MR SIMON LAMBRICHTS (Orcid ID : 0000-0002-8951-407X)

DR AXEL NORDENSKJÖLD (Orcid ID : 0000-0001-7454-3065)

MS JASMIEN OBBELS (Orcid ID : 0000-0001-6351-1543)

PROFESSOR PASCAL SIENAERT (Orcid ID : 0000-0002-0650-415X)

Article type : Systematic Review or Meta-analysis

Corresponding author mail id : simon.lambrichts@upckuleuven.be

Does lithium prevent relapse following successful electroconvulsive therapy for major depression? A systematic review and meta-analysis

Lithium for post-ECT depressive relapse prevention

Simon Lambrichts[1], Johan Detraux[2], Kristof Vansteelandt[1], Axel Nordenskjöld[3], Jasmien Obbels[1], Didier Schrijvers[4], Pascal Sienaert[1]

[1]KU Leuven, Department of Neurosciences, Research Group Psychiatry, Neuropsychiatry, Academic Center for ECT and Neuromodulation (AcCENT), University Psychiatric Center KU Leuven (UPC KU Leuven), Leuvensesteenweg 517, 3070 Kortenberg, Belgium

[2]KU Leuven, Department of Neurosciences, Research Group Psychiatry, University Psychiatric Center KU Leuven (UPC KU Leuven), Leuvensesteenweg 517, 3070 Kortenberg, Belgium

[3]University Health Care Research Centre, Faculty of Health and Medical Sciences, Örebro University, Örebro, Sweden

[4]UAntwerp, Collaborative Antwerp Psychiatric Research Institute (CAPRI)

Acknowledgements

The authors wish to thank Thomas Vandendriessche, Kristel Paque and Krizia Tuand, the biomedical reference librarians of the KU Leuven Libraries – 2Bergen – Learning Centre Désiré Collen (Leuven, Belgium), for their help in conducting the systematic literature search. This project was supported by the FWO (grant T000218N).

Abstract

Objective: The risk of relapse following successful antidepressant treatment, including electroconvulsive therapy (ECT), is substantial. Lithium has been suggested to effectively prevent relapse, yet data remain limited and inconclusive. We performed a systematic review and meta-analysis to examine the efficacy of continuation treatment with lithium in preventing relapse following a successful acute course of ECT in patients with major depression, in comparison to continuation treatment without lithium. We also assessed the role of several study characteristics, possibly impacting the treatment effect.

Methods: A systematic literature search, using the PubMed, Embase, Web of Science and Cochrane Library databases (up to June 2020), was conducted for prospective and retrospective studies, including patients with unipolar or bipolar depression, that assessed the efficacy of lithium for post-ECT depressive relapse prevention.

Results: Of 2556 records screened, 14 articles reporting on 9748 participants who received continuation treatment either with (N=1571) or without lithium (N=8177) were included in the meta-analysis. Patients receiving lithium were less likely to experience depressive relapse after a successful acute course of ECT, compared to patients receiving post-ECT prophylaxis without lithium (weighted odds ratio (OR)=0.53, 95% confidence interval (CI)=0.34, 0.82), with a number needed to treat (NNT) of 7 (95% CI=4, 21). We found some limited evidence that older patients may benefit more from continuation treatment with lithium, compared to younger patients. Using the GRADE criteria, the quality of evidence for our outcome measure (i.e., relapse rate) was rated as very low.

Conclusion: Continuation treatment with lithium may have superior efficacy in reducing the risk of relapse after a successful acute ECT course for major depression, in comparison to continuation treatment without lithium. High-quality studies are needed to confirm this finding.

Keywords

Depressive Disorder – Electroconvulsive Therapy – Relapse – Lithium – Continuation Treatment

Summations and limitations

Summations

- Continuation treatment with lithium may have superior efficacy in post-ECT depressive relapse prevention, in comparison to continuation treatment without lithium (OR=0.53, 95% CI=0.34, 0.82) with a NNT of 7 (95% CI=4, 21).
- When considering lithium to prevent relapse after a successful ECT course for major depression, psychiatrists should weigh the possible risks against its suggested benefits in a case-by-case manner.

Limitations

- We were not able to include all seemingly suitable studies since the authors of these studies did not provide the necessary additional data.
- Using the GRADE criteria, we rated the quality of evidence for our outcome measure (i.e., relapse rate) as very low, since most studies included were observational, heterogeneity was substantial and indications for publication bias were found.

Data availability statement

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

Introduction

Major depressive disorder affects one in six adults in their lifetime and has a considerable burden of disease[1]. Despite the widespread use of antidepressant medication, at least 30% of patients do not achieve remission[2]. For these 'difficult-to-treat' patients, not responding to several augmentation or combination attempts, electroconvulsive therapy (ECT) has the best empirical evidence[1]. ECT is also used when a rapid antidepressant response is required, such as in patients who are either severely depressed, or highly suicidal, or both[3].

In patients who achieve remission after two or more medication treatment steps, 12-month relapse rates mount up to 50%[2]. Relapse rates 12 months after a successful course of ECT are similar (51%), with the first 6-month period encompassing the greatest risk (37%), despite continuation pharmacotherapy or continuation ECT (C-ECT)[4]. Consequently, continuation treatment has become a central issue in ECT research.

Lithium, with its unique efficacy in preventing mood episodes[5-9] alongside well recognized anti-suicidal[10] and neuroprotective[11] effects, has entered the ECT field, especially since the randomized controlled trial of Sackeim et al. in 2001[12]. These authors reported a substantially lower 6-month relapse rate with the combination of lithium and nortriptyline (39%) compared to placebo (84%) or nortriptyline alone (60%). Although various other articles have addressed the efficacy of post-ECT prophylaxis with lithium, data remain limited and inconclusive. Several narrative reviews[13,14] suggested that lithium therapy effectively prevents relapse after an acute ECT course. However, to the best of our knowledge, its efficacy has not been investigated in a meta-analysis.

Aims of the study

We performed a systematic review and meta-analysis to examine the efficacy of continuation treatment with lithium in preventing relapse following successful electroconvulsive therapy in patients with major depression, in comparison to continuation treatment without lithium. In addition, we assessed the role of several study characteristics, possibly impacting the treatment effect.

Materials and methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[15].

Eligibility criteria

In order to obtain details of original studies reporting on the efficacy of lithium in the prevention of relapse following successful ECT in patients with major depression, we applied the following eligibility criteria:

(a) prospective or retrospective studies;
(b) including adults (≥18 years of age) diagnosed with unipolar or bipolar depression;
(c) assessing the efficacy of continuation treatment following a successful course of ECT for major depression;
(d) comparing post-ECT prophylaxis with lithium to prophylaxis without lithium;
(e) including relapse rates enabling the calculation of the effect size (ES) of treatment with versus without lithium. If necessary, corresponding authors were contacted to obtain additional data.

