Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Lithium in drinking water associated with adverse mental health effects

Keywords:
Lithium
Drinking water
Tap water
Schizophrenia
Bipolar disorder

Shimodera and colleagues find an inverse association between lithium levels in tap water and psychotic experiences (Shimodera et al., 2018). Together with other recent studies using individual-level data that found inverse associations with dementia and depression (Ando et al., 2017; Kessing et al., 2017a), suggestions for considering the promotion of intake of lithium-rich water as a public health strategy are appealing and indeed have been made, under the provision that any adverse effects can be excluded (e.g. McGrath and Berk, 2017; Shimodera et al., 2018). Since the biological mechanisms underlying such protective mental health effects of lithium in drinking water remain unclear, studies on the full range of mental and physical health outcomes associated with lithium exposure are warranted to avoid unintended negative consequences.

We have studied the association between lithium in drinking water and schizophrenia, schizophrenia spectrum disorder (SSD), and bipolar disorder in a nationwide population-based prospective cohort study in the Danish registers under the hypothesis that lithium-rich drinking water has a protective effect on these outcomes. However, we find a positive association with schizophrenia and SSD, and no association with bipolar disorder. While there is still a need for further studies, our results necessitate caution: lithium in drinking water may be associated with adverse as well as advantageous mental health outcomes.

We included all persons born in Denmark between January 1, 1985 and December 31, 2002, who were alive on their 10th birthday and whose parents were both born in Denmark. Drinking water samples from 139 public waterworks were analyzed for lithium using ICP-MS in 2013 (Voutchkova et al., 2015). Kessing, Knudsen and colleagues used these data to spatially interpolate lithium concentrations for all of Denmark to study the associations with suicide, bipolar disorder, and dementia (Kessing et al., 2017a, 2017b; Knudsen et al., 2017). In contrast, we only included persons whose household was within the supply area of a waterworks (Schullehner and Hansen, 2014), where a lithium sample was taken (Supplementary Fig. 1), and excluded private well users, resulting in a smaller study population but more accurate exposure estimation. Exposure was estimated as the lithium concentration at the location a person was living at on their 10th birthday.

From the Danish Psychiatric Central Register, we identified incident cases of schizophrenia (ICD10: F20 and eq. ICD8), SSD (ICD10: F20-F29 and eq. ICD8), and bipolar disorder (ICD10: F30-F31 and eq. ICD8). Accurate linkage at individual-level is possible in the Danish registers based on the unique personal identification number. The geographical distribution of lithium in Denmark follows an east-west gradient (Supplementary Fig. 1). Therefore, we included both urbanization, population density and family socioeconomic status (all measured at each cohort member's 10th birthday), which vary geographically and are associated with schizophrenia risk (Agerbo et al., 2015; Pedersen and Mortensen, 2001; Vassos et al., 2016). Study population characteristics and a description of the covariates are shown in Supplementary Table 1.

Individuals were followed from their 10th birthday until the date of disorder of interest, death, emigration from Denmark, or December 31, 2013, whichever came first. Incidence rate ratios (IRRs) for each disorder were estimated by log linear Poisson regression. All IRRs were adjusted for calendar period, age, and sex, and the interaction between age and sex. Age and calendar period were treated as time-dependent variables. *P* values and 95% confidence intervals (CIs) were based on likelihood ratio tests. The adjusted-score test suggested that the regression models were not subject to over-dispersion. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, N.C.). The study was approved by the Danish Data Protection Agency.

During follow-up, 3459 of 374,737 cohort members had their first contact with SSD, 1714 with schizophrenia, and 700 with bipolar disorder. Modelling exposure as quantiles, persons who lived in areas with the highest lithium levels had a 1.88 (95% CI: 1.69–2.10) fold increased risk of SSD, compared to those in areas with the lowest level. There was a tendency of a dose-response relationship. A similar pattern was seen for schizophrenia, while there was no association with bipolar disorder (Table 1).

We also considered exposure as a continuous variable scored from 0 to 1. This summary estimate assumes a dose-response association and utilizes information on all lithium levels. The summary estimate showed a 1.75 (95% CI: 1.59–1.92) fold increased risk of SSD for persons living in high level areas, compared to those living in low level areas (Table 1).

Adjustment for urbanization, population density, and parental socioeconomic status attenuated the association slightly. Adjusting for all these covariates, there was a modest positive association between lithium levels in drinking water and SSD (IRR = 1.21, 95% CI: 1.07–1.35). Adjusted associations between lithium and narrow schizophrenia were nearly identical to those for SSD (Supplementary Table 2). There was no association with bipolar disorder under these confounder adjustment scenarios (results not shown). Additionally, we estimated summary associations between lithium and SSD and schizophrenia stratified by degree of urbanization and found robust results, with the exception of provincial cities (Supplementary Table 3). The association of tap water lithium with these two outcomes was consistent across year of birth and sex (Supplementary Table 3). The effect of lithium in drinking water was invariant, when persons with bipolar affective disorder were censored from schizophrenia analyses. When censoring persons with schizophrenia from the bipolar analyses, the risk estimate was attenuated slightly below nil.

https://doi.org/10.1016/j.schres.2019.06.016
0920-9964/

Table 1
Incidence rate ratios of schizophrenia spectrum disorder, schizophrenia and bipolar disorder associated with concentrations of lithium in drinking water among 374,737 persons born in Denmark 1985–2002.

