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Review article

Relationship between suicide mortality and lithium in drinking water: A systematic review and meta-analysis

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ABSTRACT

Background: : Lithium at therapeutic doses has protective effects against suicide in clinical practice. This meta-analysis aimed to investigate the relationship between lithium concentration in drinking water and suicide mortality in the general population.
Methods: : A systematic search was conducted in Web of Knowledge, PubMed, ScienceDirect, and Scopus to find papers reporting the crude relationship between drinking water lithium and suicide incidence in the general population until June 2019. The pooled effect measure was expressed as odds ratio (OR) and 95% confidence interval (CI) using the random-effects model.
Results: : We retrieved 308 English original articles, of which 13 ecologic studies with a total sample size of 939 regions and one cohort study with a sample size of 3,740,113 people were eligible for the meta-analysis. A significant relationship was found between the lithium concentration in drinking water and reduced suicide mortality (OR = 0.42; 95% CI: 0.27–0.67; p-value < 0.01). Ten studies reported gender-specific responses to lithium, with the pooled estimates as follows: OR = 0.54; 95% CI: 0.35–0.84; p-value < 0.01 for men, OR = 0.70; 95% CI: 0.48–1.01; p-value = 0.057 for women, and OR = 0.63; 95% CI: 0.47–0.83; p-value < 0.01 for total.
Limitations: : The study was limited to the assessment of the crude relationship between lithium exposure and suicide rate without considering the role of confounders.
Conclusions: : Lithium in drinking water is dose-dependently associated with reduced suicide mortality at least in ecological studies. However, we need well-designed clinical trials to confirm the protective effect of drinking water lithium intake against suicide.

1. Introduction

Suicide is a widespread serious problem of the modern era that may occur throughout the lifespan. It is a major leading cause of death around the world for the general population. Based on the World Health Organisation 2019b) statistics, suicide was the cause of 793,000 deaths worldwide in 2016, with an annual global age-standardized rate of 10.5 per 100,000 population. Suicide rates vary widely from country to country and even among regions within a country. There is also a gender difference in suicide incidence. According to the World Health Organisation (2019a), the rate of completed suicide is about two times higher in men than in women. However, it is shown that suicide attempts are more frequent in women than in men (Eskin et al., 2019).

Suicide is a complex phenomenon with many contributing factors

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including psychological, social, economic, biological, and environmental factors (Sinyor et al., 2017). There is strong evidence that suicide mostly occurs among people with mood disorders (Smith and Cipriani, 2017). The suicide risk has been estimated at 6–10% in the mood disorder population, which is 10 times the corresponding risk in non-psychiatric populations (Cipriani et al., 2013). Due to the devastating consequences of suicide in the individual and family life of attempters, much effort has been made to prevent suicidal ideation and attempts.

Lithium (Li) is a medication used for the treatment of a wide spectrum of mental disorders such as mood disorders, including depressive and bipolar disorders (Cipriani et al., 2005; Goodwin et al., 2003; Guzzetta et al., 2007). The therapeutic levels of Li in plasma, i.e., 0.6–1.0 mmol/L (Vita et al., 2015), act through exerting mood-stabilizing effects Machado-Vieira et al., 2009 and decreasing aggressive behaviors including life-threatening acts Silva and Silva, 2019(). Lithium also has anti-suicidal effects that can be exerted irrespective of its mood-stabilizing properties (Sarai et al., 2018). A systematic review and meta-analysis showed that treatment with lithium could reduce the risk of death by suicide up to 60% compared to placebo among people with mood disorders (Cipriani et al., 2013). Kanehisa et al. (2017) found that serum lithium levels were significantly lower in suicide attempters than in control patients who had just a history of intoxication or injury.

As a naturally occurring trace element, lithium is found in some minerals such as amblygonite, petalite, lepidolite, and spodumene in rock and soils (Fuchsloch et al., 2018). Therefore, it can be absorbed by the roots of plants to enter the food chain through lithium-rich food such as grains and vegetables (Figueroa et al., 2013; Law et al., 2017). Like other chemical elements in the earth's crust, lithium can be washed out after rainfall and weathering of minerals to naturally occur in groundwater (Ferrante et al., 2014; Karimzade et al., 2014; Mohammadi et al., 2017). Unlike many chemical constituents such as heavy metals, nitrate and fluoride (Aghaei et al., 2015; Yousefi et al., 2018; Kheradpisheh et al., 2018), there are no recommendations and standards for lithium in drinking water based on WHO and United States Environmental Protection Agency (USEPA). The lithium concentration of drinking water has been reported in a wide range from 0–12 μg/L in Aomori, Japan (Sugawara et al., 2013) to 2.8–219 μg/L in Texas, USA (Blüml et al., 2013). After being ingested, lithium is absorbed in the intestine by sodium channels (Erdemir and Gucer, 2018; Koenig et al., 2015). Lithium may appear in serum, saliva, and urine of consumers (Shetty et al., 2012). It is mostly excreted through kidneys (Sriraman and Kumaran, 2018) so that a significant positive correlation was found between drinking water lithium and urine lithium (Dawson et al., 1972). This finding can suggest that drinking water is a major source of lithium exposure in humans.

