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ORIGINAL ARTICLE

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Lithium in drinking water and the incidence of bipolar disorder: A nation-wide population-based study

Lars V Kessing[1] | Thomas A Gerds[2] | Nikoline N Knudsen[3] | Lisbeth F Jørgensen[4] | Søren M Kristiansen[5] | Denitza Voutchkova[4,5] | Vibeke Ernstsen[4] | Jörg Schullehner[4] | Birgitte Hansen[4] | Per K Andersen[2] | Annette K Ersbøll[3]

[1]Psychiatric Center Copenhagen, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[2]Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark

[3]National Institute of Public Health, University of Southern Denmark, Odense, Denmark

[4]Geological Survey of Denmark and Greenland, Copenhagen, Denmark

[5]Department of Geoscience, Aarhus University, Aarhus, Denmark

Correspondence
Lars Vedel Kessing, Psychiatric Center Copenhagen, Department O, Copenhagen, Denmark and University of Copenhagen, Faculty of Health and Medical Sciences, Copenhagen, Denmark.
Email: lars.vedel.kessing@regionh.dk

Present address
Denitza Voutchkova, Department of Geography, National University of Singapore, Singapore, Singapore

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Objective: Animal data suggest that subtherapeutic doses, including micro doses, of lithium may influence mood, and lithium levels in drinking water have been found to correlate with the rate of suicide. It has never been investigated whether consumption of lithium may prevent the development of bipolar disorder (primary prophylaxis). In a nation-wide population-based study, we investigated whether long-term exposure to micro levels of lithium in drinking water correlates with the incidence of bipolar disorder in the general population, hypothesizing an inverse association in which higher long-term lithium exposure is associated with lower incidences of bipolar disorder.

Methods: We included longitudinal individual geographical data on municipality of residence, data from drinking water lithium measurements and time-specific data from all cases with a hospital contact with a diagnosis of mania/bipolar disorder from 1995 to 2013 (N=14 820) and 10 age- and gender-matched controls from the Danish population (N= 140 311). Average drinking water lithium exposure was estimated for all study individuals.

Results: The median of the average lithium exposure did not differ between cases with a diagnosis of mania/bipolar disorder (12.7 μg/L; interquartile range [IQR]: 7.9-15.5 μg/L) and controls (12.5 μg/L; IQR: 7.6-15.7 μg/L; *P*=.2). Further, the incidence rate ratio of mania/bipolar disorder did not decrease with higher long-term lithium exposure, overall, or within age categories (0-40, 41-60 and 61-100 years of age).

Conclusion: Higher long-term lithium exposure from drinking water was not associated with a lower incidence of bipolar disorder. The association should be investigated in areas with higher lithium levels than in Denmark.

KEYWORDS
bipolar disorder, drinking water, incidence, lithium, low dose, micro dose

1 | INTRODUCTION

Lithium has for more than 60 years been the main mood stabilizer for bipolar disorder. The evidence for a prophylactic effect is strong[1] and lithium is recommended as first-line treatment for bipolar disorder in all recent international guidelines.[2-5] In recent years, there has been renewed interest in lithium within clinical practice and research,[6] including studies on prediction of lithium response in first-episode

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mania.[7] It has, however, never been investigated whether treatment with or consumption of lithium may prevent the development of bipolar disorder (primary prophylaxis). Such a trial would be impossible to conduct in view of ethical considerations, as this would imply that a large population of healthy individuals should consume lithium or placebo for many years. Animal data suggest that micro doses of lithium have effects on the central nervous system[8] and preliminary human studies suggest effects on mood.[9] Further, long-term intake of micro doses of lithium such as those found in drinking water, in the range 5-50 μg/L, have been found to correlate inversely with the rate of suicide in some studies[10,11] (but not in all studies[12]), and the rates of violent criminal behaviour and drug addiction.[13] We investigated whether higher lithium exposure from drinking water correlates with the incidence of bipolar disorder, hypothesizing an inverse association in which higher long-term lithium exposure is associated with lower incidences of bipolar disorder.