	Schizophrenia spectrum disorder			Schizophrenia			Bipolar disorder		
	No of cases	IR[a]	IRR (95% CI)[b]	No of cases	IR[a]	IRR (95% CI)[b]	No of cases	IR[a]	IRR (95% CI)[b]
Total	3459	9.36		1714	4.63		700	1.89	
Quantile of lithium in drinking water (μg/L)									
High (16.7–30.7)	900	11.87	1.88 (1.69–2.10)	438	5.76	1.65 (1.42–1.92)	132	1.73	1.03 (0.81–1.31)
Medium High (12.4–16.7)	792	11.00	1.75 (1.57–1.96)	391	5.42	1.56 (1.34–1.82)	144	1.99	1.20 (0.95–1.51)
Medium (10.3–12.4)	609	8.45	1.34 (1.20–1.51)	283	3.92	1.13 (0.96–1.33)	174	2.41	1.45 (1.16–1.82)
Medium Low (5.8–10.3)	652	9.34	1.48 (1.32–1.66)	321	4.60	1.31 (1.12–1.54)	115	1.64	0.98 (0.76–1.25)
Low (0.6–5.8)	506	6.35	1 (ref)	281	3.52	1 (ref)	135	1.69	1 (ref)
Summary estimate[c]									
High versus low			1.75 (1.59–1.92) $p < 0.0001$[d]			1.60 (1.41–1.83) $p < 0.0001$[d]			1.11 (0.90–1.36) $p = 0.34$[d]

[a] IR: incidence rate, number of new cases per 10,000 person-years at risk.
[b] IRR: incidence rate ratio, adjusted for calendar year, age and sex.
[c] The summary estimate measures the IRR for a person exposed to the highest quantile of lithium in drinking water compared to a person exposed to the lowest quantile of lithium in drinking water, utilizing information on all levels of lithium.
[d] Likelihood ratio-based *p*-value.

To our knowledge, this is the largest cohort study on the association between lithium in drinking water and schizophrenia. We find a positive association, which contrasts with some previous studies that found protective associations of drinking water lithium with mental health. Limitations of our study include potential residual confounding, lack of data on actual water intake, and co-exposure to other drinking water quality parameters.

Shimodera and colleagues studied tap water lithium's association with prevalence of psychotic experiences measured using Diagnostic Interviews (Shimodera et al., 2018), while the outcome assessment in our prospective nationwide cohort study was based on clinical diagnoses. In addition, the different choice of lithium analysis method and substantially lower exposure range in Shimodera et al. (2018) (between 0.01 and 2.1 μg/L) make direct comparison between studies difficult. Collectively, studies of exposure to lithium in drinking water have not yielded a clear picture of its potentially beneficial mental health effects. Further studies are needed to investigate whether our findings can be replicated. A better understanding of underlying mechanisms is needed, as well as future studies disentangling the effects of other naturally occurring drinking water components.

Contributions

JS and CBP designed the study. JS conducted the exposure assessment with data collected by JS, BH and SMK. CBP undertook the statistical analysis. DP, CBP and JS wrote the first draft. SD reviewed the first draft. All authors contributed to interpretation of results and writing of the manuscript.

Funding

This study was supported by The Lundbeck Foundation (grant no R102-A9118 and R155-2014-1724); the Stanley Medical Research Institute; the Novo Nordisk Foundation (Big Data Centre for Environment and Health, grant number NNF17OC0027864; and grant no 22018); Aarhus University Research Foundation (AUFF-E-2015-FLS-8-61); National Institute of Health (R01, grant no ES026993); the European Commission (Horizon 2020, grant no 667302); and the Intramural Research Program of the National Institute of Mental Health. The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or the U.S. government.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.06.016.

References

Agerbo, E., Sullivan, P.F., Vilhjálmsson, B.J., Pedersen, C.B., Mors, O., Børglum, A.D., Hougaard, D.M., Hollegaard, M.V., Meier, S., Mattheisen, M., Ripke, S., Wray, N.R., Mortensen, P.B., 2015. Polygenic risk score, parental socioeconomic status, family history of psychiatric disorders, and the risk for schizophrenia: a Danish population-based study and meta-analysis. JAMA psychiatry 72, 635–641. https://doi.org/10.1001/jamapsychiatry.2015.0346.