Some researchers have indicated that the anti-suicidal properties of lithium can be significant even at concentrations lower than the therapeutic doses (Sarai et al., 2018). Therefore, considering the clinical relevance of lithium in reducing life-threatening attempts and the daily intake of lithium through drinking water throughout the lifespan, it is hypothesized that the long-term lithium exposure through drinking water consumption may be associated with decreased rates of suicide even in the general population. Numerous studies, especially epidemiologic studies, have been conducted all around the world to establish this hypothesis. They have shown that although the natural intake of lithium is limited, there is evidence of anti-suicidal effects of lithium on both mood disorder patients and the general population upon chronic exposure to microdoses of lithium (Terao et al., 2009; Tondo and Baldessarini, 2018).

Epidemiologic studies are widely used to investigate the relationship between water-bearing chemicals and human health consequences (Moghaddam et al., 2018; Yousefi et al., 2017). The first epidemiologic study concerning the direct relationship between trace lithium concentrations in drinking water and the suicide rate was published in 1972, finding no significant correlation between the variables in 24 counties of Texas, USA (Dawson et al., 1972). However, Schrauzer and Shrestha (1990) for the first time reported a significant inverse relationship between the lithium content of drinking water and suicide incidence in the same state of the USA, Texas. Since then, numerous epidemiologic studies have sought to investigate this relationship assuming that public water networks are the main sources of drinking water supply for the general population. However, the obtained results have been conflicting. There are studies showing the possible protective role of lithium in long-term consumption against suicide (Ohgami et al., 2009) while some others indicated no relationship (Pompili et al., 2015) or postulated even a predisposing effect for lithium (Knudsen et al., 2017). Moreover, lithium concentration in drinking water has been associated with men-only suicide mortality in some regions (Liaugaudaite et al., 2017) and with women-only suicide rates in some other regions (Sugawara et al., 2013). In addition, the roles of confounding factors and the effective concentration of lithium in drinking water have been matters of controversy. Although a few review studies, including three published in 2018, have tried to draw a firm conclusion (Brown et al., 2018; Ishii and Terao, 2018; Koenig et al., 2015; Tondo and Baldessarini, 2018; Vita et al., 2015), none has led to a quantitative analysis of the published studies. Therefore, there was a need for a meta-analysis to quantitatively aggregate the results of studies in this regard, as emphasized by Brown et al. (2018).

Hence, the current study aimed to conduct a systematic review and meta-analysis of studies investigating the relationship between the lithium concentration in drinking water and the suicide rate in the general population.

2. Methods

2.1. Study protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) was used for reporting the current study. The study protocol was registered in the International Prospective Register of Systematic Reviews Database (PROSPERO) (available at https://www.crd.york.ac.uk/prospero) in November 2018 with registration number CRD42018118789.

2.2. Search strategy

A systematic search was conducted to find studies investigating the relationship between lithium concentration in drinking water and suicide incidence in the general population, irrespective of study design. Therefore, we searched the Web of Knowledge (ISI), PubMed, Science Direct, and Scopus electronic sources by the MeSH and non-MeSH terms in title, abstract, or keywords until June 2019, with no limitation in time. The search strategy included the following terms: suicide, anti-suicidal, suicidality, drinking water, tap water, potable water, bottled water, lithium, and Li.

2.3. Eligibility criteria

We included original English papers reporting the crude relationship (without adjustment for confounding factors) between the lithium concentration in drinking water and suicide incidence in the general population without any restriction to study design. We excluded non-English papers and those with non-extractable or incomplete data from the study.

2.4. Study selection

The retrieved papers were reviewed by two authors (FBA and MD) for inclusion and exclusion criteria and any discrepancies were discussed and resolved by a third author (MGh). Furthermore, the reference lists of the eligible studies, as well as relevant review articles, were manually screened for the possibly missing papers in the electronic search.

