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Review article

Patients with rheumatoid arthritis have a higher risk of bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

The current study was conducted with the aim to investigate the relationship between rheumatoid arthritis (RA) and bipolar disorder (BD). Potentially eligible studies were identified from Medline and EMBASE databases from inception to May 2019. Eligible cohort studies must include patients with RA and comparators without RA, follow them for incident BD and report the relative risk, hazard risk ratio or standardized incidence ratio and associated 95% confidence intervals (CI) comparing the incidence of BD between the two groups. Eligible case-control studies must include cases with BD and controls without BD, explore prior history of RA and report the odds ratio and associated 95% CI for this association. Point estimates with standard errors were extracted from individual study and were combined together using random-effect model, generic inverse variance method. A total of six studies fulfilled the inclusion criteria and were included into the meta-analysis. The risk of developing BD was significantly higher among patients with RA than individuals without RA with the pooled relative risk of 2.06 (95% CI, 1.34–3.17; I^2 86%). Chronic inflammation is a potential mechanism and could be a modifiable risk factor of BD. However, further studies are still required to confirm this.

1. Introduction

Bipolar disorder (BD) is a spectrum of chronic mental illnesses characterized by periods of prolonged and profound depression alternating with episodes of excessively elevated or irritable mood known as mania or hypomania (Jann, 2014). BD causes a tremendous burden on patients and healthcare systems with decreased quality of life, work impairment, increased medical costs, and increased risk of suicidality (Ferrari et al., 2016). The estimated incidence of first-episode bipolar mania is 5 per 100,000 person-years (Baldwin et al., 2005). A bimodal distribution of the incidence of BD has been demonstrated by a large population-based cohort study showing two peaks in age of onset at 15–24 years and 45–54 years (Kroon et al., 2013). Several risk factors involved in etiopathogenesis of BD have been identified, such as genetic predisposition, neurophysiological dysregulation, psychodynamic disturbance and environmental factors (Rowland and Marwaha, 2018). In addition, it has been proposed that chronic neuro-inflammation and immune dysregulation might also contribute to the development of BD (Muneer, 2016) and it is possible that patients with chronic inflammatory disorders may have a higher risk of BD.

Rheumatoid arthritis (RA) is a common systemic inflammatory disorder primarily affecting synovial joints. RA is associated with increased morbidity and mortality, decreased functional ability, and negative socioeconomic impact (Uhlig et al., 2014). The incidence of RA is approximately 40 cases per 100,000 person-years, with the peak incidence between 50 and 60 years of age (Cross et al., 2014; Scott et al., 2010). Previous studies have demonstrated an increased risk of major depressive disorder and anxiety disorder among patients with RA (Covic et al., 2012; Dickens et al., 2003). In addition, some studies also suggested an increased risk of BD among these patients although the results were inconsistent (Cremaschi et al., 2017; Forty et al., 2014; Hsu et al., 2014; Marrie et al., 2018; Sundquist et al., 2008; Wang et al., 2018). The current systematic review and meta-analysis was conducted with the aim to investigate the relationship between RA and BD by identifying all available studies and summarizing their results.

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2. Methods

2.1. Search strategy

Three investigators (P.U., B.P., N.C.) independently searched published studies indexed in Embase and MEDLINE from inception to May 2019. Search terms were compiled from terms related to bipolar disorder and rheumatoid arthritis. The detailed search strategy is provided in the Supplemental Material 1. No language limitation was applied.

2.2. Inclusion criteria

Studies that were eligible to be included into the meta-analysis were either cohort studies (either prospective or retrospective) or case-control studies. Eligible cohort studies had to include patients with RA and comparators without RA, follow them for incident BD and report the relative risk (RR), incidence rate ratio (IRR), hazard risk ratio (HR) or standardized incidence ratio (SIR) and associated 95% confidence intervals (CI) comparing the incidence of BD between the two groups. Eligible case-control studies had to include patients with BD and controls without BD, explore prior history of RA and report the odds ratio (OR) and associated 95% CI for this association.