The International Classification of Diseases (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM), Research Diagnostic Criteria (RDC)[16], Feighner criteria[17], as well as clinical judgement were accepted as diagnostic criteria for major depression.

Data sources and study selection

Two authors (SL and JD) and an experienced biomedical information specialist conducted a systematic literature search (from 1950 up to June 2020) without language restriction, using the PubMed, Embase, Web of Science and Cochrane Library databases, linking the search terms 'depression', 'electroconvulsive therapy' and 'lithium'. Full search strategies are available as supplementary material. Duplicates were removed using EndNote X9 (SL) and Rayyan QCRI (JD). After removing duplicates, titles and abstracts were screened independently by SL and JD. Articles that were deemed potentially relevant were selected. SL and JD independently reviewed the full-text of the selected articles and assessed their eligibility. They also attempted to identify additional studies through a systematic search of the reference lists of selected articles. To maintain statistical independence of ESs, studies that reported on the same population were identified.

Data-collection process and data extraction

When reported results were insufficiently detailed, but the remaining inclusion criteria were fulfilled, corresponding authors were contacted to provide the necessary data. Three authors (of 6 studies) were contacted; one provided the necessary data to include 3 studies in the meta-analysis[18-20]. Data were independently extracted from each article by two investigators (SL and JD) to collect the following information:

(a) study characteristics: publication year, design (prospective versus retrospective, observational versus interventional), relapse definition (whether or not at least one of the criteria was based on clinical judgement or a cutoff score on a depression rating scale) and follow-up duration;
(b) characteristics of the study sample: total sample size, proportion female patients, diagnosis (whether or not patients with bipolar depression were excluded), proportion of patients with psychotic features and mean age;
(c) continuation therapy: details of treatment in the group with and without lithium and number of participants in both groups;
(d) outcome measure: relapse rate in both treatment groups.

Quality assessment

Two authors (SL and JD) independently assessed the risk of bias for each randomized study in the quantitative analysis using the Cochrane Collaboration's tool for assessing risk of bias (high, unclear or low)[21]. Since blinding is hard to achieve when C-ECT is used in one of the treatment arms, this was not considered a key domain. The quality of each cohort study was rated using the Newcastle-Ottawa Scale (NOS)[22], with a score of 0-3 indicating low quality, 4-6 moderate quality and 7-9 high quality (i.e., low risk of bias)[23]. Conflicting scores among the reviewers SL and JD were resolved by consensus and discussion.

Statistical analyses

We performed a meta-analysis comparing relapse rates between the group that received continuation treatment with lithium and the group that received treatment without lithium. The log odds ratio (LOR) was used as ES and final results were transformed to the odds ratio (OR). In each study, the relapse rate was computed for both treatment groups and then used to calculate an OR with 95% confidence interval (CI). Summary associations were interpreted as statistically significant (i.e., $P<0.05$) if the 95% CIs did not include 1 in their range. Since we expected variability among studies (i.e., heterogeneity) in the participants (e.g., mean age and whether or not patients with bipolar depression were excluded) and the interventions studied (i.e., the diverse composition of the lithium and the comparator condition) alongside variability in study design (e.g., follow-up duration), we produced a random-effects model

implying that the observed variance stems from three sources: variance from subject-level sampling error, variance from identifiable study characteristics and variance from other systematic random or unmeasured sources. To formally examine the homogeneity of the ES distribution, we used Cochran's Q test. When the null hypothesis for this test is rejected, the ES distribution is not homogeneous, implying that the variability in the LORs between studies is larger than can be expected on the basis of sampling error (the error associated with the fact that the estimated LORs are based on different samples of subjects). Furthermore, we calculated the I^2 statistic[24], which describes the percentage of the variability in ESs that is due to heterogeneity rather than sampling error. An I^2 statistic of 0-40% is interpreted as heterogeneity that might not be important, 30-60% may represent moderate heterogeneity, 50-90% substantial heterogeneity and 75-100% considerable heterogeneity. τ^2 was reported as an estimate of the between-study variance. In addition, we computed the number needed to treat (NNT) from the results of the meta-analysis (of ORs), as it can be easily understood as the number of patients that need to be treated with lithium to prevent depressive relapse in one patient who would not have benefited otherwise. For this computation, the median of the relapse rates in the group not receiving lithium was used as assumed control risk[21]. We also calculated the relapse percentage for patients receiving continuation treatment with lithium and for those receiving treatment without lithium, by pooling all the available data. Furthermore, to explain the heterogeneity among studies, several study characteristics were incorporated in the random-effects analyses, including mean age, proportion of patients with psychotic features, diagnosis (whether or not patients with bipolar depression were excluded), whether or not it was a prospective (versus retrospective) study, whether or not it was an observational (versus interventional) study, definition of relapse, follow-up duration, and study quality (whether or not the risk of bias was low).

Publication bias was formally assessed using the arcsine-Thompson test proposed by Rücker et al.[25], with $P<0.05$ suggesting the presence of bias. In addition, we created a funnel plot to display the study-specific effect estimates in relation to the standard error.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the quality of evidence for our outcome measure (i.e., relapse rate) on the basis of the study limitations (risk of bias), imprecision, inconsistency, indirectness, and publication bias[26,27]. The GRADE approach specifies four levels of quality of evidence: high, moderate, low, and very low. Randomized controlled trials start as high-quality evidence and observational studies as low-quality evidence. The level of evidence is downgraded when any of the following criteria are met[28]: (a) less than 75% of the included

studies are at low risk of bias, (b) heterogeneity is significant and the I^2 value is greater than 40%, (c) more than 50% of the participants were outside the target group, (d) fewer than 300 events, and (e) publication bias is significant.

The data analysis for this paper was generated using SAS software, Version 9.4 of the SAS System for Windows.

Results

Study selection and study characteristics

Fourteen studies were included in this meta-analysis. The results of the study selection are shown in the PRISMA flow diagram (Figure 1). Overall, the included studies reported on 9748 participants who received continuation treatment, either with (N=1571) or without lithium (N=8177), after successful ECT. As Table 1 shows, studies had between 27 and 7350 participants (median=88); women constituted the majority of all subjects (60.60%, range=50.00, 76.27); 22.70% of the participants had psychotic features (range=17.85, 49.15). The proportion of patients with psychotic features was missing in three studies[29-32]. Mean age of study participants ranged from 51.0 to 69.8 years and was not reported in one study[33]. Patients with bipolar depression were excluded in seven studies[12,18,20,29-31,34,35], six studies comprised patients with unipolar as well as bipolar depression[32,33,36-39], and one study included patients with bipolar depression only[19]. Ten of the included studies were prospective[12,18-20,29,30,34-38] and four had a retrospective design in the continuation phase[31-33,39]. Three studies had an interventional design[12,29,30,34], eleven of them were observational[18-20,31-33,35-39]. In six studies, at least one of the relapse criteria was based on clinical judgement or a cutoff score on a depression rating scale[12,34-38]. Follow-up duration ranged from 15 to 58 weeks (median=26) and was not reported in one study[33]. Two studies involved lithium monotherapy, either compared to placebo[29,30] or tricyclic antidepressant (TCA) monotherapy[31]. In three studies, lithium plus TCA was compared to TCA monotherapy[12,35] or C-ECT[34]. One study reported relapse rates of patients using lithium plus antidepressant compared to antidepressant monotherapy, without further specifying the type of antidepressant[33]. In eight studies, continuation treatment in the group using lithium consisted of lithium monotherapy or lithium plus either antidepressant(s), or antipsychotic(s), or mood stabilizer(s), or C-ECT, or a combination[18-20,32,36-39].