2.5. Qualitative study

A modified version of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Von Elm et al., 2007) was used for scoring the finally selected studies. It included 22 items addressing three main study designs in analytical epidemiology, namely cohort, case-control, and cross-sectional studies.

2.6. Data extraction

The following data were extracted from the selected articles: authors' name, publication year, region/country of origin, duration of suicide data collection, duration of lithium data collection, Li concentration in drinking water, suicide incidence rate, sample size, and data indicating the relationship between the lithium content of drinking water and suicide rate.

2.7. Statistical analysis

The data of each study were quantitatively analyzed using comprehensive meta-analysis software (CMA; version 2.2.064) to calculate an effect size for each study. The pooled effect measure was expressed as the Odds Ratio (OR) and a 95% Confidence Interval (CI). Significant heterogeneity between studies was proven by the p-value of the Q-statistic below 0.10 and the I^2 statistic above 50%. Therefore, a random-effects model was used to analyze the data. Moreover, subgroup analysis was applied to determine the possible source of heterogeneity. Moreover, a sensitivity analysis was performed by removing studies one by one and checking the p-value of the pooled effect (leave-one-out sensitivity analysis). The Begg's funnel plots and the asymmetry tests (Egger's and Begg's test) were employed to investigate the publication bias. P-values of $^{<}$0.05 were considered statistically significant.

3. Results

3.1. Flow and characteristics of the included studies

Fig. 1 illustrates the PRISMA 2009 flow diagram of the study selection process. As can be seen, our search retrieved 308 English original journal articles (106 from Scopus, 50 from Web of Knowledge, 37 from PubMed, 113 from Science Direct, and 2 from the reference list of relevant articles), of which 14 articles had the criteria for inclusion in the qualitative assessment (Dawson et al., 1972; Giotakos et al., 2013; Helbich et al., 2015; Ishii et al., 2015; Kabacs et al., 2011; Knudsen et al., 2017; Liaugaudaite et al., 2017; Ohgami et al., 2009; Oliveira et al., 2019; Palmer et al., 2019; Pompili et al., 2015; Schrauzer and Shrestha, 1990; Shiotsuki et al., 2016; Sugawara et al., 2013). The quality score of the finally retrieved articles ranged from 0.52 to 0.87 based on the STROBE. Thus, all 14 articles were qualified for quantitative meta-analysis. Moreover, 82 non-duplicate English review articles were retrieved. The reference lists of the nine relevant review studies (Franklin et al., 2017; Gallicchio, 2011; Ishii and Terao, 2018; Koenig et al., 2015; Rihmer, 2011; Sinyor et al., 2017; Terao et al., 2009; Tondo and Baldessarini, 2018; Vita et al., 2015) were searched for possibly missing papers. However, no additional article emerged.

The characteristics of the 14 studies used in the meta-analysis with a total sample size of 939 regions in 13 ecologic studies and 3740,113 people in one cohort study are summarized in Table 1. All of the papers reported the crude relationship between the lithium content of drinking water and suicide incidence in the general population. However, 10 studies reported the relationship of lithium concentration with both male-only and female-only suicide deaths. We used these studies to investigate the gender difference in response to lithium exposure.

3.2. Relationship of lithium concentration in drinking water with suicide incidence

Fig. 2 depicts the forest plot summarizing the pooled effect of the relationship between lithium concentration in drinking water and suicide incidence. Due to a significant between-study heterogeneity (Q-statistic *p*-value <0.01, $I^2 = 85.51\%$), a random-effects model was employed for data analysis. Based on the meta-analysis of the 14 studies, the odds of suicide decreased by increasing lithium concentration in drinking water (OR= 0.42; 95% CI: 0.27 to 0.67; *p*-value <0.01). This pooled effect was robust in the leave-one-out sensitivity analysis (Fig. S1).

3.3. Subgroup analysis

A subgroup analysis was performed based on the study location and the results are shown in Fig. S2. As can be seen, the relationship of interest remained significant in Japan (OR= 0.57; 95% CI: 0.37 to 0.88; *p*-value =0.012) but it was insignificant in the USA (OR= 0.03; 95% CI: 0.00 to 1.15; *p*-value =0.060) and Europe (OR= 0.65; 95% CI: 0.40 to 1.04; *p*-value=0.071). Moreover, the heterogeneity disappeared between the Japanese studies (Q-statistic p-value =0.219, $I^2 = 32.22\%$), but remained in the American (Q-statistic *p*-value <0.01, $I^2 = 88.66\%$) and European (Q-statistic p-value <0.01, $I^2 = 77.26\%$) studies.

