogeneity. A p-value<0.10 for Q statistic and I^2>50% meant substantial heterogeneity. p<0.05 was considered statistically significant for the outcome of the meta-analysis.

Results

The entire literature search revealed 4,106 articles (Figure 1). After the removal of duplicates, 1,584 studies remained. These underwent screening by the study investigators, and 16 were chosen for complete text analysis. Based on the eligibility criteria, six[13-18] were selected for inclusion.

Characteristics of the included studies are shown in Table I. The six studies[13-18] were published between 2010 and 2023. However, the study period ranged from 1955-2012. All were registry-based studies conducted on populations of Taiwan, Sweden, South Korea, the USA, and Denmark. In all studies except one[18], MI was identified based on international classification of diseases (ICD) codes. In the study of Ramsey et al[18], MI was self-reported by the patients based on questionnaires. The combined sample size of all six studies was 19,862,894. Of these, 46,627 were diagnosed with BD (0.23%). The median follow-up of the studies varied from 7.6 to 20 years. Ramsey et al[18] did not report the adjustment of any confounders, while the remaining studies adjusted several different confounders in

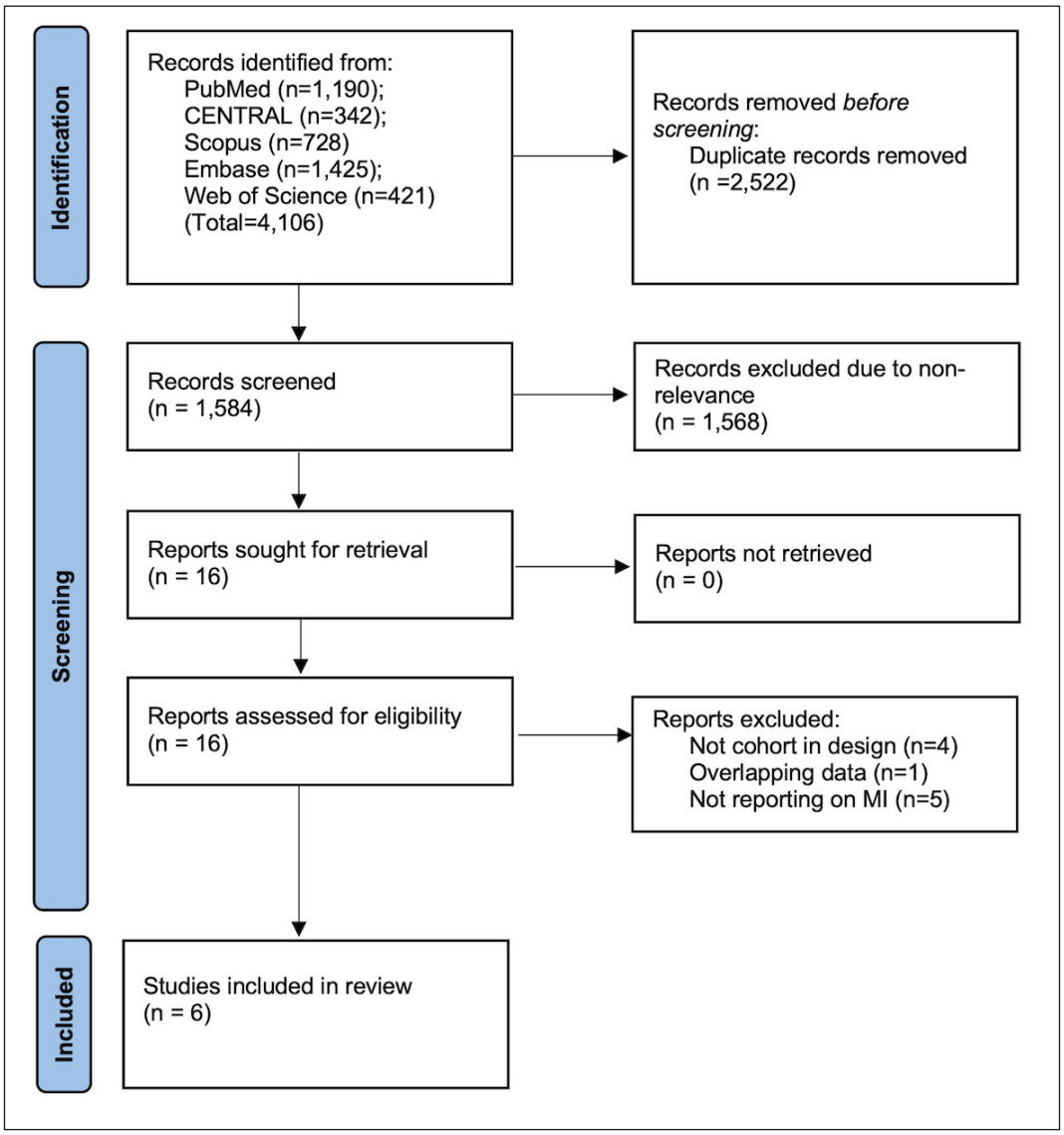


Figure 1. Study flow chart.

the analysis. On risk of bias analysis, the reviewers gave the included studies 6-8 points on the NOS scale.

Meta-analysis of all six studies[13-18] showed that BD patients do not have a higher risk of MI as compared to the general population (OR: 1.36 95% CI: 0.99, 1.86). The overall analysis had substantial heterogeneity with I^2=86% (Figure 2). There was no publication bias noted among the studies (Figure 3).

A sensitivity analysis was performed by removing one study at a time from the meta-analysis. Details are shown in Table II. The association between BD and risk of MI remained non-significant in the sensitivity analysis.

Discussion

