DR ANDRE DELGADO (Orcid ID : 0000-0002-0339-4872)

MISS TAIANE CARDOSO (Orcid ID : 0000-0003-1925-8709)

Article type : Systematic Review or Meta-analysis

**Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review
and meta-analyses**
Risk of dementia in bipolar disorder

Jorge Velosa, MD^{1, 2, *}, Andre Delgado, MD^{1, 2, *}, Elizabeth Finger, MD, FRCPC, FAAN³,
Michael Berk, MD, PhD⁴, Flavio Kapczinski, MD, MSc, PhD, FRCPC¹, Taiane de Azevedo
Cardoso, PhD¹

* AD and JV should be considered joint first author

¹ McMaster University, Department of Psychiatry and Behavioural Neurosciences,
Hamilton, ON, Canada

² Hospital Beatriz Angelo, Department of Psychiatry and Mental Health, Loures,
Portugal

³ University of Western Ontario, Clinical Neurological Sciences, London, ON, Canada

⁴ Deakin University, School of Medicine, IMPACT Strategic Research Centre, Orygen
Youth Health, Melbourne, Australia

This is the author manuscript accepted for publication and has undergone full peer review
but has not been through the copyediting, typesetting, pagination and proofreading
process, which may lead to differences between this version and the [Version of Record](#).
Please cite this article as [doi: 10.1111/ACPS.13153](https://doi.org/10.1111/ACPS.13153)

This article is protected by copyright. All rights reserved

Corresponding author

Taiane de Azevedo Cardoso, MSc, PhD

Postdoctoral Fellow

Department of Psychiatry and Behavioural Neurosciences, McMaster University

Email: deazevet@mcmaster.ca

Abstract

Objectives: To assess whether bipolar disorder (BD) increases the rate of dementia, and whether lithium is related to a lower risk of dementia in BD.

Methods: A total of 10 studies (6,859 BD; 487,966 controls) were included in the meta-analysis to test whether BD is a risk factor for dementia. In addition, five studies (6,483 lithium; 43,496 non-lithium) were included in the meta-analysis about the potential protective effect of lithium in BD.

Results: BD increases the risk of dementia (odds ratio(OR): 2.96 [95%CI: 2.09-4.18], $p < 0.001$), and treatment with lithium decreases the risk of dementia in BD (OR:0.51 [95%CI:0.36-0.72], $p < 0.0001$). In addition, secondary findings from our systematic review showed that the risk of progression to dementia is higher in BD than in major depressive disorder (MDD). Moreover, the number of mood episodes predicted the development of dementia in BD.

Conclusion: Individuals with BD are at higher risk of dementia than both the general population or those with MDD. Lithium appears to reduce the risk of developing dementia in BD.

Keywords: Bipolar disorder, dementia, lithium, aging, neuroprogression, Alzheimer's, mania, depression, treatment, prevention.

Summations:

The diagnosis of bipolar disorder increases the risk to develop dementia three-fold.

Treatment with lithium decreased the risk for dementia by 49% in individuals with bipolar disorder.

Dementia can be seen as the endpoint of bipolar disorder staging model.

Limitations:

There is a possibility that publication bias may have potentially inflated our results.

The majority of the evidence comes from registry-based studies that have several limitations such as data collection, reliability of diagnosis, selection bias and confounders.

Additional studies are needed to understand the pathophysiology of BD that leads to cognitive deterioration, brain abnormalities and to the development of dementia.

Data availability statement:

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflict of Interest:

The authors have no conflict of interest in relation to this work.

Introduction

Bipolar disorder (BD) is an episodic illness with a heterogeneous clinical course. The lifetime prevalence of BD ranges from 0.6% to 2.4% worldwide^{1,2}. Many studies have shown that during the course of BD, cognitive impairment is an important feature in both acute and euthymic phases³. A systematic review showed that although the clinical course of mood disorders is heterogenous, both BD and MDD demonstrate evidence of clinical progression. In this sense, a higher number of mood episodes seems to be related to (a) increased risk of recurrence, (b) longer episodes, (c) increased severity of episodes, (d) decreased threshold for subsequent episodes, and (e) increased risk for dementia⁴. However, conflicting data about aging and cognitive

decline is found in the literature and despite positive findings, studies did not demonstrate faster cognitive deterioration in BD compared to controls^{5,6}.

One important consideration is whether cognitive impairment in BD may progress to dementia. To our knowledge, there is only one published meta-analysis showing that a BD diagnosis is a risk factor for dementia⁷. In addition, despite some evidence about the neuroprotective effects of lithium (in terms of protecting brain structure, relating to - increases in hippocampal volume and preventing white matter changes; - and cognition, relating to improvements in verbal memory⁸⁻¹¹), no meta-analysis has been performed to assess whether treatment with lithium decreases the risk of developing dementia in patients with BD. Thus, we aimed to: (1) update the literature examining BD as a risk factor for developing dementia; and (2) verify whether lithium protects against dementia in patients with BD.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed for the present review.

Search strategy

A literature search was conducted on July 8, 2019 according to the PRISMA statement, with no year or language restrictions, using the following databases: Pubmed, PsycInfo, and Scopus. We searched for a combination of the following search items (bipolar disorder OR bipolar disorders OR mania OR hypomania OR manic OR hypomanic OR manic-depressive disorder OR manic depressive disorder OR bipolar affective disorder) AND (dementia OR Alzheimer OR frontotemporal dementia). The search yielded 5080 articles: (Pubmed= 1556, PsycInfo= 1452, and Scopus= 2472), with 3926 remaining after duplicate removal.

To determine whether an article was relevant to our study, we used the following inclusion criteria: the study should (1) present original data, and (2) require a diagnosis of bipolar disorder preceding a diagnosis of dementia. The exclusion criteria were: (1)

1 reviews and meta-analyses, (2) case reports, and (4) studies where dementia was
2 considered as comorbidity and not as an outcome.

3 The studies were assessed by two blinded raters (AD and JV) who determined if studies
4 met inclusion criteria. The two raters assessed manuscripts independently and
5 divergences were resolved in a meeting with another researcher (TC). Firstly, the raters
6 screened articles by title and abstract, and after by full-text. All articles not fulfilling the
7 search criteria were excluded. The details of the search strategy are presented in
8 Figure 1.

10 **Data extraction**

11 Two researchers (AD and JV) were involved in the data extraction process. We
12 extracted: authorship, year of publication, country where the study took place, study
13 aims, study design, assessments, and main results.