3.4. Effect of gender

As mentioned earlier, there were 10 studies reporting the outcome separately for males and females. As shown in Fig. 3, subgrouping of these studies for sex showed that the odds of suicide significantly decreased by increasing lithium concentration in drinking water in men (OR= 0.54; 95% CI: 0.35 to 0.84; *p*-value <0.01) but non-significantly in women (OR= 0.70; 95% CI: 0.48 to 1.01; *p*-value =0.057). However, the inverse relationship remained highly significant in the total population (OR= 0.63; 95% CI: 0.47 to 0.83; *p*-value <0.01).

3.5. Publication bias

As can be seen in the funnel plot in Fig. 4, the 14 studies (white circles) are not symmetrically distributed around the pooled effect size, which can be a sign of publication bias. This is confirmed by the results of Egger's linear regression (intercept = −2.18; S.E. = 0.39; 95% CI: −3.04 to −1.32; t = 5.51; df=12; one-tailed *p*-value < 0.01). Duval and Tweedie's Trim and Fill test showed that there were possibly four missing studies (black circles) to the right side of the mean effect. By including the missing papers, there is a strong possibility that the imputed point estimate changes to OR=0.62 (95% CI: 0.38–1.01).

4. Discussion

As a mood stabilizer, lithium has long been used for the treatment of mental disorders. However, the beneficial effects of lithium are questioned at doses quite below the therapeutic doses, e.g. when it is consumed through drinking water. To shed light on the issue, the current meta-analysis used the results of 14 studies with a total sample size of 939 regions and 3749,113 people to determine the direct relationship between the lithium content of drinking water and suicide rate. Based on the results, higher lithium concentrations in drinking water are attributed to the reduced odds of suicide prevalence in the general population (OR= 0.42; 95% CI: 0.27 to 0.67; *p*-value <0.01). A relatively comprehensive literature review conducted by Giotakos et al. (2013)