The results of this updated meta-analysis, with a sample size of about 19 million participants, show that BD does not increase the risk of MI. Overall, the effect size indicated a 36% non-significant increased risk of MI, with the 95% CI showing no risk to up to 86% increased risk. Importantly, out of the six included studies[13-18], only the recent study by Park et al[17] found a significantly increased risk of MI in BD patients, but none of the other studies found such a significantly increased risk. We also conducted a sensitivity analysis to check for outliers only to find no change in the significance of the results on the exclusion of any study.

Table I. Details of the included studies.

Study	Country	Study duration	Exposed group	Unexposed group	Assessment of MI	Sample size	Patients with BD	Follow-up	Covariates adjusted	NOS score
Ramsey et al[18] 2010	USA	1981-1996	BD patients with age ≥18 years	Individuals without history of mania hypomania	Self-reported	2,768	58	11.5 years	None	6
Laursen et al[15] 2011	Denmark	1955-1995	BD patients with age ≥15 years	Individuals aged ≥ 15 years without psychiatric admission	ICD codes	2,450,812	6,215	12 years	Age, gender, calendar time	7
Westman et al[14] 2013	Sweden	1987-2006	Hospitalized BD patients	Individuals without BD on admission	ICD codes	10,631,208	17,101	20 years	Age, gender, calendar time	7
Wu et al[13] 2015	Taiwan	1996-2000	BD patients with age ≥18 years	Age ≥18 years without any mental disorder	ICD codes	219,711	12,119	11 years	Age, gender, levels of income and urbanization, hypertension, diabetes, hyperlipidemia, and psychotropic use	8
Prieto et al[16] 2016	USA	1966-1996	BD patients without history of MI or stroke	Age and sex matched individual free of BD, MI, and stroke	ICD codes	668	334	18.7 years	Alcohol use disorder, hypertension, diabetes and smoking	8
Park et al[17] 2023	Korea	2009-2012	BD patients aged 20-39 years	Age 20-39 years without BD	ICD codes	6,557,727	10,800	7.6 years	Age, sex, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, chronic kidney disease, current smoking, heavy alcohol consumption, regular physical activity, and low-income level	8

ICD, international classification of diseases; BD, bipolar disorder; MI, myocardial infraction; NOS, Newcastle Ottawa scale.