2 | METHODS

2.1 | The registers

Data were obtained by linking Danish population-based registers using the unique personal identification number (CPR), which is assigned to all 5.6 million persons living in Denmark.[14] Data are available at Statistics Denmark at an individual level for all individuals in Denmark from 1986 and onwards.[15] Data from Statistics Denmark[15] were linked with data on diagnoses and corresponding dates from the Danish National Patient Register[16] and the Danish Psychiatric Central Research Register[17] and data on death from the Danish Register of Causes of Death.[18]

The Danish Psychiatric Central Register[17] and the Danish National Patient Register[19] contain data on all inpatients from 1970 onwards and from 1976 onwards, respectively, treated at psychiatric and somatic hospitals in Denmark and include data on outpatients from 1 January 1995 onwards as a part of the official Danish health survey.[19] Since 1 January 1994, the ICD-10 has been in use in both registers.[20] The Danish Register of Causes of Death[21] contains data on death.

The study was approved by the Danish Data Protection Agency (No. 2013-41-2281).

2.2 | Selection of cases

All patients with a hospital contact with a main diagnosis of mania/bipolar disorder (ICD-10 code DF30-31.9 + 38.0) as inpatients or outpatients were identified in the Danish Psychiatric Central Register in the study period 1 January 1995 to 31 December 2013. Patients in the Danish National Hospital Register and the Danish Psychiatric Central Register with a diagnosis of dementia, organic psychosis, schizophrenia or mania/bipolar disorder (ICD-8 codes 290-299.09 incl.; ICD-10 codes F00-09 and F20-31.9 and G30.0–G30.9) prior to entry into the study and back to the start of the registers in 1976 and 1970, respectively, were excluded.

2.3 | Selection of controls

A nested case–control study was used. For each case, we randomly sampled 10 age- (to within 1 year), calendar- (to within 1 year) and gender-matched controls from a 25% random sample of the Danish population under the additional condition that controls were alive and non-cases at the index date. Cases and controls were excluded from all analyses if all municipalities of residence were missing.

2.4 | Lithium exposure from drinking water

Drinking water samples from 151 waterworks taken in 2013,[22,23] supplying approximately 42% of the Danish population, were used to approximate a value for each Danish municipality. The lithium level in the remaining municipalities was estimated by the geostatistical method kriging. Based on the kriging map, a mean lithium level in each of the 276 municipalities in Denmark was calculated.[22,24] The Danish municipality to which the home address of a study subject (either case or control) belonged in a certain year was available in all years in the period from 1986 to 2013. This information was used to compute the average drinking water lithium exposure of all study individuals based on the years between 1986 and the case date of the respective case–control set (details are described in Knudsen et al.[12]).

2.5 | Statistical analyses

The distributions of lithium exposure were compared among cases with mania/bipolar disorder and controls using the Wilcoxon rank sum test. The association between average drinking water lithium exposure and the incidence rate of mania/bipolar disorder was estimated using a Cox regression model fitted to the nested case–control sample.[25] Thereby, ratios between incidence rates of mania/bipolar disorder (incidence rate ratios [IRRs]) were obtained. In the main analysis, average drinking water lithium exposure per year was categorized into four groups (2-5, 5-10, 10-15 and 15-27 μg/L). The lowest group (2-5 μg/L) was used as a reference for the calculation of IRRs. A sensitivity analysis was performed where the continuous association between average lithium level in drinking water and the incidence rate of mania/bipolar disorder was analysed by using restricted cubic splines with five knots set at the quantiles of the average drinking water lithium exposure.[26]

By sampling controls from the risk set at the dates of mania/bipolar disorder diagnosis and by matching for age, the association between average lithium exposure and mania/bipolar disorder incidence rate can be interpreted as IRRs between individuals within the same age interval (since beginning of exposure ascertainment and even since birth) living constantly in areas with given drinking water lithium levels. All analyses were adjusted for the time-varying covariate employment status available from Statistics Denmark (working [=reference], unemployed, in receipt of an old age pension, disabled, and other, including student).

All analyses were repeated within age categories (0-40, 41-60 and 61-100 years of age), when the outcome measure was a diagnosis of mania/bipolar disorder at the first contact ever after 1995 (and not at any contact after 1995) and finally for birth cohorts born before and after 1986.

3 | RESULTS

After excluding patients with a prior diagnosis of dementia, organic psychosis, schizophrenia or mania/bipolar disorder, a total of 14 982 patients were identified with a diagnosis of mania/bipolar disorder during the study period from 1995 to 2013 inclusive. For each case, 10 age- and gender-matched controls from the Danish population were identified under the additional condition that controls were alive and non-cases at the case date. Municipality of residence was missing in the entire study period for 0.66% of patients and 0.26% of matched controls. After removing patients and controls older than 100 years or without information on employment status or without any information on municipality of residence in the whole study period, the analyses included 14 820 cases with mania/bipolar disorder and 140 311 controls. Table 1 shows socio-demographic characteristics of the cases with bipolar disorder.