Quality assessment

One randomized study[12] was at low risk of bias, whereas 2 randomized studies[29,34] were at unclear risk of bias. Two cohort studies[31,37] received moderate and 9 cohort studies[18-20,32,33,35,36,38,39] received high (i.e., low risk of bias) scores on the NOS. Overall, 10 of 14 (71.43%) included studies were at low risk of bias. Results of the quality assessment are available as supplementary material.

Meta-analysis

In total, 14 studies provided relapse data on continuation treatment with and without lithium. We estimated a random-effects model, assuming that the observed variance is due to subject-level sampling error and other (unknown) sources of systematic variation. Cochran's Q test indicated that the distribution of the LORs was not homogeneous (Q=34.17, df=13, P=0.0011), implying that the variability in the LORs between studies was larger than can be expected on the basis of sampling error. The I^2 statistic was 62.0% (95% CI=32.1, 78.7), representing substantial heterogeneity. The forest plot in Figure 2 shows the distribution of the estimated ORs, together with the weighted OR from the random-effects model. The estimated weighted OR from the random-effects model was 0.53 (95% CI=0.34, 0.82, τ^2=0.1357 (95% CI=0.0180, 1.2272)). The NNT was 7 (95% CI=4, 21). When pooling all results, relapse rates for patients receiving continuation treatment with lithium versus without lithium were 50.35% and 56.70%, respectively.

Analyses examining the potential role of several study characteristics to explain systematic differences in the ES between studies revealed that the mean age of the samples was related to the estimated LOR in these studies (β=-0.12, 95% CI=-0.20, -0.05, P=0.0050). Figure 4 shows that the OR for relapse was smaller in studies including subjects with a higher mean age (dashed black line) (the circles in this figure are proportional to the study's weight in the analysis with larger studies having more weight). However, after removal of the study with the highest mean age[32], the association between mean age and OR did not hold (solid grey line) (β=-0.08, 95% CI=-0.21, 0.06, P=0.2384). For the other study characteristics, no significant associations were found: proportion of patients with psychotic features (β=-2.81, 95% CI=-6.53, 0.90, P=0.1184), diagnosis (whether or not patients with bipolar depression were excluded) (β=0.52, 95% CI=-0.36, 1.40, P=0.2164), design (whether or not the study was prospective (versus retrospective) (β=0.73, 95% CI=-0.31, 1.76, P=0.1513), or observational (versus interventional) (β=0.37, 95% CI=-0.74, 1.48, P=0.4827)), definition of relapse (β=-0.28, 95% CI=-1.22, 0.65, P=0.5156)), follow-up duration (β=-0.01, 95% CI=-0.04, 0.03, P=0.5935), and study quality (whether or not the risk of bias was low (β=-0.47, 95% CI=-1.49, 0.55, P=0.3374)). These analyses were performed for each study characteristic separately. Due to missing data for a number of study characteristics, an analysis including all study characteristics

simultaneously was not feasible. The forest plots showing the distribution of the estimated ORs, together with the weighted OR per subgroup (i.e., definition of relapse, diagnosis, design and study quality) from the random-effects model are available as supplementary material. We found no association between these study characteristics and the size of the effect based on visual inspection of the plots.

From the funnel plot in Figure 3 it is apparent that in the left bottom corner of the graph there are somewhat more studies compared to the right bottom corner, indicating that small studies showing a favorable treatment effect were more likely to be published. In addition, the arcsine-Thompson test for funnel plot asymmetry was significant (t(12)=-3.32, P=0.0062), suggesting the presence of publication bias.

Using the GRADE criteria, we rated the quality of evidence for our outcome measure (i.e., relapse rate) as very low. Since 11 of 14 studies included were observational, we started with a low rating. Next, the level of evidence was downgraded because less than 75% of the included studies were at low risk of bias, heterogeneity was significant and the I^2 value was greater than 40%, and publication bias was significant.

Discussion

Our results show that, after a successful acute course of ECT for major depression, continuation treatment with lithium yielded significantly lower relapse rates, compared to a continuation treatment without lithium. Post-ECT prophylaxis with lithium had a weighted OR of 0.53 (95% CI=0.34, 0.82), corresponding to a small to medium effect[40]. This effect size is consistent with those of meta-analyses on lithium treatment for depressive relapse prevention in non-ECT treated samples, both in bipolar disorder and major depressive disorder. In patients with bipolar disorder, the meta-analysis of Severus et al.[6] showed that lithium was more effective than placebo in preventing depressive episodes. The authors reported a weighted relative risk of 0.73 (95% CI=0.60, 0.88), indicating a small to medium effect[40]. A recent meta-analysis of 21 randomized controlled trials comparing continuation treatment with lithium to a treatment without lithium (lithium versus placebo (N=7), lithium augmentation versus antidepressant monotherapy (N=9), or lithium versus antidepressant monotherapy (N=5)) in patients with major depressive disorder yielded a weighted OR of 2.80 (95% CI=1.59, 4.92) (also representing a small to medium effect size) favoring continuation treatment that included lithium[9].

The NNT was 7 (95% CI=4, 21), a clinically relevant effect in this 'difficult-to-treat' population. This NNT is substantially lower than the NNT of 16 (95% CI=10, 38) reported in the large-scale population-based register study on the effect of lithium on post-ECT relapse risk in patients with unipolar depression by Brus et al.[20]. As relapse was defined as readmission in the latter study, one could therefore hypothesize that lithium is less effective in the prevention of more severe depressive relapse, i.e., relapse necessitating hospitalization. In our meta-analysis, however, the way relapse was defined (whether or not at least one of the criteria was based on clinical judgement or a cutoff score on a depression rating scale) was not associated with the size of the effect. Moreover, the study by Brus et al.[20], like the study by Popiolek et al.[19], another large-scale population-based register study, was prospective and observational, and thus reflective of clinical practice. Since both studies showed only a modest effect of lithium (see Figure 2) and accounted for the vast majority of participants included in our analyses, one could argue that the protective effect of lithium may not be realized in daily medical care. However, in our meta-analysis, the study design (whether or not the study was prospective (versus retrospective) or observational (versus interventional)) was not associated with the size of the effect.

