**Supplementary Materials**

**Methods**

We conducted our analysis according to standard methodology as described in the Cochrane Handbook.[1](#_ENREF_1) We reported our results according to the PRISMA guidelines.[2](#_ENREF_2) Because our systematic review serves as an update to a prior published meta-analysis by Riblet *et al.* (2017),[3](#_ENREF_3) we reported the results of our search using the PRISMA 2020 flow diagram for updated systematic reviews.[2](#_ENREF_2" \o "Page, 2021 #367)

We submitted the protocol to Prospero on December 1, 2021. At the time of submission, we had not begun data abstraction. Because Prospero is currently experiencing a high demand, reviewers are instructed to continue with their review process. Our protocol was officially posted to the Prospero website on January 1, 2022 (CRD42022295822).

**Literature sources**

We searched with the intent of updating the results of a previous search completed by Riblet *et al.* (2017) in their meta-analysis of strategies to prevent suicide.[3](#_ENREF_3) Specifically, Riblet *et al.* (2017) searched Medline (via Ovid), Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO from inception to 31 December 2015.[3](#_ENREF_3) This search yielded six randomized controlled trials (RCTs) of lithium.[4-9](#_ENREF_4) We updated these results by searching the same electronic databases from January 1, 2015 through November 30, 2021 to identify published articles (including Epub ahead of print) that met our study inclusion criteria. We deliberately allowed for one year of overlap in our search strategy to address any concerns that studies could have been indexed in 2015 after Riblet *et al.* (2017) completed their search.[3](#_ENREF_3)

To identify any studies that may have been missed in our primary search, we also reviewed the references of included studies and searched ClinicalTrials.gov.

**Search terms**

We used MeSH terms and key words to generate the following themes: suicide and lithium. We then used the Boolean term “AND” to find the intersection between these two themes. In addition, we applied a highly sensitive search strategy to identify RCTs in Medline (via Ovid).[10](#_ENREF_10) We used the following MeSH terms and key words to search Medline for potentially eligible studies.

*Search terms for the themes of suicide and lithium*

* Suicide.mp or Exp Suicide/ or Exp Suicide, Attempted/or Exp Suicide, Completed
* Suicidal ideation.mp or Exp Suicidal Ideation/
* Exp Antimanic Agents/pd [Pharmacology/]
* Exp Lithium
* Exp Lithium Carbonate
* Lithium.mp
* Lithium Citrate.mp

*Search terms for the highly sensitive search strategy to identify RCTs in Medline (via Ovid).10*

* (randomized controlled trial.pt OR controlled clinical trial.pt OR randomized.ab OR placebo.ab OR drug therapy.fs. OR randomly.ab OR trial.ab OR groups.ab) **AND** (not Exp animals/not humans.sh)

We modified the aforementioned terms as necessary to search the remaining electronic databases and ClinicalTrials.gov. As suggested in the literature, we applied a highly sensitive search strategy to identify RCTs in Excerpta Medica Database (EMBASE),[10](#_ENREF_10) Cumulative Index to Nursing and Allied Health Literature (CINAHL),[11](#_ENREF_11) and PsycINFO.[12](#_ENREF_12)

**Eligibility criteria**

We included studies that randomly assigned adult patients to lithium or a control condition (placebo, usual care, placebo or waitlist). We required that the study population were mostly 18 years or older. In addition, we required that studies reported on death by suicide as a primary or secondary outcome. Consistent with recommendations from the literature, we included studies even if there were no suicide events.[13](#_ENREF_13) We applied no language limits to our search.

We did not restrict our study population to a particular diagnostic condition or set of symptoms. We made this decision because there is evidence in the literature that lithium may have a role in suicide prevention in a range of populations. For example, population-level research has suggested an association between the trace element lithium in drinking water and lower suicide rates.[14](#_ENREF_14)

**Study identification and data abstraction**

One reviewer (NR) applied our study inclusion (and exclusion) criteria to the titles and abstracts of potentially eligible publications. Two reviewers (NR, BS) then independently assessed the full text of the remaining publications to make a final determination regarding study eligibility. Discrepancies were resolved by involving a third reviewer (BW) who independently evaluated the full texts to make a final determination about study inclusion.