The median of the average lithium exposure did not differ significantly between cases with a diagnosis of mania/bipolar disorder (12.7 μg/L; interquartile range [IQR]: 7.9-15.5 μg/L) and controls (12.5 μg/L; IQR: 7.6-15.7 μg/L; *P*=.2). Table 2 shows that when average lithium exposure was categorized in conditional logistic regression models, the IRR of mania/bipolar disorder did not decrease significantly with higher long-term lithium exposure. On the contrary, the incidence rate of mania/bipolar disorder was statistically significantly increased among individuals exposed to 5-10 and 10-15 μg/L lithium per year compared with exposure to 2-5 μg/L per year. Similar patterns were observed within age categories (0-40, 41-60 and 61-100 years of age) and when analyses were repeated with the outcome measure of a diagnosis of mania/bipolar disorder at the first contact ever after 1995 (N=5690 cases and 56 343 controls) (results not presented). Finally, in analyses of individuals born before or after 1986 (where municipality is known from time of birth), the dose−response patterns were the same as in the main analysis of the full data set (results not presented).

In all analyses, being unemployed, on an old age pension, disabled, or "other" was associated with a higher incidence rate of mania/bipolar disorder than for individuals in work (results not presented).

TABLE 1 Socio-demographic characteristics of cases with bipolar disorder

Sex [n (%)]	
Male	6273 (42.1)
Female	8610 (57.9)
Age, years	
Median (IQR)	46.6 (34.1, 58.7)
Age group [n (%)]	
0-20 years	479 (3.2)
21-40 years	4968 (33.4)
41-60 years	6036 (40.6)
61-100 years	3400 (22.8)
Employment status [n (%)]	
Working	5894 (39.6)
Unemployed	1303 (8.8)
Retired	2525 (17.0)
Disabled	3965 (26.6)
Other	1196 (8.0)

IQR, interquartile range.

4 | DISCUSSION

We did not confirm the hypothesis that higher long-term lithium exposure from drinking water is associated with a lower incidence of mania/bipolar disorder. This is the first study investigating the association between lithium in drinking water and the incidence of mania/bipolar disorder de novo. The study has a number of advantages. The hypothesis was posed prior to undertaking the study. The study was a nation-wide population-based longitudinal cohort study including individualized longitudinal data on lithium exposure based on the municipality of residence of study individuals (either case or control) during a 28-year period from 1986 to 2013 and drinking water lithium samples from 151 locations spatially covering all of Denmark combined with hospital data on incident mania/bipolar disorder. In this way, the study took into account whether individuals moved from one municipality to another with a different lithium level in the drinking water. Further, the study included all incident cases with mania/bipolar disorder resulting in hospital contact as an outpatient or inpatient within psychiatric hospitals/wards nation-wide as well as 10 controls without a hospital contact for mania/bipolar disorder per case. The same pattern was repeated within age categories (0-40, 41-60 and 61-100 years of age) and in analyses when diagnosis of mania/bipolar disorder at the first contact ever was the outcome measure, showing that the hazard ratio of mania/bipolar disorder did not decrease with higher long-term lithium exposure.

The study is the first of its kind and argues against the hypothesis that micro doses of lithium taken long term decrease the risk of incident mania/bipolar disorder. Drinking water is a major source for human lithium intake in addition to vegetables.[27] In Denmark, drinking water derives from groundwater only, and the levels of lithium in groundwater and drinking water are likely stable over time due to the chemical properties of lithium and its geological origin.[22,28] Spatially, the lithium level in groundwater and drinking water in Denmark varies from around 2 μg/L in some areas to near to 30 μg/L in others,[22] although the level is significantly higher in some other parts of the world,[27] while on a European scale the values in the present study are slightly higher than observed medians and means obtained from lithium statistics for >500 drinking water

TABLE 2 Average lithium exposure and incidence rate ratios (IRRs) of mania/bipolar disorder (0-100 years of age and within age categories), adjusted for employment status