Despite the significant protective effect of lithium, still half of the patients who received continuation treatment with lithium relapsed, meaning that relapse rates after successful ECT, even with lithium, remain high. Nevertheless, lithium can serve as a crucial component of continuation treatment after a successful acute course of ECT for major depression. In this light, the combination of continuation pharmacotherapy (including lithium) and C-ECT is an interesting treatment modality for post-ECT depressive relapse prevention. In a recently conducted meta-analysis of 4 randomized controlled trials of C-ECT with concomitant pharmacotherapy for the prevention of relapse after successful ECT, this strategy had superior efficacy compared to pharmacotherapy alone[41]. The largest and most recent trial that was included is the Prolonging Remission in Depressed Elderly (PRIDE) study[42], in which older adults were randomized to receive either pharmacotherapy alone (venlafaxine plus lithium), or pharmacotherapy plus flexible C-ECT. At 6-month follow-up, 20.3% and 13.1% of patients had relapsed, respectively. In considering the concomitant use of lithium and ECT, the possible risks should be weighed against its suggested benefits in depressive relapse prevention in a case-by-case manner. Although there are reports of patients receiving the combination of lithium and ECT without any problems[43,44], lithium may induce adverse effects, such as cognitive side effects[45] and neurological abnormalities[46]. Close monitoring for signs of adverse effects is therefore necessary. Moreover, it has been suggested to use a low dose of lithium and hold it for at least 24 hours before each ECT session[45].

Although our meta-analysis supports the use of lithium in the prevention of relapse following successful ECT for major depression, and positive effects on relapse rates are equally seen with lithium in combination with C-ECT, it seems that only a minority of patients in clinical practice receive lithium for prophylaxis after ECT. According to the population-based study of Brus et al.[20] only 9% (638 out of 7350) of patients with unipolar depression received post-ECT prophylaxis that included lithium. Concerns about the side effects of lithium have discouraged its prescription. However, lithium is generally well tolerated with few long-term adverse effects[47]. Furthermore, regular monitoring of plasma levels is often regarded as an inconvenience. This should, however, be considered an asset, since it enables accurate review of the efficacy of lithium, along with any potential tolerability issues. Should the possible risks of lithium therapy outweigh the benefits, other post-ECT relapse prevention strategies can be considered. In these circumstances, continuation pharmacotherapy with a TCA has the largest evidence base[4].

Analyses examining the potential role of several study characteristics to explain systematic differences in the treatment effect between studies revealed that the protective effect of lithium was stronger in studies that included patients with a higher mean age, especially in the study with the highest mean age (69.8 years). This finding could be related to the fact that the prophylactic effect of lithium has been suggested to be stronger in melancholic depression[48], and that melancholic depression is more common in older adults[49]. However, the finding of an age-related protective effect of lithium in post-ECT depressive relapse prevention in our study has to be interpreted with caution, since the association between mean age and treatment effect did not hold after removal of the study with the highest mean age. Whether or not patients with bipolar depression were excluded did not impact the efficacy of lithium in depressive relapse prevention. This is in agreement with the above-mentioned findings of a similar prophylactic effect of lithium in major depressive disorder and bipolar disorder. Although all included studies used relapse as the main outcome measure, it was defined in different ways. While some studies used marked clinical deterioration (evaluated by clinical judgement or by using a standardized rating scale) or need to change antidepressant medication to determine relapse, others used hospitalization (as it was difficult to identify relapses from charts). Although hospitalization is a robust marker of relapse, some patients may experience depressive relapse without requiring hospitalization. This means that the relapse rates (even with lithium) of the studies included in this meta-analysis might have been higher if more data had been based on symptomatic worsening. However, in our analyses, the way relapse was defined was not associated with the size of the effect.

Limitations

The current findings should be placed within the context of the following limitations. First, 3 seemingly suitable studies could not be included since the authors of these studies did not provide the necessary additional data. Omori et al. included 255 patients with unipolar or bipolar depression, schizophrenia, or schizoaffective disorder in a retrospective study and found the use of lithium to be a significant preventive measure against relapse after successful ECT[50]. In an earlier retrospective study by this group, 100 patients with unipolar or bipolar depression were included. Patients treated with lithium following successful ECT had a lower tendency to relapse, but this tendency was not statistically significant[51]. And in the naturalistic follow-up phase of a study by Sackeim et al., the protective effect of post-ECT continuation pharmacotherapy with a TCA plus lithium (compared to all other strategies) was not established[52].

Second, we would like to point out that we did not only use data from studies that were designed specifically to look at the protective effect of post-ECT prophylaxis with lithium. Part of the data were extracted from studies with a different aim. Although this is certainly an advantage from the perspective of avoiding publication bias, this is an extra source of between-study variation as different populations were studied, and various study designs and definitions of relapse were used. To assess their impact on the differences in treatment effect across studies, we included these study characteristics in our analyses. Unfortunately, not all possible confounders to the treatment effect of lithium, such as the proportion of patients with medication resistance, the severity of depressive symptoms at the start of continuation treatment, whether lithium was started during the acute ECT course or after completion and lithium plasma levels, could be included due to the large number of missing values.

Third, it should be noted that the findings of this study are restricted to continuation treatment either with or without lithium, irrespective of other relapse prevention strategies used. Since in the majority of studies continuation treatment details were not available, assessment of the specific effect of adding lithium to other prophylactic treatments (e.g., antidepressant(s) and C-ECT) was not possible. Nevertheless, our findings seem to imply that lithium itself is a potent prophylactic regardless of possible concomitant treatments, since the comparator group consisted of established relapse prevention

strategies in all but one study. In this light, a large-scale population-based register study on the effect of pharmacological treatments on relapse risk in patients with unipolar depression observed the greatest risk reductions for lithium when used without a concomitant antidepressant[53].

Fourth, a potential source of bias in any meta-analysis is an inability to retrieve a comprehensive sample of studies. Our rigorous search and the fact that we contacted a number of authors for additional data contributed to a large sample and a more complete analysis of studies. Nevertheless, we did find indications for publication bias based on a funnel plot and Rücker's arcsine-Thompson test, i.e., that studies with a smaller sample size reported higher ESs than studies with a larger sample.

Fifth, using the GRADE criteria, we rated the quality of evidence for our outcome measure (i.e., relapse rate) as very low, meaning that the true effect is likely to be substantially different from the estimated effect. It should, however, be noted that the three largest studies included in the quantitative synthesis[18-20] (reporting on 9100 of the 9748 participants) generated high-quality data (NOS score=9) and provided support for the protective effect of lithium, albeit modest. In addition, study quality (whether or not the risk of bias was low) was not associated with the size of the effect in our meta-analysis. Nevertheless, future high-quality studies are needed to confirm our findings. Furthermore, we should remain aware of the fact that we are dealing with a 'difficult-to-treat' population that is prone to relapse, together with the finding that lithium is generally well tolerated with few long-term adverse effects[47].