15 **Quality assessment**

16 Each manuscript included was independently assessed by two blind researchers (AD
17 and JV) using the Newcastle-Ottawa Quality Assessment Scale (NOQAS)¹².
18 Disagreements were resolved by consensus in a meeting with another researcher (TC).

20 **Statistical analysis**

21 Random effects meta-analyses were performed using the RevMan 5.3. We conducted
22 two analyses: (1) to analyze the studies that investigated BD as a risk factor for
23 dementia, we used the number of cases diagnosed with dementia in both bipolar
24 disorder and non-bipolar disorder groups to calculate the odds ratio (OR); and (2) we
25 analyzed the studies that assessed whether treatment with lithium was associated
26 with a reduced risk of dementia in patients with BD. For this aim, we used the number
27 of cases diagnosed with dementia in lithium users and non-lithium users groups to
28 calculate the odds ratio (OR). Significance was set as $p < 0.05$. Cochrane's Q test was
29 performed to assess for statistical heterogeneity and the Higgins I² statistic was used
30 to determine the extent of variation between sample estimates with values ranging
31 from 0-100%. Studies were not included in the meta-analyses if the population
32 overlapped with another included study population or if it was not possible to

calculate the OR. If the information was not reported in the paper, we contacted the authors to request access to the data. We contacted four authors, and three of them answered our questions.

Results

The literature search yielded 5480 studies. Of these, 1554 were duplicates, 3888 studies were excluded as the titles and abstracts were not relevant to the research topic, leaving 38 potentially eligible studies for which the full text was reviewed. After this stage, 20 studies did not meet the inclusion criteria. A total of 18 studies met all criteria to be included in the systematic review (Figure 1). In addition, we searched the references of the included studies and found no additional studies to include.

From the 18 included studies, 10 (4 cohort, 6 case-control studies) were included in the meta-analysis to assess whether BD is a risk factor for dementia, and 5 (4 cohort, 1 case-control studies) were included in the meta-analysis to assess if lithium reduces the risk of dementia in BD. Finally, 4 cohort studies presenting preliminary evidence of differences between BD and MDD regarding the risk for developing dementia were included, and one study assessed which clinical characteristics contribute to risk for developing dementia in BD was also included, both as secondary outcomes of our systematic review.

1. Increased risk for dementia in bipolar disorder

1.1. Characteristics of included studies

Table 1 shows an overview of the included studies. Among the 11 studies, publication dates ranged from 1998 to 2018. Three studies were conducted in Taiwan, 3 in Australia, 2 in Denmark, 1 in the United Kingdom, 1 in Finland, and 1 in Brazil. The total sample size ranged from 209 to 190,041. All studies assessed the impact of BD on the development of dementia. Five studies had a longitudinal cohort design and 6 studies were case-control. For the cohort studies, the time of follow-up assessments ranged

from 3 to 17 years. Regarding the assessment of BD, the majority of the studies used ICD-9 (n=7), and the diagnosis of dementia was mainly performed using ICD-9 (n=7).

1.2. Increased risk for dementia in bipolar disorder: evidence from cohort studies

The systematic review included five cohort studies assessing whether BD is a risk factor for dementia. All studies showed that BD presents with an increased risk for developing dementia^{13–17}. Kessing et al. (2003) included all inpatients with a main diagnosis of BD, major depression, osteoarthritis or diabetes from January 1, 1977 to December 31, 1993, with no history of dementia before selection¹³. In this study BD patients had a higher risk of being diagnosed with dementia (HR 3.38, 95% CI 2.39-4.79 vs controls with osteoarthritis; HR 2.28, 95% CI 1.62-3.20 vs controls with diabetes). This study suggests that the cognitive impairment in mood disorders patients is not explained by a chronic disorder but by the mood disorder itself¹³. The impact of 19 severe chronic diseases in patients with BD and Schizophrenia was reported by Laursen et al (2011) in a population-based cohort study. The highest incidence rate ratios (IRR) for dementia were observed in both disorders (Schizophrenia: 5.84, 95% CI: 3.96-9.25; and BD: 11.52, 95% CI: 6.76-19.65) in comparison to the individuals without psychiatric contact¹⁴.

Additionally, Chen et al. (2015) included individuals older than 55 years with MDD or BD and without dementia in a 10 year period. Diagnosis of any type of dementia was identified during the 3 years follow-up or until death. The findings showed that BD had a higher risk of developing dementia when compared to controls (HR 5.58, 95% CI 4.26-7.32)¹⁵. Moreover, Almeida et al. (2016) included men aged 65–85 years, without dementia until 2 April 1996. Past diagnosis of BD was retrieved from another database that has been recorded prior to 2 April 1996. Follow-up started from this date until the outcome appeared (dementia or death) or until 30 June 2009 (database endpoint). Their findings showed that BD had a higher adjusted hazard of dementia (HR 2.30, 95% CI 1.80–2.94). Their data showed that elderly men with past diagnosis of BD are at higher risk of dementia which is greater for those with either a long-standing or recent history of BD. Thus, it appears that changes in mood later in life may represent, in at least some cases, an early clinical expression of neurodegenerative processes that will ultimately lead to the diagnosis of dementia¹⁶. Finally, Almeida et al. (2018) included

men aged 65–85 during 1996–1998 from a specific Australian population. Then, they retrieved information about the diagnosis of BD from another database and started a follow-up until 31 December 2013. The results showed that regardless of the age of BD onset, these individuals had an increased risk for dementia (Age < 50 - HR 3.46, 95% CI 2.41 - 4.95; Age ≥ 50 - HR 2.26, 95% CI 1.76 - 2.90). Incident dementia was higher when onset of BD illness was before 50 years and after 60 years, even though this effect was not significant¹⁷.

1.3. Increased risk for dementia in bipolar disorder: evidence from case-control studies

Six case-control studies were included in the systematic review. In five of them, BD patients had higher risk of developing dementia^{18–22}, while one study did not find this association²³. Cooper et al. (1998) included all residents above 60 years from a database including patients with dementia from May 1993 to April 1995. They then matched the ones with a previous history of psychiatric disorder with other patients with dementia without history of psychiatric illness (controls). Their results suggest that history of psychiatric disorders, especially a major mental disorder like BD, appears to be a risk for dementia. They also found that this association is not linked to a specific subtype of dementia, like Alzheimer's disease (AD)¹⁸. Furthermore, Wu et al. (2013) selected patients with 45 years or above who were diagnosed with dementia between January 2000 and December 2009. Then, they searched for the presence of a previous BD diagnostic. The findings demonstrated that the diagnosis of dementia is higher in BD patients as compared to controls (OR 4.07; 95% CI 3.08–5.37) and these patients had greater risk for both pre-senile and senile dementia¹⁹.