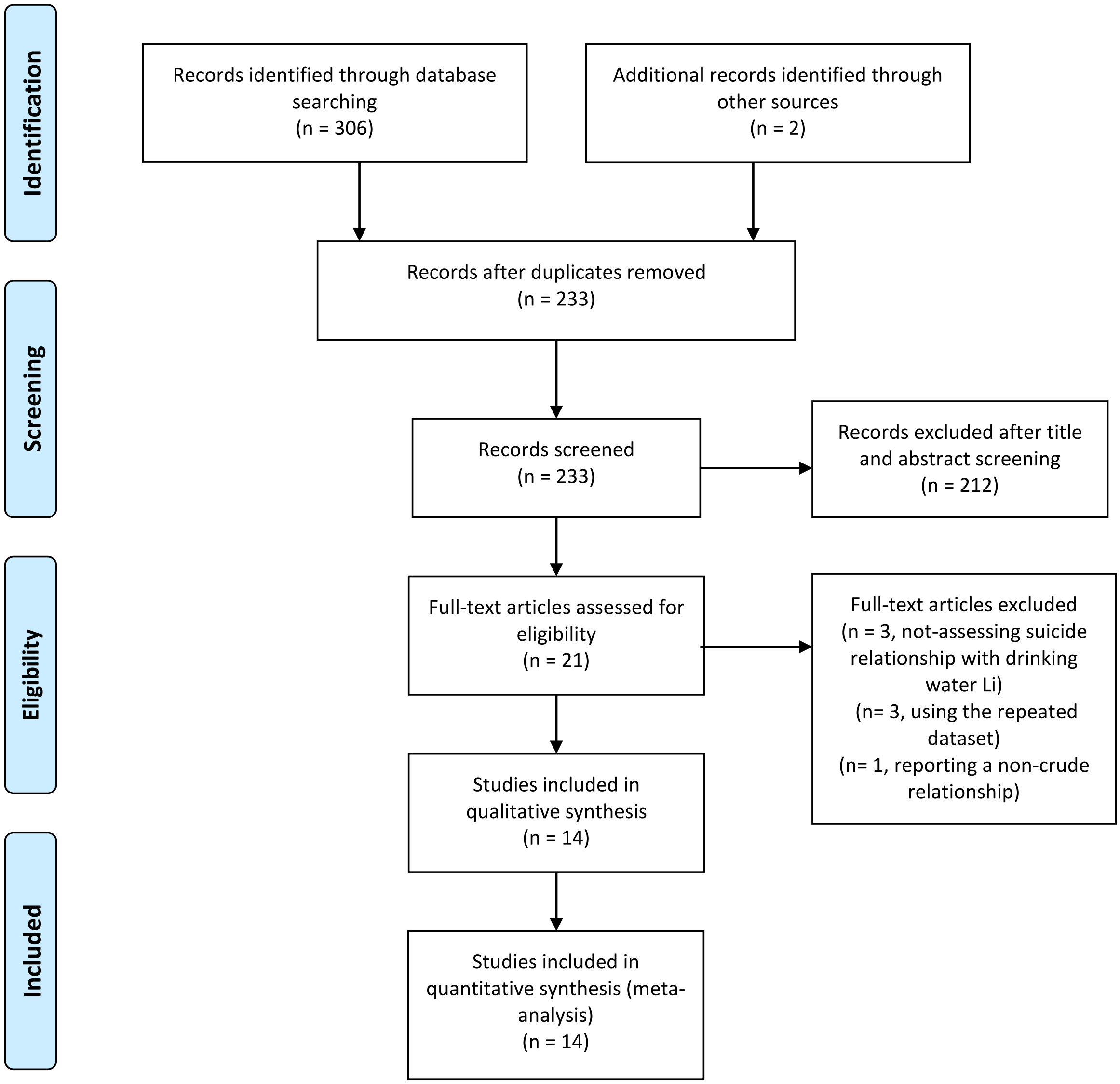

Fig. 1. PRISMA flow diagram of the study selection.

explored the possible biochemical mechanisms of lithium effect on suicide reduction. The anti-suicidal effect of lithium at therapeutic doses may be associated with its mood-stabilizing properties. However, it has been observed that lithium may play this role without any change in mood symptoms (Sarai et al., 2018). Although the exact action mechanism of lithium at trace doses remains unclear, the cumulative effect of lithium after microdose consumption over the years is a strong possibility (Pompili et al., 2015). Brown et al. (2018) developed a hypothesis that lithium exerts its psychiatric benefits through mitigating the neurologic adverse effects of chronic exposure to lead as a toxic heavy metal found in drinking water. This may be supported by the fact that lithium can inhibit the activity of adenosine triphosphatase (ATPase) transporter, which is the main transporter responsible for crossing calcium ions, and alternatively lead ions, through the blood-brain barrier. However, as the authors mentioned, this hypothesis needs evidence from randomized controlled trials to be confirmed.

The results of the subgroup analysis showed that the study location was a possible source of heterogeneity between the studies. As observed, the significant relationship between drinking water lithium and suicide rate disappeared in the USA and Europe but remained in Japan. It is well known that some geographical factors may play a role in this regard. For example, Helbich et al. (2013) observed that the lithium content of drinking water and the suicide rate had a direct relationship in regions with high altitude and an inverse relationship in regions with low altitude in Austria. This result also indicates that some modifiers can substantially change the direction in the relationship between natural lithium exposure and suicide incidence, making the relationship very complicated.

As another finding, the present study showed the increased lithium concentration in drinking water could significantly reduce the odds of suicide mortality in men but not in women. This finding may contrast a Danish cohort study (Kessing et al., 2005) that reported no gender difference in response to lithium therapy for suicide risk reduction. Moreover, Sugawara et al. (2013) reported a significant association between high-level lithium in tap water and the reduced suicide rate only in women in Aomori prefecture, Japan. They explained their results based on differences in the inherited characteristics of men and women, as well as the Japanese tradition. On the other hand, there are several studies reporting significant associations between lithium exposure through drinking water and male-only suicide rate (Blüml et al., 2013; Ishii et al., 2015; Kapusta et al., 2011; Liaugaudaite et al., 2017; Shiotsuki et al., 2016). When interpreting the results, the use of different methods for suicide attempt by men and women should be taken into account, as it is known that men usually use more violent means of suicide (Kumar et al., 2013) and lithium may exert its anti-suicidal effects by reducing impulsivity and aggression (Goldstein and

Table. 1
Characteristics of studies included in the meta-analysis .