Sixth, ecological bias, i.e., the issue of aggregating participants' results, should be considered when using meta-regression[54]. This has to do with the fact that both the proportion of patients with psychotic features and follow-up duration might vary substantially within studies, but can only be summarized at the level of the study. Consequently, although we found no significant association between these characteristics and OR, both study characteristics might yet have effects on how well post-ECT prophylaxis with lithium works. In addition, it should be noted that a small number of studies was included in the subgroup and meta-regression analyses. Therefore, the failure to find a statistically significant association could mean that the effect (if any) is quite small, but could also mean that the analysis had poor power to detect even a large effect. However, visual inspection of the forest plots showing the distribution of the

estimated ORs, together with the weighted OR per subgroup (available as supplementary material), did not show evidence for an association between these study characteristics and the size of the effect.

Finally, one should be aware of the possibility of confounding by indication when interpreting the results of observational studies. If patients using lithium are more severely ill or have had more depressive episodes in the past, the protective effect of lithium will seem smaller. In fact, in the largest study included in this meta-analysis, the effect of lithium was not statistically significant in the unadjusted model, whereas it was larger and statistically significant in the adjusted model[20]. Therefore, since we did not adjust for possible confounders, the effect of lithium may have been underestimated in this meta-analysis.

In conclusion, this meta-analysis suggests that continuation treatment that includes lithium has superior efficacy in reducing the risk of relapse after successful ECT for major depression, compared to continuation treatment without lithium. High-quality studies are needed to confirm our findings. When considering the use of lithium, psychiatrists should weigh the possible risks against its suggested benefits in post-ECT depressive relapse prevention in a case-by-case manner.

References

1. Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. *Nature reviews Disease primers.* 2016;2:16065.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *The American journal of psychiatry.* 2006;163(11):1905-1917.
3. Kellner CH, Obbels J, Sienaert P. When to consider electroconvulsive therapy (ECT). *Acta psychiatrica Scandinavica.* 2019:10.1111/acps.13134.
4. Jelovac A, Kolshus E, McLoughlin DM. Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2013;38(12):2467-2474.
5. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *The American journal of psychiatry.* 2004;161(2):217-222.
6. Severus E, Taylor MJ, Sauer C, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *International journal of bipolar disorders.* 2014;2:15.
7. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry.* 2014;1(5):351-359.
8. Davis JM. Lithium maintenance of unipolar depression. *Lithium in neuropsychiatry—the comprehensive guide Abingdon: Informa Healthcare UK Ltd.* 2006:99-108.
9. Undurraga J, Sim K, Tondo L, et al. Lithium treatment for unipolar major depressive disorder: Systematic review. *Journal of psychopharmacology (Oxford, England).* 2019;33(2):167-176.
10. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ (Clinical research ed).* 2013;346:f3646.
11. Vo TM, Perry P, Ellerby M, Bohnert K. Is lithium a neuroprotective agent? *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists.* 2015;27(1):49-54.
12. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Jama.* 2001;285(10):1299-1307.
13. Rasmussen KG. Lithium for post-electroconvulsive therapy depressive relapse prevention: a consideration of the evidence. *The journal of ECT.* 2015;31(2):87-90.

14. Abou-Saleh MT, Muller-Oerlinghausen B, Coppen AJ. Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. *International journal of bipolar disorders.* 2017;5(1):11.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical research ed).* 2009;339:b2535.
16. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry.* 1978;35(6):773-782.
17. Feighner JP, Robins E, Guze SB, Woodruff RA, Jr., Winokur G, Munoz R. Diagnostic Criteria for Use in Psychiatric Research. *Archives of General Psychiatry.* 1972;26(1):57-63.
18. Nordenskjold A, von Knorring L, Engstrom I. Predictors of time to relapse/recurrence after electroconvulsive therapy in patients with major depressive disorder: a population-based cohort study. *Depression research and treatment.* 2011;2011:470985.
19. Popiolek K, Brus O, Elvin T, et al. Rehospitalization and suicide following electroconvulsive therapy for bipolar depression-A population-based register study. *Journal of affective disorders.* 2018;226:146-154.
20. Brus O, Cao Y, Hammar Å, et al. Lithium for suicide and readmission prevention after electroconvulsive therapy for unipolar depression: population-based register study. *BJPsych Open.* 2019;5(3):e46.
21. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions.* 5.1.0 ed: The Cochrane Collaboration; 2011.
22. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Web site. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed2020.
23. Duko B, Ayano G, Pereira G, Betts K, Alati R. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. *Soc Psychiatry Psychiatr Epidemiol.* 2020;55(12):1549-1562.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-1558.
25. Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Stat Med.* 2008;27(5):746-763.
26. Goldet G, Howick J. Understanding GRADE: an introduction. *Journal of Evidence-Based Medicine.* 2013;6(1):50-54.

27. Meader N, King K, Llewellyn A, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Syst Rev.* 2014;3:82.
28. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev.* 2018;4(4):Cd008208.
29. Coppen A, Abou-Saleh MT, Milln P, et al. Lithium continuation therapy following electroconvulsive therapy. *Br J Psychiatry.* 1981;139:284-287.
30. Abou-Saleh MT. How long should drug therapy for depression be maintained? *The American journal of psychiatry.* 1987;144(9):1247-1248.
31. Perry P, Tsuang MT. Treatment of unipolar depression following electroconvulsive therapy. Relapse rate comparisons between lithium and tricyclics therapies following ECT. *Journal of affective disorders.* 1979;1(2):123-129.
32. Atiku L, Gorst-Unsworth C, Khan BU, Huq F, Gordon J. Improving relapse prevention after successful electroconvulsive therapy for patients with severe depression: completed audit cycle involving 102 full electroconvulsive therapy courses in West Sussex, United kingdom. *The journal of ECT.* 2015;31(1):34-36.
33. Moksnes KM. Relapse following electroconvulsive therapy. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke.* 2011;131(20):1991-1993.
34. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry.* 2006;63(12):1337-1344.
35. Birkenhager TK, van den Broek WW, Mulder PG, de Lely A. One-year outcome of psychotic depression after successful electroconvulsive therapy. *The journal of ECT.* 2005;21(4):221-226.
36. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry.* 2000;57(5):425-434.
37. Rehor G, Conca A, Schlotter W, et al. [Relapse rate within 6 months after successful ECT: a naturalistic prospective peer- and self-assessment analysis]. *Neuropsychiatrie : Klinik, Diagnostik, Therapie und Rehabilitation : Organ der Gesellschaft Osterreichischer Nervenarzte und Psychiater.* 2009;23(3):157-163.
38. Nordenskjold A, von Knorring L, Ljung T, Carlborg A, Brus O, Engstrom I. Continuation electroconvulsive therapy with pharmacotherapy versus pharmacotherapy alone for prevention of relapse of depression: a randomized controlled trial. *The journal of ECT.* 2013;29(2):86-92.