Moreover, Zilkens et al. (2014) included all persons with Incident dementia between 2000 and 2009 aged 65 to 84 years, from 4 databases. Then, they assessed the exposure of medical risk factors such as BD, which had to be present 10 years before dementia onset. Their results showed that BD had a higher risk for dementia (OR 4.71, 95% CI 2.29–9.65)²⁰. In addition, Taipale et al. (2015) included all patients with AD diagnosis alive on 31 December 2005 (n=28093) and matched a comparison individual without that diagnosis. They searched for psychiatry history, including BD, before the onset of AD. Although the aim of the study was not to determine whether BD is a risk

factor for dementia, their data shows a higher risk of being diagnosed with dementia in subjects with BD²¹. Finally, Cheng et al. (2017) included individuals with 65 years old or older who had an AD diagnosis, from a national database between January 2007 to December 2009. For each subject, 2 controls without dementia were matched. Their findings suggest that BD had a higher risk of developing dementia (OR 2.34, 95% CI 2.18–2.51)²².

In contrast, Aprahamian et al. (2014) included older adults whom they divided into 2 groups, one without dementia and a second with mild AD. Their results showed no association between BD and dementia. However, their findings demonstrated that BD patients commonly had cognitive impairments, even in euthymia²³.

1.4. Increased risk for dementia in bipolar disorder: results from the meta-analysis

Our meta-analysis included 10 out of the 11 studies described above, including 6,859 BD individuals and 487,966 non-BD, and our results confirmed that the diagnosis of BD is associated with a 3 fold increase in the risk of developing dementia (OR: 2.96 [95% CI: 2.09 - 4.18], $p < 0.001$) (Figure 2). The funnel plot for this association was asymmetric indicating potential publication bias (Supplementary Figure 1).

2. Effects of lithium

2.1. Characteristics of included studies

Table 2 shows an overview of the included studies. Among the 6 studies, publication dates ranged from 2007 to 2017. Two studies were conducted in the United States, 1 in Taiwan, 1 in Denmark, 1 in Switzerland, and 1 in Brazil. Total sample size ranged from 114 to 41,251. All studies assessed the use of lithium and the development of dementia in BD individuals. Five studies had a longitudinal cohort design and 1 study was case-control.

2.2. Neuroprotective effect of lithium: results from the extant literature

Six studies assessed the neuroprotective effect of lithium in patients with BD^{22,24–28}. Four of these studies found that lithium seems to reduce the risk of dementia in BD patients.

Angst et al. (2007) included 406 patients with major mood disorders and did not find a reduced risk of dementia with any medication (including lithium). However, when

examining only patients with BD, long-term lithium and clozapine use were associated with better functioning in demented patients²⁴. In addition, Nunes et al. (2007) in a study including 114 elderly patients with BD found that recent use of lithium was associated with a reduced prevalence of AD. Their results indicate that lithium seems to reduce the risk of dementia in patients with BD and raises the question of whether lithium may have neuroprotective effects that protect against the development of dementia in BD²⁵.

Moreover, Kessing et al. (2010) included 4,856 patients with BD doing different treatments (lithium, anticonvulsants, antidepressants, and antipsychotics) using a registry-based study. The findings suggest that only continued treatment with lithium was related to a lower rate of dementia²⁶. Finally, Gerhard et al. (2015) included 41,931 patients and demonstrated that continued use of lithium in elderly BD patients was associated with a lower incidence of dementia (hazard ratio (HR) = 0.77, 95% CI 0.60–0.99)²⁷.

Gildengers et al. (2009) found no differences between lithium or divalproex users versus those not exposed regarding the development of dementia in an underpowered study including 33 patients with BD²⁸. Also, Cheng et al. (2017) in a study with 63,347 patients with AD found that in overall population, there was an increased risk of AD with lithium use (as well as other mood stabilizers, valproic acid and carbamazepine). However, no excess risk was discernible among people with BD (aOR=1.36; 95% CI, 0.89–2.09). No association was seen between any use of lithium and AD risk, nor for associations between higher levels of use (cumulative dose, cumulative period of use, or mean daily dose) and AD risk²².

2.3. Neuroprotective/neurotrophic effect of lithium: results from the meta-analysis

We included 5 out of 6 studies described above in our meta-analysis. The four studies included 6,483 lithium users, and 43,496 non-lithium users. Our results showed that lithium treatment decreased the risk for dementia by 49% in BD individuals (OR:0.51 [95%CI:0.36-0.72], $p<0.0001$). (Figure 3). The funnel plot for this association was symmetric indicating no publication bias (Supplementary Figure 2).

3. Secondary findings from the systematic review

3.1. Differences between bipolar disorder vs major depressive disorder and rates of dementia

The systematic review included four studies assessing the differences between BD and MDD in terms of risk to develop dementia. Overall, the findings showed that both MDD and BD are associated with an increased risk for developing dementia^{13,29,30}. Additionally, the risk seems to be greater for BD as compared to MDD^{15,29,30}.

Kessing et al (1999) in a case-registry study including patients with MDD (n=3,363), BD (n=518), schizophrenia (n=1,025) and neurotic disorder (n=8,946), estimated the rate of developing dementia during 21 years of follow-up. The findings showed that BD patients had a higher risk of developing dementia, followed by MDD, schizophrenia and finally neurotics²⁹. Also, Kessing et al. (2004), in a study including 22,788 patients with a diagnosis of affective disorders, showed that the ones with one manic episode had an increased risk of dementia (HR 1.46 (95% CI 1.01 to 2.13)) when compared with the ones with one depressive episode³⁰. In a sample of 2,291 patients aged 55 years with MDD or BD, Chen et al. (2015) reported that BD patients had an 87% increased risk of developing dementia when compared to MDD patients during the study follow-up (HR 1.87, 95% CI 1.48-2.37)¹⁵. To evaluate the risk of receiving a dementia diagnosis, Kessing et al. (2003) recruited a sample of patients with mania (n=2,007), depression (n=11,741), osteoarthritis (81,380) and diabetes (69,149) with a first-ever discharge from hospital between 1977 and 1993. The results showed that patients diagnosed with MDD at the first discharge had significantly higher risk of being diagnosed with dementia during long-term follow-up than patients with mania at first discharge (χ^2 14.5, $p=0.0001$)¹³.