Grouped average lithium exposure (μg/l)	Cases n (%)	Controls n (%)	IRR (95% CI)	P
0-100 years of age				
2-5	1356 (9.1)	15870 (10.7)	1	
5-10	3500 (23.6)	33595 (22.6)	1.23 (1.15; 1.32)	<.0001
10-15	5864 (39.6)	55928 (37.6)	1.23 (1.15; 1.31)	<.0001
15-27	4100 (27.7)	43304 (29.1)	1.06 (0.99; 1.13)	.0956
0-40 years of age				
2-5	434 (8.0)	5277 (9.6)	1	
5-10	1373 (25.3)	13086 (23.9)	1.34 (1.19; 1.51)	<.0001
10-15	2263 (41.7)	20821 (38.0)	1.35 (1.21; 1.51)	<.0001
15-27	1360 (25.0)	15545 (28.4)	1.06 (0.94; 1.19)	.3144
41-60 years of age				
2-5	560 (9.3)	6543 (10.9)	1	
5-10	1394 (23.2)	13162 (21.9)	1.23 (1.11; 1.37)	.0001
10-15	2306 (38.4)	22710 (37.8)	1.16 (1.05; 1.28)	.0037
15-27	1750 (29.1)	17689 (29.4)	1.05 (0.95; 1.16)	.3435
61-100 years of age				
2-5	362 (10.7)	4050 (12.0)	1	
5-10	733 (21.7)	7347 (21.7)	1.11 (0.97; 1.27)	.1235
10-15	1295 (38.3)	12397 (36.6)	1.18 (1.04; 1.33)	.0085
15-27	990 (29.3)	10070 (29.7)	1.08 (0.95; 1.22)	.2459

CI, confidence interval.

samples in Europe.[29] It is possible that the levels of lithium in drinking water in Denmark (and most of Europe) are too low to have any long-term effects on the risk of bipolar disorder.

Further, it should be noted that a proportion of the daily intake of lithium may originate from consumption of food,[25] on which we had no information.

Arguments supporting the view that micro doses of lithium may affect human behaviour derive from prior cross-sectional studies based on ecological, non-individualized data showing that levels of lithium in drinking water correlate inversely with the rates of suicide,[10,11] violent criminal behaviour and drug addiction.[13] It should be emphasized that all those prior studies on lithium in drinking water had an ecological design investigating associations cross-sectionally and on a group-based level, in contrast to the present study investigating the lithium level in the drinking water longitudinally on an individual level by taking account of whether individuals moved from one municipality to another with different lithium levels. This is in line with another new Danish study from our group that did not confirm the protective effect of exposure to low-level lithium in drinking water on the risk of suicide, also using individual longitudinal data.[12]

In addition to studies on lithium in drinking water, preliminary human data suggest effects of nutritional lithium supplementation on mood,[9] and animal data suggest effects on the central nervous system.[8] No brain imaging studies have been published on the effects of micro doses of lithium on human brain functioning. Nevertheless, there is level I evidence for a positive association between lithium treatment in therapeutic doses and brain grey matter volume in multiple brain regions of relevance for bipolar disorder, including the hippocampus, amygdala, anterior cingulate, subgenual cingulate and inferior frontal gyrus.[30,31] The association between lithium treatment and grey matter volume occurs regardless of mood state, diagnostic subtype, and the presence or absence of concomitant medications, and the effects have been shown even in healthy individuals.[30]

Nevertheless, we find that the results of the present study argue strongly against the hypothesis that micro doses of lithium may decrease the risk of developing mania or bipolar disorder. The same pattern was repeated within age categories (0-40, 41-60 and 61-100 years of age) and in sensitivity analyses when diagnosis of mania/bipolar disorder at the first contact ever was the outcome measure, showing that the hazard ratio of mania/bipolar disorder did not decrease with higher long-term lithium exposure.

It is recommended that the association between lithium levels in drinking water and the incidence of bipolar disorder is investigated in areas with significantly higher lithium levels than in Denmark.[27]

5 | CONCLUSION

Higher long-term lithium exposure from drinking water was not associated with a lower incidence of mania/bipolar disorder, showing that long-term exposure of micro doses of lithium does not modulate the risk of developing mania or bipolar disorder.

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DISCLOSURES

It is verified and confirmed that all conflict of interest disclosure information for all authors is accurate, complete and up to date. Potential conflicts of interest involving the work: none. Financial activities outside the work: Lars Vedel Kessing has within the preceding 3 years been a consultant for Lundbeck, AstraZenica and Sunovion. Other authors report no financial activities.

AUTHOR CONTRIBUTIONS

LVK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. TAG conducted and is responsible for the data analysis in cooperation with LVK and PKA.

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