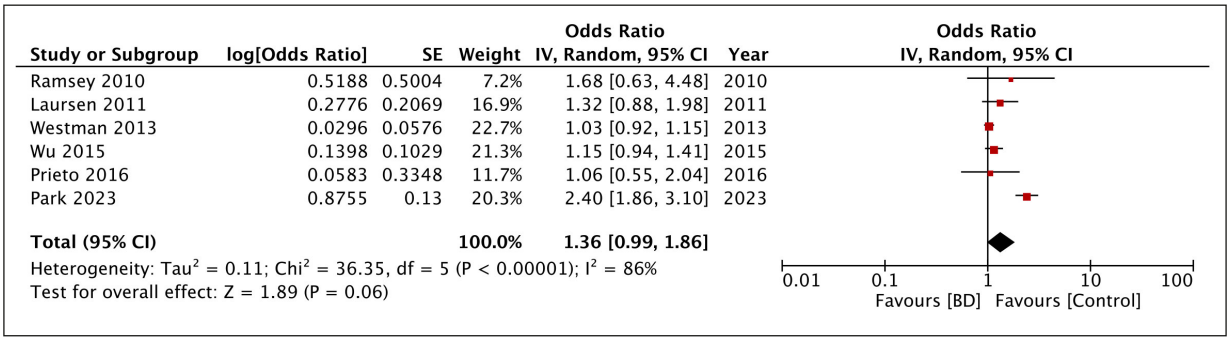
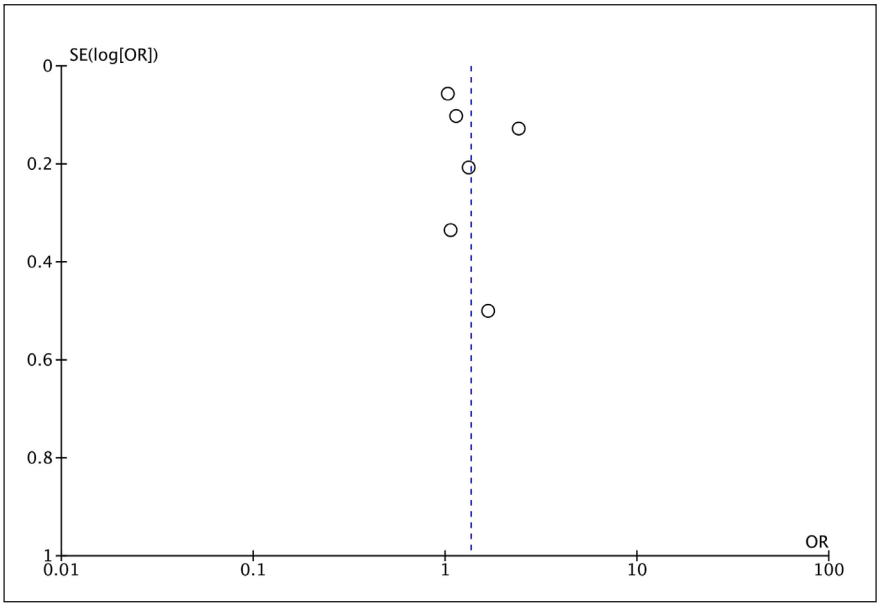


Figure 2. Meta-analysis of the association between BD and risk of MI.

Figure 3. Funnel plot to check publication bias.



Our study concurs with the prior meta-analysis of Prieto et al[10], which, too, found a non-significant increase in the risk of MI in BD patients (risk ratio: 1.09 95% CI: 0.96, 1.24). However, a major difference between the current study and the prior review[10] is the addition of three new studies[13,16,17] and the exclusion of one overlapping study[19].

Despite being an updated analysis, there are several important points to be considered while interpreting the results. Firstly, the high heterogeneity in the meta-analysis is a cause of concern. The differences in the study populations, method of assessment of exposure and outcomes, and different follow-up periods are one source of heterogeneity. The other can be attributed to the variation in the confounders adjusted in the individual studies. Except for one study[18], all studies adjusted for age and gender. However, cardiovascular comorbidities were not completely adjusted in all studies except for the one by Park et al[17]. Half of the studies[14,15,18] did not take into account diabetes, which is an important risk factor for MI[20]. Another confounder missed by the majority of studies was physical activity, which has a direct correlation with MI[21]. A meta-analysis[22] of about 44 studies has shown

Table II. Details of the included studies.

