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**Title page**

**Title:** Severe methodological problems in a recent review and analysis of the association between lithium concentration in potable water and suicide rates

**Running Title:** Lithium in potable water and suicide rates

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## Text

The recent paper by Fadaei (2023) that explored the association between suicide mortality and lithium concentrations in potable water deserves comments. While this paper is presented as a review, the main analysis is rather an ecological study, a design known for having major methodological limitations. Furthermore, the literature search is hardly reproducible and the data analysis is flawed.

The first serious problem in the paper is that the results from the 16 studies reported in Table 1 are a mix of standardized mortality *rates* (SMRates) and standardized mortality *ratios* (SMRatios), and mixing both outcomes in the regression analysis is wrong. The SMRatio is the ratio between the expected suicide rate (based on a reference population, usually the country of interest) and the observed suicide rate in an area within the country of interest. In contrast, SMRates correspond to the proportion of people dying by suicide, usually standardized to suicides per 100,000 in a year. We did not look at all original studies, but at least for the Danish study (Kessing *et al.*, 2017) and a Lithuanian study (Liaugaudaite *et al.*, 2017), the results reported in Table 1 are SMRates, not SMRatios. Moreover, there is a very inconsistent use of terms throughout the paper which should have raised concern. For example, in Table 1, the header uses “suicides rates”, whereas the corresponding column refers to “standardized mortality ratios”. In Figure 2, the y-axis is labeled “Total Standardad suicide rate”, whereas the figure caption refers to “standardized mortality ratio”.

The second serious problem is that it is wrong to compare studies from different regions based on SMRatios, because standardization usually leads to a loss of information about the absolute rates of suicides in these regions. For example, in the Austrian study (Helbich *et al.*, 2012), standardization was used to account for different distributions of age and gender in the investigated districts of Austria, with the general Austrian population as reference population. Consequently, the SMRatios

of the districts in Austria varied around 1, and the mean value of SMRatios across districts converged to around 1. We assume that this approach was used by several other studies, thus the information about the absolute suicide rate is lost for these studies. This could explain why several data points at the bottom of the scatterplot in Figure 1 are located on a horizontal line with intercept of 1.

A third major issue is that the studies from Japan and England seem to have used SMRatios standardized to 100, not to 1. This could explain why the results from Japan and England form a separate cluster at the top of the figure. We were able to contact the author of one of those studies (Kugimiya *et al.*, 2021) who confirmed that SMRatios were standardized to 100 in this specific study. We leave it to the author to clarify this for other studies. Using results standardized to 1 or 100 in the same analysis makes no sense and invalidates any conclusion drawn for the regression analysis. Put differently: if the author had used SMRatios (standardized to 1) for all studies, the results would all be along a horizontal line with intercept 1 in the figure, because between country information is lost through standardization. It would be different if the world population was used as reference population to calculate the SMRatios, but this was never done in related studies, to our knowledge. Using SMRates would have been a better option, but this comes with problems, too, for example because suicide might be assessed and classified differently across countries.

Forth, despite the author merely – and inappropriately – refer to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher *et al.*, 2009) by stating that “16 were used for this review, excluding the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reference”, there are serious issues regarding reporting. The method sections mention systematic searches on “databases like Google Scholar, Science Direct, and Web of Science”. However, the chart presentation of the review only refers to “Google search” and does not detail the number of

identified references. Furthermore, selection criteria of included studies (e.g., regarding population and outcomes) are poorly specified. Similarly, the selection and data collection processes are unclear. It is unclear how many reviewers were involved in the searches as there is only one author but the text often refers to “we”.

Fifth, while Figure 1 indicates that 16 international studies were included, Figure 2 only presents 15 data-points included in the ecological analysis. No reason is given for the missing study. According to Table 1, each data point corresponds to the “lithium concentrations in drinking water” and the “total standardized mortality ratio”. In the regression analysis, lithium concentration explained one third of the variance in suicide mortality (i.e., “ $R^2 = 0.3323$ ”). This is a large effect and already should have raised doubts when looking at the much smaller effects in most individual studies or that from a previous meta-analysis [3] that was not even referenced in the current paper. It turns out that there are at least three fatal flaws in the analysis making the results invalid.

Finally, even if the regression analysis was based on accurate data, the analysis relied on aggregate-level data and is therefore prone to ecological fallacy. The ecological fallacy may occur in this example when correlations at the aggregate level (each country is a data-point) differ from correlations at the lower level (e.g, each district is a data-point). In addition, the statistical analysis displayed in the paper is not appropriate as there is no attempt to weight each study regarding precision of its estimation, neither for lithium concentrations in drinking water, nor mortality, nor their association. Worst, some studies are from the same geographic area (2 are from Lithuania, 2 from the Kyushu Island, Japan). One more appropriate choice of method would have been to meta-analytically aggregate the correlations from the studies (e.g. Eyre-Watt *et al.*, 2021). Last, it was suggested that publication bias may affect the related literature (Eyre-Watt *et al.*, 2021).

In summary, no conclusions can be drawn from this study.

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Both authors declare that they have read and approved the paper, that they have met the criteria for authorship as established by the International Committee of Medical Journal Editors, that they believe that the paper represents honest work, and that they are able to verify the validity of the results reported.

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