Study eligibility was independently determined by the two investigators (B.P. and N.C.). Different opinions were resolved by conference with the senior investigator (P.U.). The quality of each study was evaluated by two investigators (B.P. and P.U.) using the Newcastle-Ottawa quality assessment scale for cohort and case-control studies (Wells et al., 2000).

2.3. Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, country where the study was conducted, study design, year of publication, total number of participants, recruitment of participants, diagnosis of RA, diagnosis of BD, follow-up period (for cohort studies), average age of participants, percentage of female participants, comorbidities, variables adjusted in multivariate analysis and adjusted effect estimates with 95% CI.

2.4. Statistical analysis

Review Manager 5.3 software from the Cochrane Collaboration was used for data analysis. Point estimates with standard errors were extracted from individual study and were combined together using the generic inverse variance method as described by DerSimonian and Laird (1986). A random-effects model, rather than a fixed-effect model, was used because the included studies were of different methodologies and background populations. Odds ratios of case-control studies were used as an estimate for relative risk to calculate pooled effect estimates along with relative risk of cohort studies. Statistical heterogeneity was assessed using the Cochran's Q test. This statistic is complemented with the I^2 statistic which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and >75% high heterogeneity (Higgins et al., 2003). Presence of publication bias would be assessed by visualization of funnel plot if enough studies were eligible for the meta-analysis.

3. Results

3.1. Search results

A total of 1542 articles were retrieved from the MEDLINE and Embase databases in which 186 articles were duplications and were removed, leaving 1356 articles for title and abstract review. Based on title and abstract review, 1328 articles were excluded as they clearly did not fulfill the inclusion criteria on the basis of type of article and study design. A total of 28 articles underwent full-length article review in which five studies fulfilled the eligibility criteria while 23 articles were excluded as they did not report the outcome of interest. Review of bibliographies of the five included studies and selected review articles identified one additional eligible study. Finally, four retrospective cohort studies (Hsu et al., 2014; Marrie et al., 2018; Sundquist et al., 2008; Wang et al., 2018) and two case-control studies (Cremaschi et al., 2017; Forty et al., 2014) met the inclusion criteria and were included into the meta-analysis. The search methodology and selection process are described in Fig. 1. The basic characteristics of the included cohort and case-control studies are summarized in Tables 1 and 2, respectively.