3.2. Clinical characteristics associated with the risk of dementia in bipolar disorder

In a study including 22,788 patients with the diagnosis of affective disorders, Kessing et al. (2004) showed that the number of episodes foretold the rate of dementia: every new episode leading to admission increased the rate by 13% (95% CI: 9% to 16%) for patients with MDD and by 6% (95% CI: 3% to 10%) for patients with BD³⁰.

Quality of assessment of the included studies

1 For the BD progression to dementia meta-analysis, overall, the mean Newcastle-
2 Ottawa Quality Assessment Scale score was 7.16. We identified eight good quality
3 studies and eleven poor quality studies (Supplementary Table 1). Most of the poor
4 quality studies failed in comparability and/or adequate follow-up.

5 Regarding lithium use and the risk for dementia in BD meta-analysis, overall, the mean
6 NOQAS score was 7.67. We identified five good quality studies and one poor quality
7 studies (Supplementary table 2). The poor quality study failed in terms of adequate
8 follow-up.

10 Discussion

11 This meta-analysis showed that BD is a risk factor for developing dementia. We also
12 found that lithium is associated with a reduced risk of dementia in BD patients. In
13 addition, secondary findings from the systematic review showed that the risk of
14 progression to dementia is higher in BD than in MDD. Finally, the number of episodes
15 in both MDD and BD patients predicts the progression to dementia.

16 Our findings are in line with two prior meta-analyses showing that BD is a risk factor
17 for dementia^{7,31,40}, and also with a recent large study (published after our literature
18 search was performed) showing that BD is a predictor of Alzheimer's disease³². Due to
19 our wider search strategy, we were able to include four older studies (not included in
20 the most updated previous meta-analysis⁷) and two studies that were conducted after
21 the publication of the most updated previous meta-analysis⁷. It is important to
22 highlight that BD and dementia present some similarities in the clinical
23 manifestation³³⁻³⁵(agitation, psychotic, mood and cognitive symptoms), regarding the
24 structural brain neuroimaging^{33,36}(enlarged lateral ventricles and white matter
25 hyperintensities using magnetic resonance imaging), and a recent study showed that
26 both disorders presented a shared genetic basis³⁷. Those data together indicates a
27 potential shared pathophysiology, which can, in turn, contribute for the misdiagnosis
28 between these two disorders. Despite the above similarities, a recent study showed
29 that a set of clinical, neuropsychological, and blood biomarker assessments were able
30 to discriminate the two conditions, such as: overall functioning, memory, and oxidative
31 stress³⁸. As an attempt to minimize the bias of misdiagnosis in our systematic review

1 and meta-analysis, we selected only studies of incident dementia in patients previously
2 diagnosed as BD. By excluding the cases of patients with dementia who reported
3 comorbid manic symptoms at baseline, we attempted to access the progression of the
4 bipolar disease into dementia.

5 Our findings can be interpreted in light of the theory of neuroprogression^{39,40}.
6 Neuroprogression is marked by progressive cognitive⁴¹ and functioning impairment⁴²,
7 as well as altered brain scans and biomarkers of underlying processes (inflammation,
8 oxidative stress, apoptosis, neurogenesis) that are evident in some cases of bipolar
9 disorder^{43,44}. Recent evidence suggests that structural brain abnormalities in gray and
10 white matter similar to those observed in age-related neurodegenerative diseases
11 such as dementia can also be observed in BD and may be linked to accelerated brain
12 aging^{45,46}. Staging is a concept related to neuroprogression which has been introduced
13 to explain progressive decline over the course of disease. A recent study showed that
14 there is an association between later stages of BD and increasing levels of
15 neurocognitive and social dysfunction⁴⁷. We could argue, based on our study and other
16 meta-analyses, that the risk for dementia could be seen as a potential endpoint of this
17 neuroprogressive course^{7,31}. Related to this topic, it is important to assess whether
18 cognitive impairment in BD may progress to dementia, and whether those people with
19 BD and cognitive complaints are the ones at risk of dementia. We did not found data
20 to evaluate this topic but future studies should consider this as a possibility.

21 To the best of our knowledge, this is the first meta-analysis evaluating the risk of
22 dementia associated with lithium use in BD patients. Conflicting evidence about
23 lithium and dementia is found in the literature. Dunn et al. 2005, found that patients
24 treated with lithium had an increased risk of being diagnosed with dementia⁴⁸.
25 However, the study had some limitations such as small sample size of patients treated
26 with lithium and the lack of psychiatric history. Also, Cheng et al. 2017 found that
27 lithium seems to increase the risk of AD in the general population. Nonetheless, this
28 association was not observed when patients with BD were analysed. This is important
29 because lithium is mainly used in BD and, as discussed before, BD seems to be
30 associated with a higher risk for dementia²². On the other hand, Kessing et al. 2008,
31 found that only long-term use of lithium reduced the rate of dementia in a design
32 taking account of confounding by indication⁴⁹. Long-term continued lithium treatment

has been found associated with reduction of the rate of dementia to the same level as that for the general population⁴⁹. The association between the number of prescriptions for lithium and dementia was unique and different from the association between the number of prescriptions for anticonvulsants and dementia⁴⁹. All findings were replicated in sub-analyses with AD as the outcome. Also, Kessing et al. 2017 found that in general population long-term increased lithium exposure in drinking water was associated with a lower incidence of dementia⁴. Our meta-analysis showed that lithium is associated with reduced development of dementia in BD. This effect could be due to lithium's neuroprotective and neurotrophic properties. Differential mechanisms have been proposed for the neuroprotective effects associated with lithium: (1) lithium inhibits glycogen synthase kinase-3 (GSK3)^{50,51}; (2) regulates calcium levels related with N-methyl-D-aspartate (NMDA) receptors; (3) increases brain-derived neurotrophic factor (BDNF)⁵²; (4) induces the repressor element 1-silencing transcription factor (REST)⁵³, (5) reduces apoptotic markers and enhances neurogenesis and mitochondrial dysfunctions^{54–56}. These effects of lithium overlap with the known risk pathways for dementia – for a review of the neurobiology of lithium in dementia see⁵⁷. Pilot studies of lithium in mild cognitive impairment showed that lithium may prevent further deterioration⁵⁸. Unfortunately, most lithium studies did not address the question of whether lithium users are healthier than non users, raising the question if there are other variables such as diabetes, vascular, thyroid or kidney disease increasing the risk of dementia.