39. Uchida T, Kishimoto T, Koreki A, et al. Predictors of readmission after successful electroconvulsive therapy for depression: a chart review study. *International journal of psychiatry in clinical practice.* 2016;20(4):260-264.
40. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. *Communications in Statistics - Theory and Methods.* 2017;46(14):6774-6781.
41. Elias A, Phutane VH, Clarke S, Prudic J. Electroconvulsive therapy in the continuation and maintenance treatment of depression: Systematic review and meta-analyses. *The Australian and New Zealand journal of psychiatry.* 2018;52(5):415-424.
42. Kellner CH, Husain MM, Knapp RG, et al. A Novel Strategy for Continuation ECT in Geriatric Depression: Phase 2 of the PRIDE Study. *The American journal of psychiatry.* 2016;173(11):1110-1118.
43. Thirthalli J, Harish T, Gangadhar BN. A prospective comparative study of interaction between lithium and modified electroconvulsive therapy. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry.* 2011;12(2):149-155.
44. Dolenc TJ, Rasmussen KG. The safety of electroconvulsive therapy and lithium in combination: a case series and review of the literature. *The journal of ECT.* 2005;21(3):165-170.
45. Patel RS, Bachu A, Youssef NA. Combination of lithium and electroconvulsive therapy (ECT) is associated with higher odds of delirium and cognitive problems in a large national sample across the United States. *Brain stimulation.* 2019.
46. Sartorius A, Wolf J, Henn FA. Lithium and ECT – Concurrent use still demands attention: Three case reports. *The World Journal of Biological Psychiatry.* 2005;6(2):121-124.
47. Malhi GS, Bell E, Porter RJ, et al. Lithium should be borne in mind: Five key reasons. *Australian & New Zealand Journal of Psychiatry.* 2020;54(7):659-663.
48. Valerio MP, Martino DJ. Differential response to lithium between melancholic and non-melancholic unipolar depression. *Psychiatry research.* 2018;269:183-184.
49. Brodaty H, Luscombe G, Parker G, et al. Increased rate of psychosis and psychomotor change in depression with age. *Psychological medicine.* 1997;27(5):1205-1213.
50. Omori W, Itagaki K, Kajitani N, et al. Shared preventive factors associated with relapse after a response to electroconvulsive therapy in four major psychiatric disorders. *Psychiatry and clinical neurosciences.* 2019;73(8):494-500.
51. Itagaki K, Takebayashi M, Shibasaki C, et al. Factors associated with relapse after a response to electroconvulsive therapy in unipolar versus bipolar depression. *Journal of affective disorders.* 2017;208:113-119.

52. Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain stimulation.* 2008;1(2):71-83.
53. Tiihonen J, Tanskanen A, Hoti F, et al. Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study. *Lancet Psychiatry.* 2017;4(7):547-553.
54. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. *Stat Med.* 2002;21(3):371-387.

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

First author (publication year)	Sample size‡	Proportion female§	Proportion with psychotic features§	Mean age (years)§	Bipolar depression excluded	Number of participants in analyzed sample¶	Treatment in lithium group	Treatment in comparator group	Design I	Design II	Relapse definition	Follow-up duration (weeks)	OR (95% CI)	Study quality/Risk of bias‡‡
Perry (1979)	54	0.57	NR†	51.0	Yes	54	Lithium	TCA	Retrospective	Observational	No	26	0.96 (0.24, 3.82)	Moderate quality
Coppen (1981)	38	0.63	NR†	55.0	Yes	38	Lithium	Placebo	Prospective	Interventional	No	15	0.86 (0.19, 3.85)	Unclear risk of bias
Sackeim (2000)	80	0.61	0.36	57.1	No	45	Lithium monotherapy or in combination††	Antidepressant(s), antipsychotic(s), mood stabilizer(s) or C-ECT, or a combination	Prospective	Observational	Yes	52	0.32 (0.09, 1.10)	High quality
Sackeim (2001)	84	0.67	0.42	57.4	Yes	48	Lithium plus nortriptyline	Nortriptyline	Prospective	Interventional	Yes	24	0.43 (0.13, 1.36)	Low risk of bias
Birkenhäger (2005)	59	0.76	0.49	56.5	Yes	44	Lithium plus imipramine or nortriptyline	Imipramine or nortriptyline	Prospective	Observational	Yes	17	0.15 (0.02, 1.33)	High quality
Kellner (2006)	184	0.68	0.36	57.2	Yes	148	Lithium plus nortriptyline	C-ECT	Prospective	Interventional	Yes	24	0.85 (0.44, 1.63)	Unclear risk of bias

Rehor (2009)	92	0.58	0.22	54.6	No	48	Lithium monotherapy or in combination††	Antidepressant(s), antipsychotic(s), mood stabilizer(s) or C-ECT, or a combination	Prospective	Observational	Yes	26	0.40 (0.12, 1.32)	Moderate quality
Moksnes (2011)	120	0.73	0.46	NR†	No	38	Lithium plus antidepressant	Antidepressant	Retrospective	Observational	No	NR†	0.18 (0.03, 1.03)	High quality
Nordenskjöld (2011)	486	0.57	0.20	55.0	Yes	479	Lithium monotherapy or in combination††	Antidepressant(s), antipsychotic(s), mood stabilizer(s) or C-ECT, or a combination	Prospective	Observational	No	58	0.45 (0.23, 0.89)	High quality
Nordenskjöld (2013)	56	0.50	0.38	57.0	No	56	Lithium monotherapy or in combination††	Antidepressant(s), antipsychotic(s), mood stabilizer(s) or C-ECT, or a combination	Prospective	Observational	Yes	52	0.37 (0.12, 1.09)	High quality
Atiku (2015)	102	0.74	NR†	69.8	No	102	Lithium monotherapy or in combination††	Antidepressant(s), antipsychotic(s), mood stabilizer(s) or C-ECT, or a combination	Retrospective	Observational	No	26	0.08 (0.03, 0.26)	High quality
Uchida (2016)	27	0.70	0.41	62.7	No	27	Lithium monotherapy or in combination††	Antidepressant(s), antipsychotic(s), mood stabilizer(s) or C-ECT, or a combination	Retrospective	Observational	No	26	1.25 (0.18, 8.73)	High quality
Popiolek (2018)	1255	0.66	0.18	52.2	No	1255	Lithium monotherapy or	Antidepressant(s), antipsychotic(s), mood	Prospective	Observational	No	26	0.87 (0.70, 1.09)	High quality

							in combination††	stabilizer(s) or C-ECT, or a combination						
Brus (2019)	7350	0.59	0.23	54.1	Yes	7366	Lithium monotherapy or in combination††	Antidepressant(s), antipsychotic(s), mood stabilizer(s) or C-ECT, or a combination	Prospective	Observational	No	35	0.96 (0.82, 1.14)	High quality

Numbers, proportions and means of the sample extracted from additional data were used. Therefore, values in the table may not match the values in the original papers. TCA: tricyclic antidepressant; C-ECT: continuation electroconvulsive therapy; Design I: prospective or retrospective; Design II: observational or interventional; Definition: whether or not at least one of the criteria was based on clinical judgement or a cutoff score on a depression rating scale; OR (95% CI): odds ratio (treatment with lithium versus treatment without lithium) and 95% confidence interval.