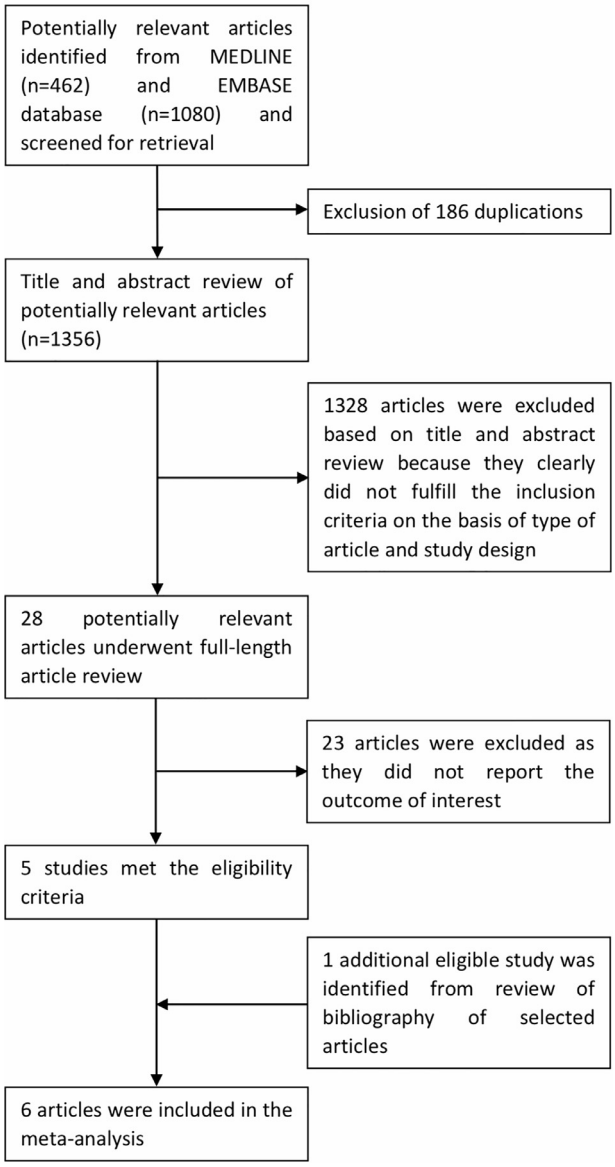

Fig. 1. Study identification and literature review process.

3.2. Risk of bipolar disorder among patients with rheumatoid arthritis

The meta-analysis found that the risk of BD in patients with RA was significantly higher than individuals without RA with a pooled RR of 2.06 (95% CI, 1.34–3.17). The statistical heterogeneity of this meta-analysis was high with I^2 of 86% (Fig. 2).

Table 1
Main characteristics of the cohort studies included in the meta-analysis.

	Sundquist et al.	Hsu et al.
Country	Sweden	Taiwan
Study design	Retrospective cohort	Retrospective cohort
Year of publication	2008	2014
Total number of participants	Patients with RA: 49,022 Comparators: N/A	Patients with RA: 2570 Comparators: 2570
Recruitment of participants	Patients with RA were identified from the MigMed database from January 1st, 1973 to December 31st, 2004. This database is a comprehensive database that has been constructed using several national Swedish data registers. Comparators without RA were general population without RA in the MigMed database	Patients with RA were identified from the Taiwan National Health Insurance Research Database from January 1st, 2000 to December 31st, 2010. This database is derived from the Taiwan National Health Insurance that covers 96% of residents of Taiwan. Comparators without RA were randomly selected from the same database. They were age, sex, comorbidities and enrollment date-matched to cases.
Diagnosis of RA	Presence of ICD-8, −9 or −10 codes for RA in the MigMed database	Presence of both ICD-9 code for RA and catastrophic illness certificate in the Taiwan National Health Insurance Research Database
Diagnosis of bipolar disorder	Presence of ICD-8, −9 or −10 for bipolar disorder in the MigMed database	Presence of both ICD-9 codes for bipolar disorder and prescriptions for mood stabilizers or atypical antipsychotics for at least one month in the Taiwan National Health Insurance Research Database
Follow-up period	Until development of bipolar disorder, death, emigration or the end of the study period (December 31st 2004)	Until development of bipolar disorder, death or the end of the study period (December 31st, 2010)
Median follow-up (years)	N/A	Patients with RA: 6.1 Comparators: 6.1
Average age of participants (years)	N/A	Patients with RA: 51.0 Comparators: 51.0
Percentage of female	Patients with RA: 69.7% Comparators: N/A	Patients with RA: 75.1% Comparators: 75.1%
Comorbidities	N/A	Patients with RA: HT: 31% DLP 29% COPD 23% DM 19% Asthma 16% CKD 13% Comparators: HT: 31% DLP 29% COPD 23% DM 19% Asthma 16% CKD 13%
Variables adjusted in multivariate analysis	Age (in 5-year groups), sex, time period and geographic region	None
Effect size (relative risk, hazard ratio or standardized incidence ratio) with 95% confidence interval	1.32 (0.76–2.29)	2.13 (1.12–4.05)
Newcastle-Ottawa score	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