Multiple reviews have shown that MDD patients have a higher risk for dementia^{31,59,60}. Our data suggest that BD patients may have an even higher risk to develop dementia as compared to MDD. This is in-line with other meta-analysis showing that the risk for dementia is higher in BD than in MDD (BD 2.36 vs MDD 1.65 to 2)^{7,59,60}. There are many possible explanations for these results: (1) different underlying pathophysiology despite symptom overlap (2) number of episodes – people with BD could have a higher number of episodes, which increases the risk for dementia, (3) (hypo)manic episodes could have a stronger impact on risk for developing dementia as compared to depressive episodes, and (4) time spent in an episode - BD could have a longer exposition to an episode, which can also increase the risk for dementia. Kessing et al. 2004 reported that the number of episodes significantly predict the rate of dementia

1 in both MDD and BD³⁰. The number of manic episodes seems to be the clinical marker
2 most robustly associated with neuroprogression in BD³⁹. Clinical studies also describe
3 an earlier onset, recurrent episodes, substance use disorder, medical comorbidities
4 and worse health related behaviors as the risk factors^{61,62}. In addition, BD is associated
5 with inflammatory dysregulation (higher concentration of C reactive protein (CRP), IL-2
6 and IL-6 receptors and tumor necrosis factor – receptor 1 (TNF1), which may also
7 contribute to the development of dementia and neuroprogression in bipolar
8 disorder^{63–67}.

9 Our findings should be interpreted in light of some limitations. As our meta-analysis
10 included only published studies it could be at risk of publication bias. Also, in order to
11 perform the meta-analyses we utilized non-adjusted results (absolute number of
12 patients who developed dementia) which may have introduced some bias (health care
13 utilization, comorbid medical and psychiatric disorders and other psychotropic
14 medication) in our results. Most of the studies included were registry-based which
15 have several study-based limitations (data collection, diagnostic reliability, selection
16 bias as well as lack of information about confounders). Also, it is important to mention
17 that usually the first manifestation of BD is at the early adulthood⁶⁸, while the
18 diagnosis of dementia is more common after 65 years old⁶⁸. In this sense, despite the
19 studies matched the sample (BD vs non-BD) by age, our findings might be somewhat
20 age-related. Despite these limitations, to the best of our knowledge, this is the first
21 meta-analysis showing the potential effect of lithium preventing dementia in BD.

22 In conclusion, even though further studies are required to understand the
23 pathophysiology of BD-related cognitive deterioration and the development of
24 dementia, our meta-analysis showed that BD patients are at higher risk for dementia
25 when compared to the general population and patients with MDD. We also showed
26 that lithium is associated with reduced risk of dementia in BD. This raises the question
27 as to whether lithium may be a preventative agent in BD against the prospective
28 development of dementia. Data from the present meta-analysis will set the stage to
29 future randomized controlled trials to test the ability of lithium to prevent incident
30 dementia among patients with BD.

Acknowledgments

MB is supported by a NHMRC Senior Principal Research Fellowship (1059660 and APP1156072).

List of legends:

Figure 1: Flow diagram showing the search, article selection and extraction process

Figure 2: Forest plot of the meta-analysis of BD as risk factor for dementia.

Figure 3: Forest plot of the meta-analysis of neuroprotective/neurotrophic effect of lithium.

Table 1: Characteristics of the studies included for the assessment whether bipolar disorder as a risk factor for dementia.

Table 2: Characteristics of the studies included for the assessment whether the neuroprotective/neurotrophic effect of lithium.

Supplementary table 1: Risk of bias for cohort and case-control studies as assessed by The Newcastle-Ottawa Scale: Bipolar disorder as a risk factor for dementia. The greater the total score, the higher the quality of the study.

Supplementary table 2: Risk of bias for cohort and case-control studies as assessed by The Newcastle-Ottawa Scale: Neuroprotective/neurotrophic effect of lithium. The greater the total score, the higher the quality of the study.

Supplementary figure 1: Funnel plot for the studies included in the meta-analysis assessing whether bipolar disorder is a risk factor for dementia.

Supplementary figure 2: Funnel plot for the studies included in the meta-analysis assessing whether lithium is related to a lower risk of dementia in bipolar disorder.

References

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder Bipolar disorder. *Lancet*. 2016. doi:10.1016/S0140-6736(15)00241-X
2. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry*. 2011. doi:10.1001/archgenpsychiatry.2011.12

3. Cardoso T, Bauer IE, Meyer TD, Kapczinski F, Soares JC. Neuroprogression and Cognitive Functioning in Bipolar Disorder: A Systematic Review. *Curr Psychiatry Rep.* 2015;17(9). doi:10.1007/s11920-015-0605-x
4. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. *Acta Psychiatr Scand.* 2017. doi:10.1111/acps.12667
5. Depp CA, Savla GN, Moore DJ, et al. Short-term course of neuropsychological abilities in middle-aged and older adults with bipolar disorder. *Bipolar Disord.* 2008. doi:10.1111/j.1399-5618.2008.00601.x
6. Santos JL, Aparicio A, Bagney A, et al. A five-year follow-up study of neurocognitive functioning in bipolar disorder. *Bipolar Disord.* 2014. doi:10.1111/bdi.12215
7. Diniz BS, Teixeira AL, Cao F, et al. History of Bipolar Disorder and the Risk of Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry.* 2017;25(4):357-362. doi:10.1016/j.jagp.2016.11.014
8. Machado-Vieira R, Zanetti MV, Otaduy MC, et al. Increased Brain Lactate during Depressive Episodes and Reversal Effects by Lithium Monotherapy in Drug-Naive Bipolar Disorder: A 3-T 1H-MRS Study. *J Clin Psychopharmacol.* 2017. doi:10.1097/JCP.0000000000000616
9. Daglas R, Cotton SM, Allott K, et al. A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study. *Eur Psychiatry.* 2016. doi:10.1016/j.eurpsy.2015.09.460
10. Yucel K, McKinnon MC, Taylor VH, et al. Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: A longitudinal MRI study. *Psychopharmacology (Berl).* 2007. doi:10.1007/s00213-007-0906-9
11. Berk M, Dandash O, Daglas R, et al. Neuroprotection after a first episode of mania: A randomized controlled maintenance trial comparing the effects of lithium and quetiapine on grey and white matter volume. *Transl Psychiatry.* 2017. doi:10.1038/tp.2016.281

