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Association Between Estimated Geocoded Residential Maternal Exposure to Lithium in Drinking Water and Risk for Autism Spectrum Disorder in Offspring in Denmark

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Editorial

Supplemental content

IMPORTANCE Lithium is a naturally occurring and trace element that has mood-stabilizing effects. Maternal therapeutic use of lithium has been associated with adverse birth outcomes. In animal models, lithium modulates Wnt/β-catenin signaling that is important for neurodevelopment. It is unknown whether exposure to lithium in drinking water affects brain health in early life.

OBJECTIVE To evaluate whether autism spectrum disorder (ASD) in offspring is associated with maternal exposure to lithium in drinking water during pregnancy.

DESIGN, SETTING AND PARTICIPANTS This nationwide population-based case-control study in Denmark identified 8842 children diagnosed with ASD born from 2000 through 2013 and 43 864 control participants matched by birth year and sex from the Danish Medical Birth Registry. These data were analyzed from March 2021 through November 2022.

EXPOSURES Geocoded maternal residential addresses during pregnancy were linked to lithium level (range, 0.6 to 30.7 μg/L) in drinking water estimated using kriging interpolation based on 151 waterworks measurements of lithium across all regions in Denmark.

MAIN OUTCOMES AND MEASURES ASD diagnoses were ascertained using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes recorded in the Danish Psychiatric Central Register. The study team estimated odds ratios (ORs) and 95% CIs for ASD according to estimated geocoded maternal exposure to natural source of lithium in drinking water as a continuous (per IQR) or a categorical (quartile) variable, adjusting for sociodemographic factors and ambient air pollutants levels. The study team also conducted stratified analyses by birth years, child's sex, and urbanicity.

RESULTS A total of 8842 participants with ASD (male, 7009 [79.3%]) and 43 864 control participants (male, 34 749 [79.2%]) were studied. Every IQR increase in estimated geocoded maternal exposure to natural source of lithium in drinking water was associated with higher odds for ASD in offspring (OR, 1.23; 95% CI, 1.17-1.29). Elevated odds among offspring for ASD were estimated starting from the second quartile (7.36 to 12.67 μg/L) of estimated maternal exposure to drinking water with lithium and the OR for the highest quartile (more than 16.78 μg/L) compared with the reference group (less than 7.39 μg/L) was 1.46 (95% CI, 1.35-1.59). The associations were unchanged when adjusting for air pollution exposures and no differences were apparent in stratified analyses.

CONCLUSIONS AND RELEVANCE Estimated maternal prenatal exposure to lithium from naturally occurring drinking water sources in Denmark was associated with an increased ASD risk in the offspring. This study suggests that naturally occurring lithium in drinking water may be a novel environmental risk factor for ASD development that requires further scrutiny.

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Lithium is a naturally occurring and trace element. Because of the mood-stabilizing effects of lithium,[1,2] the compound has long been used as a psychiatric medication to treat bipolar disorders[3,4] and depression.[5,6] Exactly how lithium affects the brain in these psychiatric disorders remains unknown but multiple intersecting mechanisms have been suggested, such as lithium's direct inhibition of glycogen synthase kinase-3β or effects on neurotrophic factors, neurotransmitters, oxidative metabolism, apoptosis, and second messenger systems.[7-14] As a naturally occurring element, lithium is present in drinking water at low concentrations because of the weathering of minerals in the subsurface. Although food items also contain lithium,[15] a major source of lithium intake in the general population is drinking water.[16,17] Recent epidemiological studies suggested that chronic and low-dose ingestion of lithium from drinking water might have preventive effects on the incidence of dementia[18-20] and suicide[21-23] but not schizophrenia spectrum disorders and bipolar disorders.[24]

It is still debated whether lithium can be safely administered to treat bipolar disorders during pregnancy,[25] as there is increasing evidence that lithium prescribed during pregnancy is associated with miscarriages[26] and cardiac malformations in newborns.[27] Since lithium can cross the placenta and the fetal blood-brain-barrier,[28,29] it is biologically plausible that the compound influences fetal brain development, especially as lithium has been shown to modulate Wnt/β-catenin signaling, an important molecular pathway involved in neurodevelopment and autism.[30] We conducted this study to estimate the association between prenatal exposure to lithium from drinking water and the risk for autism spectrum disorder (ASD) in Denmark using a population-based design.

Key Points

Question Is maternal prenatal exposure to lithium in drinking water associated with autism spectrum disorder (ASD) in offspring?