Author, year	Study location	Number of samples	Duration of suicide data	Duration of Li data	Annual mean suicide incidence		Li concentration in drinking water (μg/L)	Reported outcome for relationship			Quality score
					SMR	Number per 100,000		Male	Female	Total	
Dawson et al. (1972)	Texas, USA	24 regions	1968–1969	UN	–	9.75	29.37	–	–	$r = -0.235$; $P > 0.05$	0.6
Schrauzer and Shrestha (1990)	Texas, USA-	27 regions-	1978–1987	UN	–	13.13	Group A: 123	–	–	IR = 8.7 ± 0.85, n = 6; $P_{A\text{-}B} < 0.005$; $P_{A\text{-}C} < 0.01$	0.52
							Group B: 35			IR = 14.8 ± 2.9, n = 7; $P_{B\text{-}C} > 0.05$	
							Group C: 5	–	–	IR = 14.2 ± 1.3, n = 14	
Ohgami et al. (2009)	Oita, Japan	18 regions	2002–2006	2006	105	–	9.02	*$P = 0.008$	*$P = 0.055$	*$P = 0.004$	0.6
Kabacs et al. (2011)	East of England	47 regions	2006–2008	2010	98	–	5.2	$r = -0.054$; $P = 0.71$	$r = 0.042$; $P = 0.78$	$r = -0.03$; $P = 0.84$	0.6
Sugawara et al. (2013)	Aomori, Japan	40 regions	2 years		Men: 123.Women: 105	–	0–12.9	*$t = 0.836$; $P = 0.41$	*$t = -2.275$; $P < 0.05$	–	0.67
Giotakos et al. (2013)	Greece	34 regions	1999–2010	2012	–	3.8	11.1	–	–	*$t = -2.10$; $P < 0.05$	0.52
Helbich et al. (2015)	Austria	99 regions	2005–2009	2005–2010	79	15.7	10	$r = -0.32$; $P = 0.003$	$r = -0.28$; $P = 0.009$	$r = -0.37$; $P < 0.001$	0.87
Ishii et al. (2015)	Kyushu Island, Japan	274 regions	2011	2010–2013	114	23.8	4.2	*$P = 0.005$	*$P = 0.957$	*$P = 0.031$	0.79
Pompili et al. (2015)	Italy	145 regions	1980–2011	2009–2010	–	7.15 (for 2000–11)	5.28	$r = -0.049$; $P > 0.05$	$r = -0.062$; $P > 0.05$	$r = -0.039$; $P > 0.05$	0.81
Shiotsuki et al. (2016)	Hokkaido and Kyushu Islands, Japan	153 regions	2010–2011	2010–2015	111.2	23.8	3.8	*$P = 0.005$	*$P = 0.88$	*$P = 0.059$	0.79
Liaugaudaite et al. (2017)	Lithuania	9 regions	2009–2013	2013	27	31.7 (for 2014)	10.9	$r = -0.728$; $P < 0.05$	$r = -0.276$; $P \geq 0.05$	$r = -0.731$; $P < 0.05$	0.87
Knudsen et al. (2017)	Denmark	3740,113 people	1991–2012	2013	–	29.7 to 18.4	Group A: 2.0–7.0	–	–	IR = 19.9	0.85
							Group B: 7.1–11.0	–	–	IR = 19.3	
							Group C: 11.1–15.0	–	–	IR = 21.0	
							Group D: 15.1–19.0	–	–	IR = 24.1	
							Group E: 19.1–27.1	–	–	IR = 22.3	
Oliveira et al. (2019)	Portugal	54 regions	2011–2016	2011–2014	119	–	10.88	$r = 0.024$; $P = 0.862$	$r = 0.000$; $P = 0.999$	$r = 0.001$; $P = 0.996$	0.81
Palmer et al. (2019)	Alabama, USA	15 regions	1999–2013	2016	–	12.08	8	$r = -0.62$; $P = 0.015$	$r = -0.44$; $P = 0.103$	$r = -0.63$; $P = 0.014$	0.6

* Statistics for correlation; UN: Unknown; SMR: Standardized Mortality Ratio; IR: Incidence Rate (of suicide).

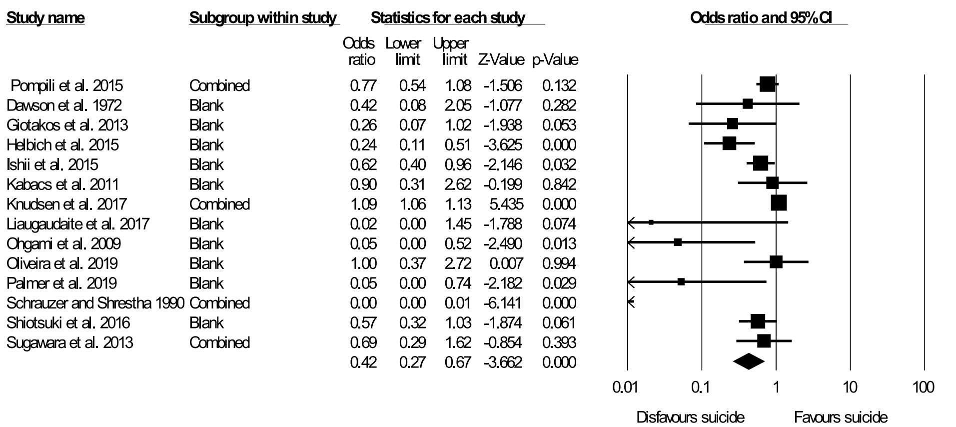

Fig. 2. The forest plot of the relationship between lithium concentration in drinking water and suicide incidence.