12. Wells G, Shea B, O'Connell D, Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON: Ottawa Hospital Research Institute.
13. Kessing LV, Nilsson FM. Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. *J Affect Disord*. 2003;73(3):261-269. doi:10.1016/S0165-0327(02)00004-6
14. Laursen TM, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. *PLoS One*. 2011;6(9). doi:10.1371/journal.pone.0024597
15. Chen MH, Li CT, Tsai CF, et al. Risk of Subsequent Dementia Among Patients With Bipolar Disorder or Major Depression: A Nationwide Longitudinal Study in Taiwan. *J Am Med Dir Assoc*. 2015;16(6):504-508. doi:10.1016/j.jamda.2015.01.084
16. Almeida OP, McCaul K, Hankey GJ, Yeap BB, Golledge J, Flicker L. Risk of dementia and death in community-dwelling older men with bipolar disorder. *Br J Psychiatry*. 2016;209(2):121-126. doi:10.1192/bjp.bp.115.180059
17. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Older men with bipolar disorder: Clinical associations with early and late onset illness. *Int J Geriatr Psychiatry*. 2018;33(12):1613-1619. doi:10.1002/gps.4957
18. Cooper B, Holmes C. Previous psychiatric history as a risk factor for late-life dementia: A population-based case-control study. *Age Ageing*. 1998. doi:10.1093/ageing/27.2.181
19. Wu KY, Chang CM, Liang HY, et al. Increased risk of developing dementia in patients with bipolar disorder: A nested matched case-control study. *Bipolar Disord*. 2013;15(7):787-794. doi:10.1111/bdi.12116
20. Zilkens R, Bruce D, Duke J, Spilsbury K, Semmens J. Severe Psychiatric Disorders in Mid-Life and Risk of Dementia in Late- Life (Age 65-84 Years): A Population Based Case-Control Study. *Curr Alzheimer Res*. 2014;11(7):681-693. doi:10.2174/1567205011666140812115004

21. Taipale H, Koponen M, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S. Long-term use of benzodiazepines and related drugs among community-dwelling individuals with and without Alzheimer's disease. *Int Clin Psychopharmacol*. 2015;30(4):202-208. doi:10.1097/YIC.0000000000000080
22. Cheng C, Zandi P, Stuart E, et al. Association between lithium use and risk of Alzheimer's disease. *J Clin Psychiatry*. 2017;78(2):e139-e145. doi:10.4088/JCP.15m10304
23. Aprahamian I, Radanovic M, Nunes PV, Ladeira RB, Forlenza OV. The use of the Clock Drawing Test in bipolar disorder with or without dementia of Alzheimer's type. *Arq Neuropsiquiatr*. 2014;72(12):913-918. doi:10.1590/0004-282x20140153
24. Angst J, Gamma A, Gerber-Werder R, Zarate CA, Manji HK. Does long-term medication with lithium, clozapine or antidepressants prevent or attenuate dementia in bipolar and depressed patients? *Int J Psychiatry Clin Pract*. 2007;11(1):2-8. doi:10.1080/13651500600810133
25. Nunes P V., Forlenza O V., Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *Br J Psychiatry*. 2007. doi:10.1192/bjp.bp.106.029868
26. Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? *Bipolar Disord*. 2010;12(1):87-94. doi:10.1111/j.1399-5618.2009.00788.x
27. Gerhard T, Devanand DP, Huang C, Crystal S, Olfson M. Lithium treatment and risk for dementia in adults with bipolar disorder: Population-based cohort study. *Br J Psychiatry*. 2015;207(1):46-51. doi:10.1192/bjp.bp.114.154047
28. Gildengers AG, Mulsant BH, Begley A, et al. The longitudinal course of cognition in older adults with bipolar disorder. *Bipolar Disord*. 2009;11(7):744-752. doi:10.1111/j.1399-5618.2009.00739.x
29. Kessing L V., Olsen EW, Mortensen PB, Andersen PK. Dementia in affective disorder: A case-register study. *Acta Psychiatr Scand*. 1999;100(3):176-185. doi:10.1111/j.1600-0447.1999.tb10843.x

30. Kessing L V., Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *J Neurol Neurosurg Psychiatry*. 2004;75(12):1662-1666. doi:10.1136/jnnp.2003.031773
31. Da Silva J, Gonçalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: Systematic review. *Br J Psychiatry*. 2013;202(3):177-186. doi:10.1192/bjp.bp.111.101931
32. Rochoy M, Bordet R, Gautier S, Chazard E. Factors associated with the onset of Alzheimer's disease: Data mining in the French nationwide discharge summary database between 2008 and 2014. *PLoS One*. 2019. doi:10.1371/journal.pone.0220174
33. Kontis D, Theochari I, Tsalta E. [Dementia and bipolar disorder on the borderline of old age]. *Psychiatrike*. 2013;24(2):132-144.
34. Ng B, Camacho A, Lara DR, Brunstein MG, Pinto OC, Akiskal HS. A case series on the hypothesized connection between dementia and bipolar spectrum disorders: Bipolar type VI? *J Affect Disord*. 2008;107(1-3):307-315. doi:10.1016/j.jad.2007.08.018
35. Masouy A, Chopard G, Vandel P, et al. Bipolar disorder and dementia: Where is the link? *Psychogeriatrics*. 2011;11(1):60-67. doi:10.1111/j.1479-8301.2010.00348.x
36. Haller S, Xekardaki A, Delaloye C, et al. Combined analysis of grey matter voxel-based morphometry and white matter tract-based spatial statistics in late-life bipolar disorder. *J Psychiatry Neurosci*. 2011;36(6):391-399. doi:10.1503/jpn.100140
37. Drange OK, Smeland OB, Shadrin AA, et al. *iv o r l a n o l*. 2019. doi:10.3389/fnins.2019.00220
38. Besga A. Discrimination between Alzheimer's Disease and Late Onset Bipolar. 2015;7(December):1-9. doi:10.3389/fnagi.2015.00231
39. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. *Acta Psychiatr Scand*. 2016. doi:10.1111/acps.12581
40. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying

- neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev*. 2011. doi:10.1016/j.neubiorev.2010.10.001
41. Van Rheenen TE, Lewandowski KE, Bauer IE, et al. Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: an overview of evidence. *Bipolar Disord*. 2019;bdi.12821. doi:10.1111/bdi.12821
42. López-Villarreal A, Sánchez-Morla, Eva María Jiménez-López E, Martínez-Vizcaíno V, et al. Progression of the functional deficit in a group of patients with bipolar disorder. A cluster analysis based on longitudinal data. *Eur Arch Psychiatry Clin Neurosci*. 2019;(0123456789). doi:10.1007/s00406-019-01050-9
43. Berk M, Conus P, Kapczinski F, et al. From neuroprogression to neuroprotection: Implications for clinical care. *Med J Aust*. 2010.
44. Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: Implications for pathophysiology and treatment. *Neurosci Biobehav Rev*. 2008. doi:10.1016/j.neubiorev.2007.10.005
45. Gildengers AG, Chisholm D, Butters MA, et al. Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: Evidence for neuroprogression? *Psychol Med*. 2013. doi:10.1017/S0033291712001614
46. Sibille E. Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. *Dialogues Clin Neurosci*. 2013.
47. Tatay-Manteiga A, Correa-Ghisays P, Cauli O, Kapczinski FP, Tabarés-Seisdedos R, Balanzá-Martínez V. Staging, Neurocognition and Social Functioning in Bipolar Disorder. *Front Psychiatry*. 2018. doi:10.3389/fpsy.2018.00709
48. Dunn N, Holmes C, Mullee M. Does lithium therapy protect against the onset of dementia? *Alzheimer Dis Assoc Disord*. 2005. doi:10.1097/01.wad.0000155068.23937.9b
49. Kessing LV, Søndergård L, Forman JL, Andersen PK. Lithium treatment and risk of dementia. *Arch Gen Psychiatry*. 2008. doi:10.1001/archpsyc.65.11.1331

50. Lovestone S, Davis DR, Webster MT, et al. Lithium reduces tau phosphorylation: Effects in living cells and in neurons at therapeutic concentrations. *Biol Psychiatry*. 1999. doi:10.1016/S0006-3223(98)00183-8
51. Foland LC, Altshuler LL, Sugar CA, et al. Increased volume of the amygdala and hippocampus in bipolar patients treated with lithium. *Neuroreport*. 2008. doi:10.1097/WNR.0b013e3282f48108
52. Leyhe T, Eschweiler GW, Stransky E, et al. Increase of bdnf serum concentration in lithium treated patients with early alzheimer's disease. *J Alzheimer's Dis*. 2009. doi:10.3233/JAD-2009-1004
53. Lu T, Aron L, Zullo J, et al. REST and stress resistance in ageing and Alzheimer's disease. *Nature*. 2014. doi:10.1038/nature13163
54. Bijur GN, De Sarno P, Jope RS. Glycogen synthase kinase-3 β facilitates staurosporine- and heat shock- induced apoptosis. Protection by lithium. *J Biol Chem*. 2000. doi:10.1074/jbc.275.11.7583
55. Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. *J Neurochem*. 2000. doi:10.1046/j.1471-4159.2000.0751729.x
56. Scaini G, Rezin GT, Carvalho AF, Streck EL, Berk M, Quevedo J. Mitochondrial dysfunction in bipolar disorder: Evidence, pathophysiology and translational implications. *Neurosci Biobehav Rev*. 2016. doi:10.1016/j.neubiorev.2016.06.040
57. Morris G, Berk M. The Putative Use of Lithium in Alzheimer's Disease. *Curr Alzheimer Res*. 2016. doi:10.2174/1567205013666160219113112
58. Andrade Nunes M, Araujo Viel T, Sousa Buck H. Microdose Lithium Treatment Stabilized Cognitive Impairment in Patients with Alzheimer's Disease. *Curr Alzheimer Res*. 2013. doi:10.2174/156720513804871354
59. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry*. 2013.

doi:10.1192/bjp.bp.112.118307

60. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and Risk for Alzheimer Disease. *Arch Gen Psychiatry*. 2006. doi:10.1001/archpsyc.63.5.530

61. Hunt GE, Malhi GS, Cleary M, Lai HMX, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: Systematic review and meta-analysis. *J Affect Disord*. 2016. doi:10.1016/j.jad.2016.07.011

62. Rise IV, Haro JM, Gjervan B. Clinical features, comorbidity, and cognitive impairment in elderly bipolar patients. *Neuropsychiatr Dis Treat*. 2016. doi:10.2147/NDT.S100843

63. Pfaffenseller B, Fries GR, Wollenhaupt-Aguiar B, et al. Neurotrophins, inflammation and oxidative stress as illness activity biomarkers in bipolar disorder. *Expert Rev Neurother*. 2013. doi:10.1586/14737175.2013.811981

64. Grande I, Magalhães P V., Chendo I, et al. Staging bipolar disorder: Clinical, biochemical, and functional correlates. *Acta Psychiatr Scand*. 2014. doi:10.1111/acps.12268

65. Tatay-Manteiga A, Balanzá-Martínez V, Bristot G, Tabarés-Seisdedos R, Kapczinski F, Cauli O. Clinical staging and serum cytokines in bipolar patients during euthymia. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2017. doi:10.1016/j.pnpbp.2017.04.028

66. Vasconcelos-Moreno MP, Fries GR, Gubert C, et al. Telomere Length, Oxidative Stress, Inflammation and BDNF Levels in Siblings of Patients with Bipolar Disorder: Implications for Accelerated Cellular Aging. *Int J Neuropsychopharmacol*. 2017. doi:10.1093/ijnp/pyx001

67. Wiener CD, Moreira FP, Cardoso TA, et al. Inflammatory cytokines and functional impairment in drug-free subjects with mood disorder. *J Neuroimmunol*. 2017. doi:10.1016/j.jneuroim.2017.03.003

68. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders 1*. American Psychiatric Association.; 2013.

Author Manuscript

Table 1: Characteristics of the studies included for the assessment whether bipolar disorder as a risk factor for dementia.