Findings In this Danish nationwide population-based case-control study, the study team found that maternal exposure to higher levels of residential lithium in drinking water during pregnancy was associated with a moderate increase in ASD risk in the offspring. The findings remained robust after adjusting for several maternal neighborhood socioeconomic factors and air pollution exposures.

Meaning This study suggests that naturally occurring lithium in drinking water may be a novel environmental risk factor for ASD development that requires further scrutiny.

Methods

This study was approved by the Danish Data Protection Agency and the institutional review board at University of California, Los Angeles. Informed consent was not required according to Danish law governing registry-based research studies with no participant contact. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed.

Study Population

We conducted a population-based nested case-control study of ASD in Denmark[31] with the source population defined as singleton births in Denmark born between 2000 and 2013 with a medical birth record available from the Danish Medical Birth Register.[32] ASD cases were identified using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (*codes F84.0, F84.1, F84.5, F84.8, or F84.9) up to 2016 extracted from the Danish National Patient Register that contains information on admissions and outpatient/emergency department consultations from all general hospitals in Denmark[33] and the Danish Psychiatric Central Register[34] that holds records of admissions or outpatient visits to psychiatric hospitals in Denmark.[35] Control participants were selected among singleton children born in Denmark during the same study period without having received a diagnosis for ASD and they were individually matched to cases on birth year and child's sex at a ratio of 1:5. We also required that the children were born between 21 and 46 weeks of gestation with a birth weight of more than 500 g and less than 6800 g and that maternal addresses were recorded in the Danish Civil Registration System to estimate prenatal residential exposures to lithium from drinking water. A total of 8842 participants with ASD and 43 864 control participants were included in the statistical analyses (eFigure in the Supplement).

Lithium Exposure Assessment

We geocoded all maternal residential addresses (including dates of having moved) recorded in the Danish Civil Registration System during the interval of 9 months before until 9 months after the pregnancy.[31] Each address, identified by municipality code, street code, and house number, was linked to the Danish Address Register to obtain geographical coordinates with a high level of precision (within 5 m).[31] We successfully geocoded 99.6% of all addresses identified for all participants in this study.[31]

Groundwater is the source of all drinking water in Denmark, typically only with limited treatment and always without chlorination.[36] We sampled the 144 largest public waterworks throughout Denmark in 2013 and analyzed for lithium levels using inductively couples mass spectrometry with a detection limit of 0.5 μg/L.[17,37] Measurements from 7 additional waterworks recorded from 2009 to 2010 and analyzed by atomic absorption spectroscopy were also included to develop a kriging model. The mean lithium level was estimated to be 11.6 (SD, 6.8) μg/L, ranging from the lowest of 0.6 μg/L in Western Denmark to the highest of 30.7 μg/L in Eastern Denmark.[21] Altogether, these 151 waterworks stand for the water supply of approximately half the Danish population.[37] For 12 waterworks, we had data on lithium levels in the raw groundwater and the finished treated drinking water, indicating treatment does not alter lithium concentrations.[37] A comparison with lithium levels in the same waterworks from 2016 to 2017 showed that concentrations were highly stable over time (R^2 = 0.94 for repeated measurements), which is expected as the source of lithium is geogenic. From our waterworks measurements, we have also found that lithium measures are not correlated with zinc (R^2 = 0.05) or nickel (R^2 = 0.04) in our samples.

We used kriging to estimate the lithium levels for the entire country of Denmark, which has been described previously.[18,21,38] The kriging map was used to compute mean lithium concentrations in each of the 275 Danish municipalities before the communal reform in 2007. For this study, geocoded maternal residential addresses for participants with ASD and control participants were linked to the kriging model estimates to compute participant-specific levels of average lithium in drinking water during pregnancy. Since lithium level estimates can be assumed to be stable over time within a municipality/grid cell, pregnant women's residential drinking water levels are expected to be constant, unless they moved during pregnancy. To account for moving, we computed time-averaged lithium estimates for participants with multiple addresses (geocoded locations) during pregnancy.