	Marrie et al.	Wang et al.
Country	Canada	Taiwan
Study design	Retrospective cohort	Retrospective cohort
Year of publication	2018	2018
Total number of participants	Patients with RA: 10,206 Comparators: 50,960	Patients with RA: 29,795 Comparators: 261,992
Recruitment of participants	Patients with RA were identified from the population-based administrative health data from Manitoba, Canada from 1989 to 2012. Comparators without RA were randomly selected from the same database. They were age, sex and region of residence-matched to cases.	Patients with RA were identified from the Registry for Catastrophic Illness Database of Taiwan in the year 2000. Comparators without RA were randomly selected from the Longitudinal Health Insurance Database 2000, which is a random subset of one million individuals enrolled in the Taiwan National Health Insurance. They were age and index year-matched to cases.
Diagnosis of RA	Presence of ICD-9 code for RA in the administrative health data of Manitoba, Canada for at least five times for contiguous claims of less than two years and for at least three times for contiguous claims of more than two years	Presence of ICD-9 code for RA in the Registry for Catastrophic Illness Database
Diagnosis of bipolar disorder	Presence of ICD-9 codes for bipolar disorder in the administrative health data of Manitoba, Canada, at least one for hospital admission or at least three for outpatient visit	Presence of both ICD-9 codes for bipolar disorder for at least two times and prescriptions for mood stabilizers or atypical antipsychotics for at least one month in the Longitudinal Health Insurance Database 2000
Follow-up period	N/A	Until development of bipolar disorder, withdrawn from the insurer or the end of the study period (December 31st, 2010)

(*continued on next page*)

Table 1 (*continued*)

	Marrie et al.	Wang et al.
Median follow-up (years)	Patients with RA: 9.2 Comparators: 9.1	N/A
Average age of participants (years)	Patients with RA: 53.7 Comparators: 53.7	N/A
Percentage of female	Patients with RA: 72.2% Comparators: 72.2%	N/A
Comorbidities	N/A	N/A
Variables adjusted in multivariate analysis	Age, sex, socioeconomic status, region, number of physician visits and calendar year	Age, sex, enrollee category, urbanization, region, comorbidities and steroid use
Effect size (relative risk, hazard ratio or standardized incidence ratio) with 95% confidence interval	1.21 (1.00–1.47)	1.70 (1.33–2.17)
Newcastle-Ottawa score	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

Abbreviation: CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DLP: dyslipidemia; DM: diabetes mellitus; HT: hypertension; IBD: inflammatory bowel disease; ICD: International Classification of Disease; N/A: Not available; RA: rheumatoid arthritis.

3.3. Sensitivity analysis

Three sensitivity analyses were conducted for this meta-analysis. The first sensitivity analysis involved two studies (Hsu et al., 2014; Wang et al., 2018) that utilized a database of Taiwanese national health insurance during overlapping calendar years, which led to a concern of double-counting of the same patients. To address this potential problem, a sensitivity analysis was performed by including only one of the two studies into the pooled analysis. Exclusion of either study did not significantly alter the pooled results with the new pooled RR of 2.07 (95% CI: 1.28–3.35; I^2 88%) and 2.31 (95% CI: 1.23–4.33; I^2 88%) after exclusion of the study by Hsu et al. and Wang et al., respectively.

The second sensitivity analysis excluded the study by Cremaschi et al. from the pooled analysis as this study had an extremely high RR driven by the very low prevalence of RA in their control group (0.1%). We believe that the low prevalence of RA in their control group is spurious, as a previous study conducted in the same country (Sweden) reported a prevalence of 0.8% (Eriksson et al., 2013). Exclusion of this study slightly decreased the pooled RR to 1.53 but the result was still of statistical significance (95% CI, 1.22–1.91). This sensitivity analysis also decreased between-study heterogeneity to low level (I^2 48%).

The third sensitivity analysis excluded the two case-control studies (Cremaschi et al., 2017; Forty et al., 2014) from the pooled analysis as case-control design is less reliable than cohort design to establish temporal relationship between RA and BD. The pooled RR of the remaining four cohort studies was lower than the original pooled RR but remained statistically significant (pooled RR 1.47; 95% CI, 1.15–1.88; I^2 52%).