†Values were not reported (NR) and could not be retrieved by contacting the corresponding authors.

‡Total sample size of the original study.

§Values were based on the total sample size of the original study.

¶Number of participants included in the analysis on the effect of continuation treatment with lithium.

††Lithium plus either antidepressant(s), antipsychotic(s), mood stabilizer(s), or C-ECT, or a combination.

‡‡The Cochrane Collaboration's tool was used to assess the risk of bias (low, unclear or high) in randomized studies. The Newcastle-Ottawa Scale (NOS) was used to assess the quality (high, moderate or low) in cohort studies.

Figure legends

Figure 1. Flow diagram of the study selection process

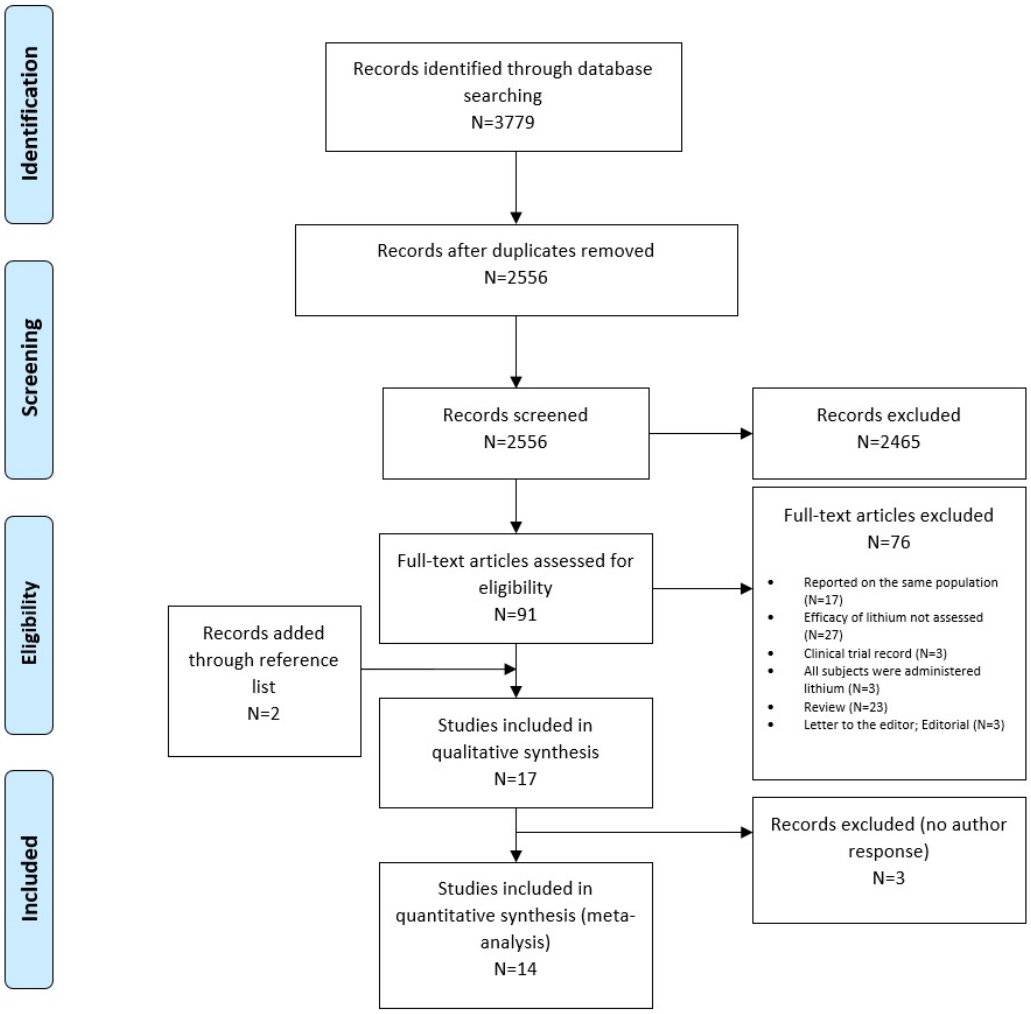
Figure 2. Forest plot of the distribution of the estimated odds ratios, together with the weighted odds ratio from the random-effects model

OR: odds ratio (treatment with lithium versus treatment without lithium); 95% CI: 95% confidence interval.

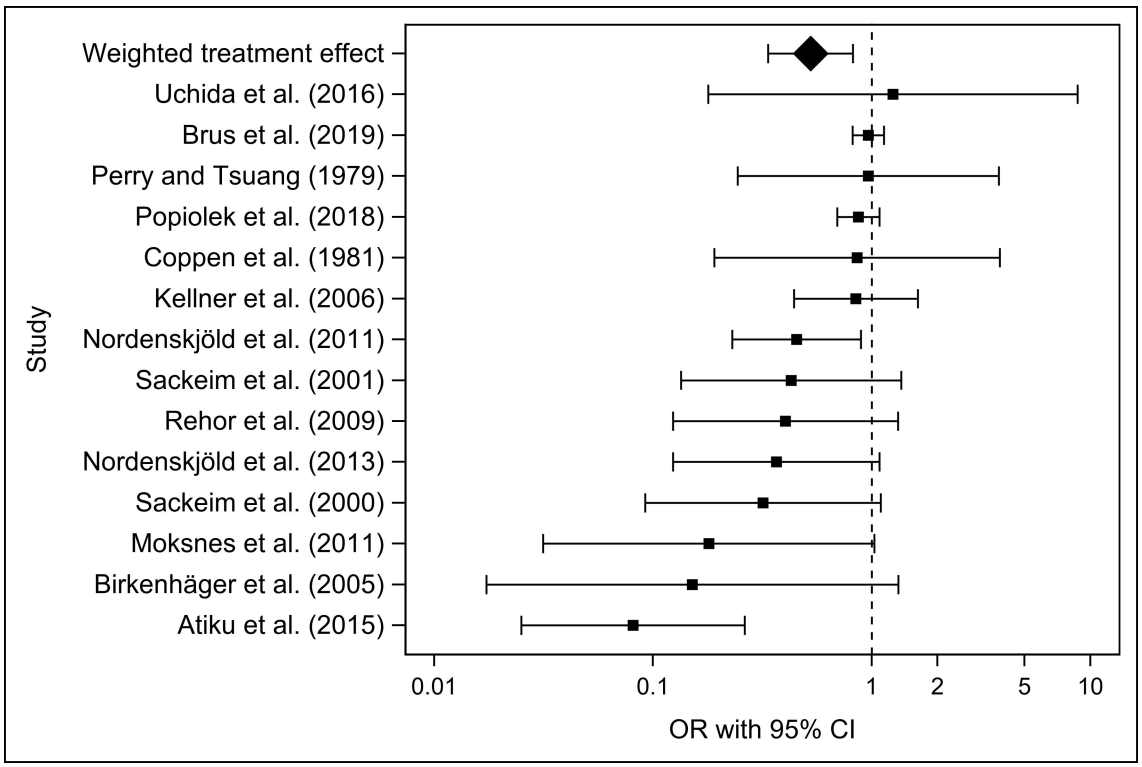
Figure 3. Funnel plot of studies included in the meta-analysis