Statistical Analysis

We estimated the odds ratios (ORs) and 95% CIs for offspring with ASD according to maternal residential lithium exposure in drinking water during pregnancy in unconditional logistic regression models adjusting for the matching variables (child's sex and the exact birth year).[39] Lithium level (in μg/L) was first analyzed continuously (per IQR increase) and we also generated estimates for exposure quartiles based on the distribution among control participants. We also used a restricted cubic spline model with 4 evenly distributed knots (at the 20th, 40th, 60th, and 80th percentiles) to investigate potential nonlinearity and thresholds for estimated effects. We adjusted for the following covariates in all analyses: maternal age (younger than 19, 19 to 25, 26 to 30, 31 to 35, older than 35 years), maternal smoking during pregnancy (yes or no), location of residence (Copenhagen, its suburbs, and large cities [Aarhus, Odense, Aalborg], provincial cities and rural towns/communities), neighborhood socioeconomic status measures, including the community employment status (ratio of unemployed to employed families based on the adult with the highest reported income in the year of birth), and a housing index (the percentage of council rented housing in the year of birth). In addition, we also adjusted for ambient air pollution levels for NO_2 and $PM_{2.5}$ during pregnancy, measures we previously generated for all study participants using the DEHM/UBM/AirGIS modeling system reflecting local pollution from street traffic in addition to contributions from urban and regional background pollution.[40,41] Complete-case analyses were conducted because of the low number of missing values for all covariates used for confounder adjustment in our models.

In addition, we performed stratified analyses by child's sex (male or female) to evaluate potential sex-differences.[31] Moreover, we stratified the data by birth year (2000 to 2003, 2004 to 2007, 2007 to 2013). Since most drinking water measurements were conducted in 2013, if our assumption of time-constant lithium levels in birth years do not hold, we would expect a stronger nondifferential measurement error affecting results from the earlier birth years. We also stratified the data by the place of maternal residence at childbirth (Copenhagen and large cities vs provincial and rural towns/communities) to assess rural/urban differences. We performed tests of heterogeneity based on 2-tailed *P* values with a significance level of .05 for the product term of the continuous exposure variable and each of the binary potential effect modifiers in regression models. We also performed analyses that distinguished between subtypes of ASD (autistic disorder, Asperger syndrome, or pervasive developmental disorder-not otherwise specified). Additionally, we performed 2 quantitative bias analyses employing the E-value method[42] and conducted a probabilistic bias adjustment[43] to evaluate the potential influence from uncontrolled confounding bias. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Table 1. Demographic and Perinatal Characteristics of Participants With Autism Spectrum Disorders (ASDs) and the Matched Population Control Participants, Denmark, 2000 to 2013

Characteristic	No. (%) Participants with ASD (n = 8842)	Control participants (n = 43 864)[a]
Child's sex		
Male	7009 (79.3)	34 749 (79.2)
Female	1833 (20.7)	9115 (20.8)
Birth year		
2000-2003	4728 (53.5)	23 407 (53.4)
2004-2007	2943 (33.3)	14 650 (33.4)
2008-2013	1171 (13.2)	5807 (13.2)
Mean (SD)		
Birth weight, g	3494.1 (655.2)	3551.8 (578.7)
Gestational age, d	275.8 (15.5)	277.0 (13.1)
Maternal age, y	29.9 (5.1)	30.0 (4.8)
Location at birth		
Copenhagen and large cities[b]	5004 (56.6)	21 587 (49.2)
Provincial cities/towns	3026 (34.2)	16 980 (38.7)
Rural communities/small towns[c]	812 (9.2)	5289 (12.1)
Missing	0	8 (.02)
Maternal smoking during pregnancy		
No	6562 (74.2)	34 945 (79.7)
Yes	2041 (23.1)	7903 (18.0)
Missing	239 (2.7)	1016 (2.3)

[a] Control participants were matched to cases by child's sex and birth year.

[b] Includes Copenhagen and its suburbs, as well as large cities (Aarhus, Odense, and Aalborg).

[c] Includes rural areas and towns with less than 10 000 inhabitants.

Results

In Denmark, ASD is about 4 times more common in male than female children (79% vs 21%) (**Table 1**). The participants with ASD had a lower mean birth weight compared with control participants. The study team estimated a 23% increase in the odds for ASD in offspring (adjusted odds ratio [aOR], 1.23; 95% CI,

Table 2. Autism Spectrum Disorder (ASD) According to Lithium (Li) Levels in Maternal Residential Drinking Water During Pregnancy, Denmark, 2000 to 2013

	No.		OR (95% CI)		
Prenatal Li exposure	Participants with ASD	Control participants	Adjusted[a]	Adjusted[b]	Adjusted[c]
Per IQR increase in Li (9.4 μg/L)	8842	43 864	1.33 (1.28-1.39)	1.24 (1.18-1.30)	1.23 (1.17-1.29)
Li quartile, μg/L					
Q1 (≤7.4)	1718	11 133	1 [Reference]	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	2185	10 931	1.30 (1.21-1.39)	1.23 (1.15-1.32)	1.26 (1.17-1.36)
Q3 (12.7-16.8)	2089	10 471	1.29 (1.21-1.39)	1.21 (1.12-1.31)	1.24 (1.14-1.34)
Q4 (>16.8)	2850	11 329	1.63 (1.53-1.74)	1.48 (1.38-1.60)	1.46 (1.35-1.59)