3.4. Evaluation for publication bias

A funnel plot (Fig. 3) was used for the assessment of publication bias. The funnel plot of this meta-analysis was relatively symmetric which did not provide the suggestive evidence of publication bias.

4. Discussion

The present study is the first systematic review and meta-analysis

Table 2
Main characteristics of the case-control studies included in the meta-analysis.

	Forty et al.	Cremaschi et al.
Country	United Kingdom	Sweden
Year of publication	2014	2017
Total number of participants	Cases: 1720 Controls: 1340	Cases: 3798 Controls: 6485
Recruitment of participants	Cases: Cases were patients with bipolar disorder who were recruited from three study centers in Birmingham, Cardiff and London Controls: Controls without bipolar disorder (and other psychiatric disorders) were recruited from the study center in London via the Medical Research Council general practice research framework or staff/student volunteers of King's College London.	Cases: Cases were patients with bipolar disorder who were identified from the Swedish Quality Register for bipolar disorder. Controls: Controls without bipolar disorder were randomly selected from Swedish population registers.
Diagnosis of bipolar disorder	Fulfillment of DSM-IV and ICD-10 criteria for bipolar disorder based on interview and physical examination	None
Diagnosis of RA	Self-reported using health questionnaire	History of RA was asked by trained research nurses using structured interview over telephone
Average age of participants (years)	Cases: 47.0 Controls: 44.0	Cases: 50.7 Controls: 56.3
Percentage of female	Cases: 70.0% Controls: 57.0%	Cases: 61.8% Controls: 48.8%
Variables adjusted in multivariate analysis	None	Age, sex and education
Effect size (odds ratio) with 95% confidence interval	1.92 (1.19–3.10)	17.9 (7.0–45.8)
Newcastle-Ottawa score	Selection: 4 Comparability: 0 Outcome: 2	Selection: 4 Comparability: 1 Outcome: 3

Abbreviation: RA: rheumatoid arthritis.

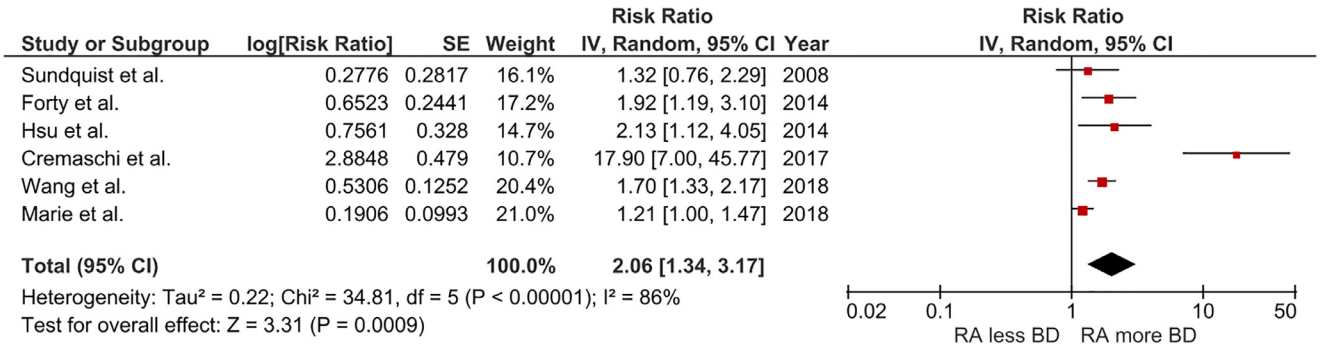

Fig. 2. Forest plot of the meta-analysis of risk of bipolar disorder in patients with rheumatoid arthritis.

that summarizes the results of all available cohort and case-control studies that report the association between RA and risk of BD. The pooled analysis found an approximately twofold elevated risk of developing BD among patients with RA. The result remained statistically significant despite various sensitivity analyses. The exact mechanisms that lead to the higher risk are not known, but there are some possible explanations.