Cooper, 1998, United Kingdom	To test if the risk for D is increased by a history of earlier psychiatric illness.	Case-Control / Registry-based	ICD-8, ICD-9	n total = 1,118; BD = 6 (0.5%) BD to D = 6 (100%) Controls to D = 553 (49.7%)	8/9	Yes
Kessing, 2003, Denmark	To assess if MDD or BD have an increased risk of developing D compared to other chronic illnesses	Cohort / Registry-base	ICD-8	n osteoarthritis total = 83,387 BD = 2,007 (2.4%) BD to D = 38 (1.9%) (OR 3.38, 95% CI 2.39-4.79) Controls to D = 895 (1.1%) n diabetes total = 71,156 BD = 2,007 (2.8%) BD to D = 38 (1.9%) (OR 2.28, 95% CI 1.62-3.20) Controls to D = 691 (1%)	7/9	Yes
Laursen, 2011, Denmark	To investigate the impact of severe chronic diseases on excess mortality in individuals with psychotic disorders	Cohort/ Registry-base	ICD-8, ICD-10	Dementia had the highest IRR (IRR: 11.52, 95% CI 6.76-19.65) in individuals with bipolar disorder	8/9	Yes†
Wu, 2013, Taiwan	To investigate if BD patients were at an increased risk for developing D.	Case-Control / Registry-based	ICD-9	n total = 64,804; BD = 229 (0.4%) BD to D = 114 (49.8%) (OR 4.32, 95% CI 3.21-5.82) Controls to D = 9,190 (14.2%)	8/9	Yes
Aprahamian, 2014, Brazil	To evaluate the performance of the CDT, in patients with BD with and without probable AD.	Case-Control	DSM-IV	n total = 209; BD = 106 (50.7%) BD to D = 27 (25.5%) Controls to D = 33 (32%)	5/9	No‡
Zilkens, 2014, Australia	To assess the association of history of psychiatric disorders with D.	Case-Control / Registry-base	ICD-10	n total = 27,136; BD = 68 (0.3%) BD to D = 59 (86.8%) (OR 4.71, 95% CI 2.29-9.65) Controls to D = 13,509 (49.9%)	8/9	Yes
Chen, 2015, Taiwan	To assess the risk of dementia among BD or MDD.	Cohort / Registry-base	ICD-9	n total = 2,408; BD = 345 (14.3%) BD to D = 92 (26.7%) (HR 5.58, 95% CI 4.26-7.32) MDD to D = 322 (HR 3.02, 95% CI 2.46-3.70) Controls to D = 133 (6.2%)	7/9	Yes

Taipale, 2015, Finland	To investigate the prevalence of BZD and BZDR use, and associated factors among individuals with and without AD	Case-Control / Registry-based	ICD-8, ICD-9, ICD-10	n total = 49,951; BD = 225 (0.4%) BD to D = 133 (59.1%) Controls to D = 24,833 (49.9%)	8/9	Yes‡
Almeida, 2016, Australia	To investigate the 13-year risk of dementia and death in older adults with BD.	Cohort / Registry-base	ICD-8, ICD-9, ICD-10	n total = 37,768; BD = 256 (0.7%) BD to D = 65 (25.4%) (HR = 2.30, 95% CI 1.80–2.94). Controls to D = 4,860 (13%)	9/9	Yes
Cheng, 2017, Taiwan	To assess the risk of AD associated with use of lithium.	Case-Control / Registry-based	ICD-9	n total = 190,041; BD = 3,537 (1.9%) BD to D = 2,074 (58.6%) (OR 2.34, 95% CI 2.18-2.51) Controls to D = 61,274 (32.8%)	8/9	Yes
Almeida, 2018, Australia	To examine associations between age of onset of BD and clinical comorbidities as well as D and mortality.	Cohort / Registry-base	ICD-8, ICD-9, ICD-10	n total = 38,003; BD = 80 (0.2%) BD to D = 6 (7.5%) (OR 17.74, 95% CI 7.52-41.84) Controls to D = 383 (1%)	9/9	Yes

† not included in the meta-analysis (no available data); ‡ based on OR value from our meta-analysis; D, dementia; BD, bipolar disorder; IRR, incidence rate ratios; CDT, clock-drawing test; AD, Alzheimer's disease; BZD, benzodiazepine; BZDR, benzodiazepine and related drugs; MDD, major depressive disorder; N/A, non-applicable; DSM, diagnostic statistical manual of mental disorders criteria; ICD, international statistical classification of diseases and related health problems criteria

Table 2. Characteristics of the studies included for the assessment whether the neuroprotective/neurotrophic effect of lithium.

Angst, 2007, Switzerland	To investigate if long-term medication with lithium, clozapine or antidepressants prevent or attenuate dementia in BD and MDD	Cohort	ICD-9	n total = 220; Lithium = 76 (34.5%) Lithium to D = 14 (18.4%) Controls to D = 26 (18.1%)	9/9	No‡
Nunes, 2007, Brazil	To assess if the continuous lithium use as a protector against AD	Cohort	DSM-IV	n total = 114; Lithium = 66 (57.9%) Lithium to D = 3 (4.5%) (OR 0.079, 95 CI 0.020-0.321) Controls to D = 16 (33.3%)	6/9	Yes
Gildengers, 2009, USA	To investigate whether older adults with BD would present with more cognitive dysfunction and a more rapid cognitive decline	Cohort	DSM-IV	n total = 33; Lithium = 9 (27.7%) No significant difference between BD patients exposed to lithium or divalproex versus those not exposed regarding the development of dementia	7/9	No†
Kessing, 2010, Denmark	To investigate whether treatment with lithium in patients with BD decrease the rate of dementia	Cohort / Registry-based	ICD-8, ICD-10	n total = 4,856; Lithium = 2,449 (50.4%) Lithium to D = 84 (3.4%) Controls to D = 132 (5.5%)	8/9	Yes
Gerhard, 2015, USA	To examine the association of lithium and dementia risk in BD	Cohort / Registry-based	ICD-9	n total = 41,251; Lithium = 3,766 (9.1%) Lithium to D = 64 (1.7%) (HR 0.77, 95 CI 0.60–0.99) Controls to D = 1,377 (3.7%)	8/9	Yes
Cheng, 2017, Taiwan	To assess the risk of AD associated with use of lithium.	Case-Control / Registry-based	ICD-9	n total = 3,537; Lithium = 125 (3.5%) Lithium to D = 32 (25.6%) Controls to D = 1431 (41.9%)	8/9	Yes‡

‡ based on OR value from our meta-analysis † not included in the meta-analysis (no available data); D, dementia; BD, bipolar disorder; MDD, major depressive disorder; AD, Alzheimer's disease; DSM, diagnostic statistic manual of mental disorders criteria; ICD, international statistical classification of diseases and related health problems criteria

Figure 1: Flow diagram showing the search, article selection and extraction process

Figure 2: Forest plot of the meta-analysis of BD as risk factor for dementia.

* Kessing et al., 2003 - We considered as a control group the patients with osteoarthritis.

**Almeida et al., 2018 - We have only included in the meta-analysis data for patients aged 50 years or younger.

Author Manuscript

Figure 3: Forest plot of the meta-analysis of neuroprotective/neurotrophic effect of lithium.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Velosa, J;Delgado, A;Finger, E;Berk, M;Kapczinski, F;Cardoso, TDA

Title:

Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses

Date:

2020-02-11

Citation:

Velosa, J., Delgado, A., Finger, E., Berk, M., Kapczinski, F. & Cardoso, T. D. A. (2020). Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. ACTA PSYCHIATRICA SCANDINAVICA, 141 (6), pp.510-521. <https://doi.org/10.1111/acps.13153>.

Persistent Link:

<http://hdl.handle.net/11343/275396>