For each study, demographics, methods, outcomes, and risk of bias were abstracted using a standardized data collection form. We used the Cochrane Risk of Bias Tool 2.0 to assess risk of bias.[15](#_ENREF_15)

The data abstraction was performed by two reviewers (NR, BS) independently and in duplicate. Discrepancies were resolved through consensus.

**Primary outcome and data analysis**

The outcome of interest was death by suicide. We did not examine other suicide-related outcomes such as suicidal ideation or non-fatal suicide attempts.

We evaluated the efficacy of lithium versus control for preventing death by suicide by calculating summary odds ratio (OR) with 95% confidence intervals (CI) and p-values. As recommended in the literature, we used the Peto Method to carry out our analysis because this method is more powerful in the case of a rare outcome.16,17 We did not apply a correction in the event that a trial reported double zero events (i.e. no event in either arm)[6](#_ENREF_6) because this is not recommended with the Peto Method.16

We considered that an OR that was smaller meant that the relative odds of suicide was reduced in the lithium versus control condition, and the opposite was true if the OR was larger than one. We defined an OR as statistically significant if the p-value was <0.05 and the 95% confidence interval did not cross one.

We assessed for heterogeneity using Cochrane’s Q and the I2 statistic. We defined substantial and significant heterogeneity using the typical threshold of p < 0.10 and an I2 > 50%.16

We conducted the analysis using STATA 17 (StataCorp).

**Confirmatory Analysis**

In order to address potential limitations of available meta-analytic methods to assess rare events, we carried out a confirmatory analysis.[18](#_ENREF_22)We used a Poisson regression model with random effects and calculated an incidence rate ratio (IRR) for suicides over person-year (PY).19,20 This method is useful because it can account for differences in exposure time across studies,19,20  addresses any potential heterogeneity between trials20 and better account for trials reporting zero events.19,20

Because PY may differ between study arms based on the number of assigned subjects and loss to follow-up, we calculated PY for each study assignment. In the event that the authors reported PY[9](#_ENREF_9) or mean total study follow-up21 for the lithium and control groups, we abstracted these data directly from the publication. Otherwise, we calculated PY by summing the total amount of follow-up time contributed by all the subjects assigned to the study arm.22 We assumed that complete follow-up data was available if the authors stated that there was no loss to follow-up[6](#_ENREF_6), [7](#_ENREF_7) or the authors stated that they had access to full data for our outcome of interest (i.e., suicide).[8](#_ENREF_8) In the case that a study reported loss to follow-up,[4](#_ENREF_4), [5](#_ENREF_5) we accounted for this variation in follow-up time in our calculations.

Prior to conducting our confirmatory analysis, we first performed a boundary likelihood-ratio test in order to assess our study data for overdispersion.23 We considered that there was over-dispersion if the alpha (the estimate of the dispersion parameter) was significantly larger than zero, defined as a *p*-value <0.05.23 We found that the alpha for our study data was equal to zero (χ2= 0.10, p-value 0.4), suggesting that it was appropriate to use a Poisson regression model.

We conducted the confirmatory analysis using STATA 17 (StataCorp).

**Reporting Bias**

In order to assess for publication bias, we generated a funnel plot for our primary outcome.24 We visually inspected the plot for asymmetry. We considered that a negative correlation between sample size and effect size (i.e., lack of small studies with negative findings) was suggestive of publication bias.24 As described earlier, we also searched ClinicalTrials.gov to identify any unpublished trials.

Because our meta-analysis included a total of seven studies, we did not perform a formal test for publication bias. The Cochrane Handbook cautions that tests for funnel plot asymmetry produce unreliable results in the case of fewer than 10 studies.24

**Quality Analysis**

We assessed the quality of the evidence and its impact on our overall results using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[25](#_ENREF_28)In our analysis, we considered risk of bias, inconsistency, indirectness, imprecision, the event rate, the effect size, certainty, importance and other factors including publication bias, magnitude of the effect size, dose-response gradient, and residual confounding.25

We conducted the GRADE analysis using GRADEpro software.26

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