First, it has been suggested that chronic neuro-inflammation is involved in the pathogenesis of BD (Rege and Hodgkinson, 2013). For instance, a post-mortem study found increased excitotoxicity and neuroinflammatory markers in the frontal cortex of patients with BD (Rao et al., 2010). Another study found increased levels of interleukin-1 beta, a marker of microglial activation, in the cerebrospinal fluid of patients with BD who recently developed manic or hypomanic episodes (Söderlund et al., 2011). In addition, several studies have demonstrated that various peripheral inflammatory markers, including IL4, IL6, IL10, soluble IL-2 receptor (sIL-2R), sIL-6R, TNF-α and soluble TNF receptor-1 (sTNFR1), were elevated in patients with BD (Modabbernia et al., 2013; Munkholm et al., 2013). More interestingly, a meta-analysis found that the levels of IL-6, TNF-α, sIL-2R and IL-1RA were significantly elevated in patients with BD who were acutely ill with the psychiatric illness compared to controls without BD, and their levels of IL-6 and IL-1RA decreased after treatment of acute episodes (Goldsmith et al., 2016). Several mechanisms on how peripheral inflammation can influence the central nervous system have been proposed. Both human and mice studies have demonstrated that peripheral inflammation of RA can up-regulate neuro-inflammation (Lampa et al., 2012), resulting in cytokine-induced neurotransmitter changes and microglial over-activation (Miller and Raison, 2016; Rosenblat and McIntyre, 2017). Reactive oxygen species and oxidative stress generated by inflammation may also induce neurological damage in regions affecting mood and cognition (Berk et al., 2011). These peripheral cytokines may cross the blood-brain barrier (BBB) and reach the brain directly through the leaky regions of BBB (such as the circumventricular organs) or through transport molecules (Quan and Banks, 2007). Activated immune cells may reach the brain parenchyma through the vasculature of the central nervous system. Peripheral cytokines may also indirectly influence signals in the brain by stimulating peripheral afferent nerves (such as the vagus nerve) (Marrie et al., 2018). Hypothalamic-pituitary-adrenal (HPA) axis overactivation is also another potential pathophysiologic mechanism, as it is known that proinflammatory cytokines can upregulate HPA axis activity (Barbosa et al., 2014; Rosenblat and McIntyre, 2017) and a recent meta-analysis showed that patients with BD has elevated levels of serum cortisol and ACTH compared to healthy controls. Moreover, higher level of cortisol is associated with manic phase (Belvederi Murri et al., 2016).

This observation may suggest that chronic inflammation could be a modifiable risk factor of BD and reduced risk of BD could be another health benefit of aggressive treatment to control inflammation in patients with chronic inflammatory disorders, especially RA. However,