Excluded study	Odds ratio [95% confidence intervals]
Ramsey et al[18] 2010	1.33 [0.96, 1.86]
Laursen et al[15] 2011	1.37 [0.94, 1.97]
Westman et al[14] 2013	1.47 [0.99, 2.18]
Wu et al[13] 2015	1.42 [0.90, 2.23]
Prieto et al[16] 2016	1.40 [0.99, 1.99]
Park et al[17] 2023	1.07 [0.98, 1.18]

a direct linear association between leisure-time physical activity and risk of cardiovascular mortality irrespective of age, gender, and prior presence of cardiovascular disease. Mood stabilizers, which are used to treat BD, are associated with weight gain, diabetes, and dyslipidemia, all important risk factors for MI[23]. Based on information available from studies, it was unclear how many patients were treated with such drugs. The use of antipsychotics was also not included as a confounder in most studies[14-18]. The lack of adjustment of all important confounders is a major limitation in the interpretation of evidence, as residual confounding may have influenced the results.

This review included only cohort studies and case-control studies, which can assess the temporality of the association between the exposure and outcomes and have a lower risk of bias[24]. In contrast to the results of our review, cross-sectional studies[25,26] have reported that BD patients may have a higher risk of cardiovascular diseases. The 2001-2002 National Epidemiologic Survey[25] conducted in the USA found that BD patients have a higher risk of hypertension and cardiovascular disease, which occur about a decade earlier than the general population. The difference in the results of cross-sectional studies and our review could be due to the high risk of bias and confounding in cross-sectional studies. Also, other studies[27,29] not specifically on MI have noted a higher risk of cardiovascular diseases in BD. Izci et al[27] have shown that the Framingham Heart Risk Score is higher in BD patients with elevated risk of cardiac arrhythmia. Foroughi et al[28] have shown that BD patients have a higher risk of major adverse cardiovascular events, which persisted after adjustment of cardiovascular risk factors, substance use disorders, and major depressive disorder. Rødevand et al[29] have shown extensive genetic overlap between BD and cardiovascular phenotypes.

Despite literature showing a higher risk of cardiovascular mortality in BD[4-6], our review failed to note a significant association between BD and MI. This could be due to several reasons. It could be possible that BD patients have a similar risk of MI as compared to the general population, but the severity of MI may be higher in BD, resulting in increased mortality[30]. Second, access to healthcare is limited in the case of BD patients and even undertreated in many cases, which can explain the high cardiovascular mortality rates. Lastly, the use of antipsychotics in BD can prolong the QTc interval and increase the risk of torsade de pointes and sudden cardiac death[31]. Thus, sudden cardiac death and post-MI cardiac arrhythmia are common in BD, which can increase cardiovascular mortality[10].

Limitations

There are several limitations in our meta-analysis. The number of studies in the review was not high. Only six were available and from a limited number of countries that have robust healthcare records. A significant proportion of the world population was not represented, and hence, there can be questions on the generalizability of evidence. The second limitation is the high heterogeneity in the meta-analysis. Due to limited studies, subgroup and meta-regression analysis could not be carried out. Thirdly, the loss of follow-up in the studies was not accounted for. The included studies also missed many important confounders. Fourthly, the assessment of outcome was mostly medical record-based. Errors in documentation can result in bias and influence the outcomes.

Conclusions

Current evidence fails to show an association between BD and subsequent risk of MI. The high heterogeneity in the meta-analysis and lack of adjustment of all important confounders is a significant limitation that needs to be overcome by future studies.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions
CJ conceived and designed the study. XZ and JW collected the data and performed the literature search. CJ was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

Conflict of Interest

The authors declare that they have no competing interests.

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