Figure 4. Odds ratio for depressive relapse per study according to the mean age of the included subjects

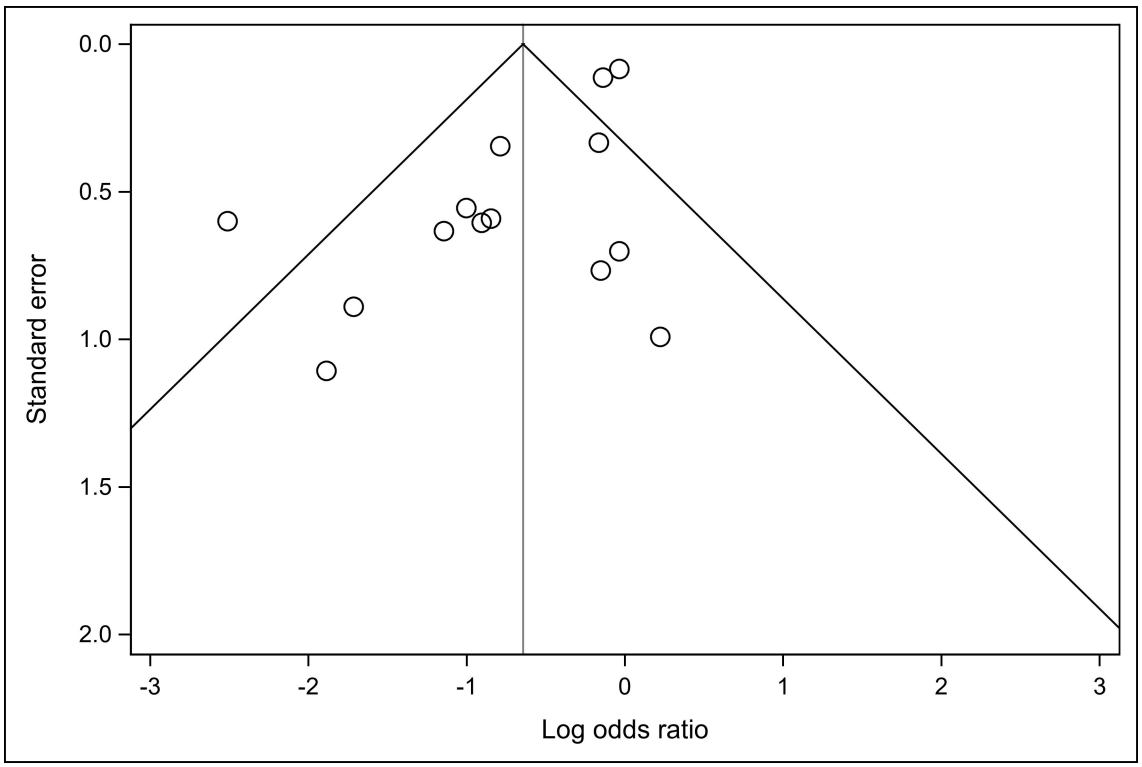
The circles in this figure are proportional to the study's weight in the meta-analysis with larger studies having more weight.



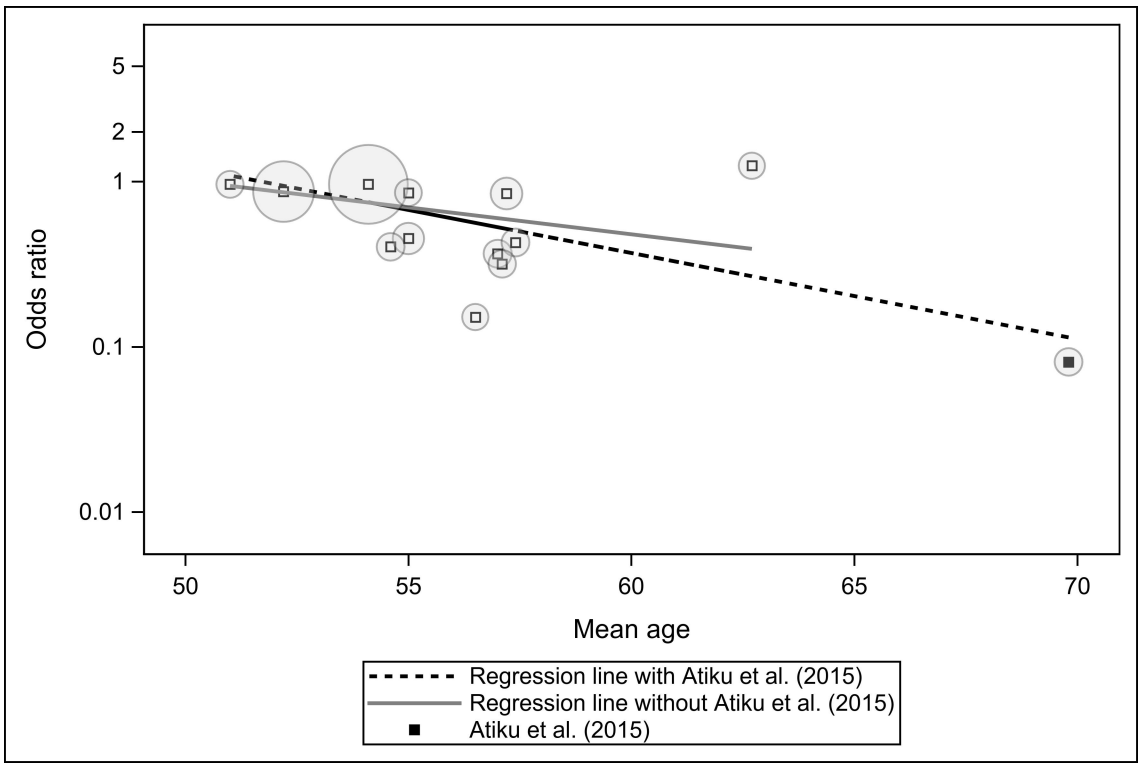
acps_13277_f1.jpg



acps_13277_f2.jpg



acps_13277_f3.jpg



acps_13277_f4.jpg