Mascitelli, 2016; Masaki et al., 2016). Therefore, the rate of completed suicides may not be sufficient to assess the epidemiology of anti-suicidal effects of lithium in gender groups. The different biological responses to lithium between men and women must not be ignored, as well, making men better responders to lithium. In this regard, it has been shown that suicidal ideation is attributed to high-level testosterone (Sher et al., 2012), which is normally observed in men rather than in women (Hyde et al., 2019). Therefore, the male response to lithium could be due to the decreased testosterone levels following lithium consumption (Elnazer et al., 2015).

The current study suffered a limitation because it analyzed the data on the crude relationship between lithium exposure and suicide rate without considering the role of confounders such as demographic, social, and geographical variables. This was because the examined studies had investigated the role of a wide variety of confounding factors in the relationship between lithium and suicide. However, it is notable that the significant relationship between lithium concentration of drinking water and the suicide rate has been proven after adjustment for some confounders. For example, Kapusta et al. (2011) established the negative association after adjustment for population density, per capita income, the proportion of Roman Catholics, and the availability of mental health service providers. Sugawara et al. (2013) found a negative relationship among women even when the correlation was adjusted for the number of medical centers per 10,000 population and unemployment rate. Shiotsuki et al. (2016) made the adjustment for meteorological factors (annual mean temperature, sunshine, rainfall, and snowfall) and could establish a significant relationship.

Moreover, the majority of the studies correlated suicide and lithium data gathered in separate periods, with lithium data duration mostly following the suicide data gathering. In other words, the outcome (suicide) was measured prior to exposure (lithium in drinking water). This procedure can be true if no change occurs in the lithium concentration over time. Although some studies claimed the stability of drinking water lithium concentrations over the years of the study (Knudsen et al., 2017), it may be questioned if effective factors in the lithium exposure level, such as rainfall and the source of public water supply, would be unchanged over time. Therefore, the water-sampling scheme remains a matter of controversy to account for yearly, seasonal, and regional lithium variations.

The lithium intake from other sources such as food (grains and vegetables) was not considered in the examined studies. This is while research has shown that drinking water can constitute only one-third of lithium intake in some regions (Goldstein and Mascitelli, 2016). Moreover, nearly all studies used public waterworks as the main source of drinking water supply, ignoring other sources such as bottled mineral water and wells, which usually have higher amounts of lithium (Kapusta et al., 2011; Pompili et al., 2015). For example, Neves et al. (2015) found lithium in the range of <1 to 191 μg/L in tap water and <1 to 2210 μg/L in bottled water in Portugal. Therefore, measuring serum lithium levels may be beneficial in future ecologic studies to overcome this obstacle.

Another source of controversy is the change to lithium exposure due to changes in the residence place of people. In an effort to resolve this problem, Knudsen et al. (2017) conducted a cohort study in the 3.7 million Danish population aged ≥21 years between 1991 and 2012. They used a national registry, updated once a year, to follow their

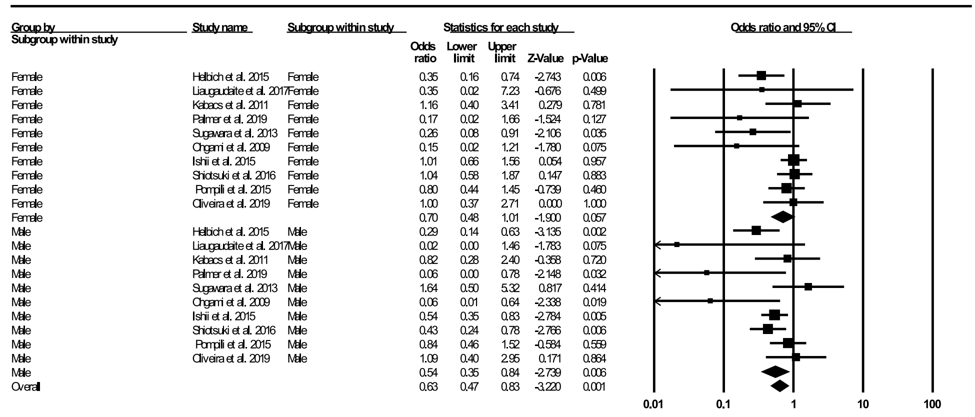

Fig. 3. The effect of gender on the relationship between lithium concentration in drinking water and suicide incidence.