Ando, S., Koike, S., Shimodera, S., Fujito, R., Sawada, K., Terao, T., Furukawa, T.A., Sasaki, T., Inoue, S., Asukai, N., Okazaki, Y., Nishida, A., 2017. Lithium levels in tap water and the mental health problems of adolescents: an individual-level cross-sectional survey. J. Clin. Psychiatry 78, e252–e256. https://doi.org/10.4088/JCP.15m10220.

Kessing, L.V., Gerds, T.A., Knudsen, N.N., Jørgensen, L.F., Kristiansen, S.M., Voutchkova, D., Ernstsen, V., Schullehner, J., Hansen, B., Andersen, P.K., Ersbøll, A.K., 2017a. Association of lithium in drinking water with the incidence of dementia. JAMA psychiatry 74, 1005–1010. https://doi.org/10.1001/jamapsychiatry.2017.2362.

Kessing, L.V., Gerds, T.A., Knudsen, N.N., Jørgensen, L.F., Kristiansen, S.M., Voutchkova, D., Ernstsen, V., Schullehner, J., Hansen, B., Andersen, P.K., Ersbøll, A.K., 2017b. Lithium in drinking water and the incidence of bipolar disorder: a nation-wide population-based study. Bipolar Disord. 19, 563–567. https://doi.org/10.1111/bdi.12524.

Knudsen, N.N., Schullehner, J., Hansen, B., Jørgensen, L.F., Kristiansen, S.M., Voutchkova, D.D., Gerds, T.A., Andersen, P.K., Bihrmann, K., Grønbæk, M., Kessing, L.V., Ersbøll, A.K., 2017. Lithium in drinking water and incidence of suicide: a Nationwide individual-level cohort study with 22 years of follow-up. Int. J. Environ. Res. Public Health 14, 563–567. https://doi.org/10.3390/ijerph14060627.

McGrath, J.J., Berk, M., 2017. Could lithium in drinking water reduce the incidence of dementia? JAMA psychiatry 74, 983–984. https://doi.org/10.1001/jamapsychiatry.2017.2336.

Pedersen, C.B., Mortensen, P.B., 2001. Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. Arch. Gen. Psychiatry 58, 1039–1046.

Schullehner, J., Hansen, B., 2014. Nitrate exposure from drinking water in Denmark over the last 35 years. Environ. Res. Lett. 9. https://doi.org/10.1007/9781107338623.

Shimodera, S., Koike, S., Ando, S., Yamasaki, S., Fujito, R., Endo, K., Iijima, Y., Yamamoto, Y., Morita, M., Sawada, K., Ohara, N., Okazaki, Y., Nishida, A., 2018. Lithium levels in tap water and psychotic experiences in a general population of adolescents. Schizophr. Res. 201, 294–298. https://doi.org/10.1016/j.schres.2018.05.019.

Vassos, E., Agerbo, E., Mors, O., Pedersen, C.B., 2016. Urban-rural differences in incidence rates of psychiatric disorders in Denmark. Br. J. Psychiatry 208, 435–440. https://doi.org/10.1192/bjp.bp.114.161091.

Voutchkova, D., Schullehner, J., Knudsen, N., Jørgensen, L., Ersbøll, A., Kristiansen, S., Hansen, B., 2015. Exposure to selected Geogenic Trace Elements (I, Li, and Sr) from drinking water in Denmark. Geosciences 5, 45–66. https://doi.org/10.3390/geosciences5010045.

Jörg Schullehner
Geological Survey of Denmark and Greenland (GEUS), Aarhus, Denmark
Centre for Integrated Register-based Research at Aarhus University (CIRRAU), Aarhus, Denmark
National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark

Please cite this article as: J. Schullehner, D. Paksarian, B. Hansen, et al., , Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.06.016

Corresponding author at: Geological Survey of Denmark and Greenland, C.F. Møllers Allé 8, 8000 Aarhus C, Denmark
E-mail address: jsc@geus.dk

Diana Paksarian
Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA

Birgitte Hansen
Geological Survey of Denmark and Greenland (GEUS), Aarhus, Denmark

Malene Thygesen
Centre for Integrated Register-based Research at Aarhus University (CIRRAU), Aarhus, Denmark
National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark
Big Data Centre for Environment and Health, Aarhus University, Aarhus, Denmark

Søren Munch Kristiansen
Department of Geoscience, Aarhus University, Aarhus, Denmark

Søren Dalsgaard
National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark
The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark
Department for Child and Adolescent Psychiatry, Hospital of Telemark, Kragerø, Norway

Torben Sigsgaard
Big Data Centre for Environment and Health, Aarhus University, Aarhus, Denmark
Department of Public Health, Aarhus University, Aarhus, Denmark

Carsten Bøcker Pedersen
Centre for Integrated Register-based Research at Aarhus University (CIRRAU), Aarhus, Denmark
National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark
Big Data Centre for Environment and Health, Aarhus University, Aarhus, Denmark
The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark

20 September 2018
Available online xxxx

Please cite this article as: J. Schullehner, D. Paksarian, B. Hansen, et al., , Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.06.016