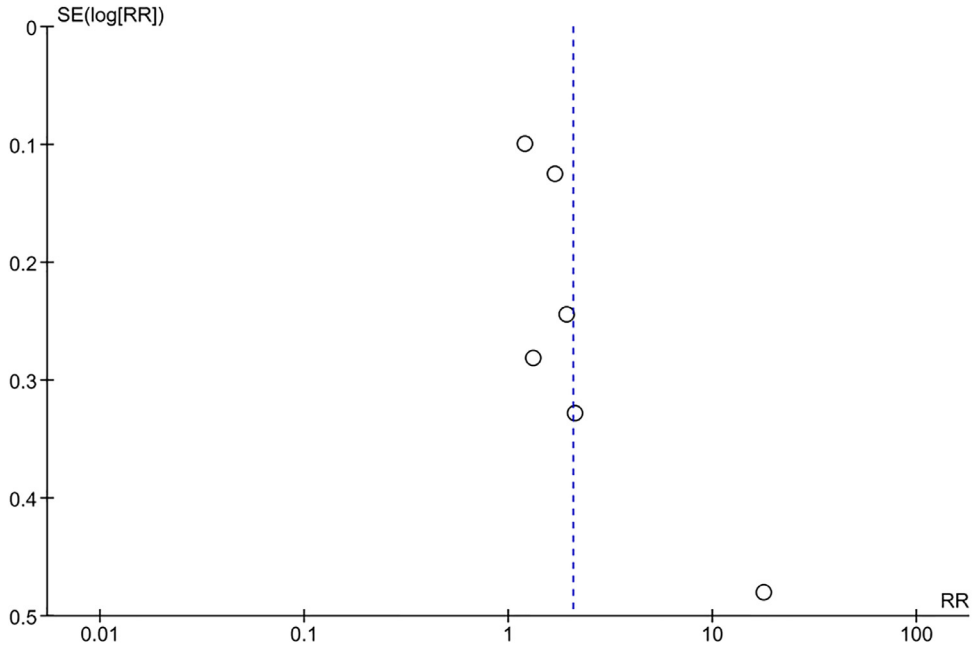

Fig. 3. Funnel plot of the meta-analysis of risk of bipolar disorder in patients with rheumatoid arthritis.

further investigations, such as cohort studies that compare the incidence of BD among patients with RA who are in remission versus those who have chronic active disease, are still required to confirm this potential benefit.

Second, corticosteroid, one of the most frequently used anti-inflammatory agents among patients with RA (Aletaha and Smolen, 2018), is known to cause psychiatric and cognitive adverse effects. Symptoms of hypomania, mania and depression, which are the major features of BD, have been reported with the use of corticosteroid as well (Brown and Chandler, 2001). Although data on how frequently these psychiatric adverse effects occur are limited, a prospective study found that 10% and 26% of patients who received an 8-day course of corticosteroid developed symptoms of depression and hypomania, respectively (Naber et al., 1996). The pathogenesis of psychiatric disturbance associated with corticosteroid therapy is not known with certainty. Possible mechanisms include toxic effects of corticosteroid on hippocampal neurons and other brain regions (Brown, 2009), effects on cholinergic and dopaminergic neurons (Gilad et al., 1987) and inhibition of serotonin release (Beshay and Pumariega, 1998).

Third, it has been suggested that functional disability and low quality of life are accountable for the increased risk of major depressive disorder and anxiety disorder in patients with RA (Covic et al., 2012; Dickens et al., 2003). In a similar fashion, they might also predispose patients to BD, especially among those with existing vulnerabilities.

It is also possible that BD and RA may share a common genetic predisposition as both diseases are known to have a strong hereditary component (Kurkó et al., 2013; Manji et al., 2003). However, no common susceptibility locus for both diseases has been identified yet. Further studies are still needed to explore this potential mechanism.

It should be noted that this systematic review and meta-analysis has some limitations and the pooled results should be interpreted with caution. First, all of the studies used large administrative databases and relied on diagnostic codes to identify RA and BD. Therefore, the accuracy of diagnoses could be limited. Second, the statistical heterogeneity in this study was high. However, the heterogeneity decreased to low level with the sensitivity analysis that excluded the study with a potentially inflated result from the pooled analysis. Third, the average age of participants across the included studies was 40–50 years, possibly due to the epidemiology of RA. This suggests that most patients included into this meta-analysis had later-onset BD and the findings of the current study may not be applicable to patients with younger-onset BD. Finally, although the funnel plot of the meta-analysis was reasonably symmetric and did not provide a suggestive evidence for the presence of publication bias, the reliability of the interpretation of the plot could be limited by the relatively small number of included studies.

5. Conclusion

In summary, this study found a significantly higher risk of developing bipolar disorder among patients with RA.

Conflict of interest

We do not have any financial or non-financial potential conflicts of interest.

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CRediT authorship contribution statement

Nipith Charoenngam: Conceptualization, Data curation, Methodology, Writing - original draft. **Ben Ponvilawan:** Conceptualization, Data curation, Methodology, Writing - original draft. **Patompong Ungprasert:** Conceptualization, Formal analysis, Methodology, Writing - review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112484.

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