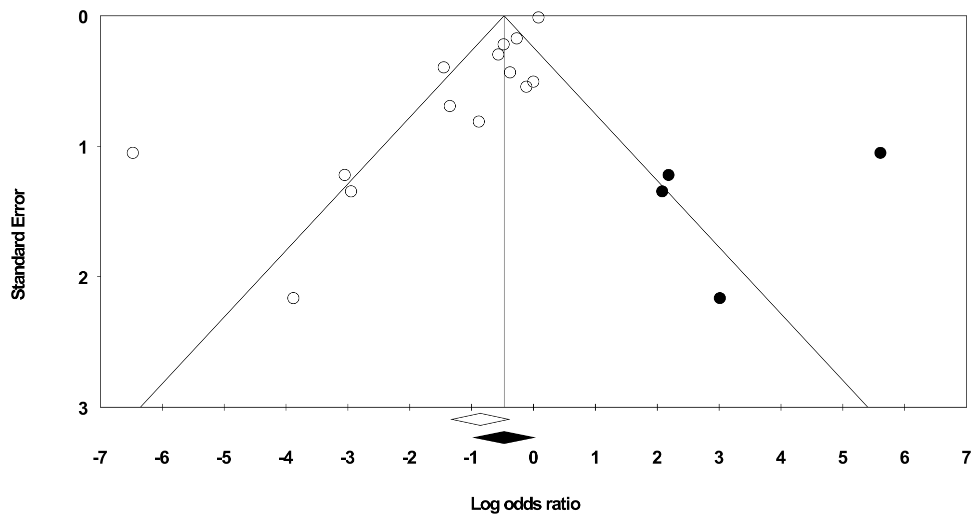

Fig. 4. The funnel plot of publication bias.

population until emigration, death, or end of the study. Therefore, they measured lithium exposure individually based on the residence period of each person in a specific location and reported it as a moving time-weighted average (TWA). Based on this design, they found no significant association between increased lithium exposure and decreased suicide rate. Although they tried their best, they failed to account for exposure changes due to relocation or emigrations within the same year.

It should be noted that our findings were obtained mostly from ecological studies while these studies are not designed to make a causal relationship and decide on the individual-level risk (Yoshimura et al., 2002). The only individual-level cohort study in our analysis was carried out by Knudsen et al. (2017) that showed suicide insignificantly increases with increasing exposure to lithium through drinking water in Denmark. Therefore, we need randomized, placebo-controlled trials for determining the definite effect of lithium intake through drinking water on suicide incidence although these studies may be the subject of ethical and clinical challenges. Moreover, the cost-benefit analyses should be conducted to ensure that drinking water enrichment with lithium is both cost-effective and safe for vulnerable people such as children, pregnant women, and patients with special medical conditions. Due to the different patterns of suicide attempts and suicide mortality among men and women, evaluating the relationship between drinking water lithium and suicide attempts, as well as other violent actions and impulsive behaviors, may be fruitful.

To the best of our knowledge, the current study is the first meta-analysis reporting the pooled effect of the relationship between lithium concentration in drinking water and suicide mortality in the general population. It seems we can step forward and conduct a series of clinical trials to test the hypothesis that the long-term lithium intake through drinking water has a protective effect against suicide.

5. Conclusion

We showed that lithium in drinking water was negatively associated with suicide mortality in the general population (OR = 0.42; 95% CI: 0.27 to 0.67; p-value < 0.01). However, there was a gender difference in response to lithium, with men being better responders. We are in a dire need of well-designed clinical trials to confirm the protective effect of lithium against suicide death and molecular studies to elucidate the mechanism of action.

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CRediT authorship contribution statement

Fateme Barjasteh-Askari: Methodology, Writing - original draft. **Mojtaba Davoudi:** Methodology, Writing - original draft. **Homayoun Amini:** Writing - review & editing. **Mohammad Ghorbani:** Formal analysis. **Mehdi Yaseri:** Formal analysis. **Masoud Yunesian:** Writing - review & editing, Formal analysis. **Amir Hossein Mahvi:** Conceptualization, Writing - review & editing. **David Lester:** Writing - review & editing.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.12.027.

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