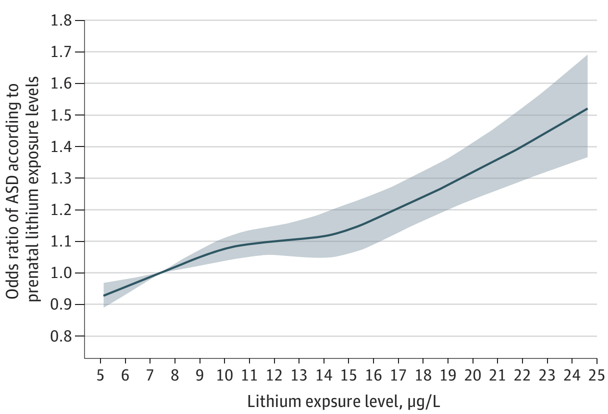
Abbreviations: OR, odds ratio; Q, quarter.

[a] Model adjusted for matching variables child's sex and birth year.

[b] Model adjusted for child's sex and birth year, maternal age, location of birth, and neighborhood socioeconomic measures, including the community employment ratio and housing index and maternal smoking during pregnancy.

[c] Model adjusted for child's sex and birth year, maternal age, location of birth, and neighborhood socioeconomic measures, including the community employment ratio and housing index, maternal smoking during pregnancy, and air pollution (NO_2, $PM_{2.5}$) during pregnancy.

Figure. Odds Ratio for Autism Spectrum Disorder (ASD) in Childhood According to Continuous Lithium Levels in Maternal Residential Drinking Water During Pregnancy



Odds ratio for ASD in childhood according to continuous lithium (Li, μg/L) levels in maternal residential drinking water during pregnancy estimated with a restricted cubic spline regression model. The reference level is set at the 25th percentile. The shading represents 95% CIs. Model adjusted for child's sex, birth year, maternal age, location of birth, neighborhood community employment ratio and housing index, and maternal smoking during pregnancy.

1.17-1.29) per IQR increase of the geospatial estimated lithium level in drinking water at maternal residence adjusting for maternal demographics, neighborhood socioeconomic factors, and ambient air pollutants (NO_2 and $PM_{2.5}$) (**Table 2**). Lithium exposures in the second and third quartiles (ranging from 7.4 to 16.8 μg/L) were associated with 24% to 26% higher odds for ASD diagnosis, and in the highest quartile (more than 16.8 μg/L) lithium was associated with 46% higher odds (aOR, 1.46; 95% CI, 1.35-1.59) compared with the lowest quartile as the reference (less than 7.4 μg/L). The spline model corroborated these results and suggested that ASD risk increased from the lower to higher exposure range with steeper slopes observed for the 5 to 10 μg/L and again the 15 to 25 μg/L ranges (**Figure**).

In stratified analyses, the estimated effect size was slightly larger in female children and for the birth years 2000 to 2003, but the interaction *P* values were greater than .10 (**Table 3**). The associations between estimated maternal exposure to lithium in drinking water and childhood ASD were slightly stronger for mothers and children living in urban areas (aOR, 1.28; 95% CI, 1.18-1.38 for ASD per IQR increase in lithium levels), including Copenhagen and other larger cities, than for those residing in provincial towns/rural area (aOR, 1.14; 95% CI, 1.07-1.22 for ASD per IQR increase in lithium levels) (eTable 1 in the Supplement).

Analyses by ASD subtypes showed similar associations for autistic disorder cases (aOR, 1.24; 95% CI, 1.15-1.34 per IQR increase of estimated maternal exposure to lithium levels and aOR, 1.49; 95% CI, 1.32-1.68 comparing the highest vs the lowest quartile of lithium levels), while for Asperger syndrome cases, the associations seemed to be driven predominantly by the highest exposure quartile. The effect sizes were smaller for pervasive developmental disorder-not otherwise specified, but the effect estimates were still elevated (aOR, 1.09; 95% CI, 1.00-1.18 per IQR increase of lithium levels and aOR, 1.23; 95% CI, 1.07-1.41 comparing the highest vs the lowest quartile of lithium levels) (**Table 4**).

The E-value was 2.02 for the observed association between ASD and the highest quartile of lithium exposure compared with the lowest (OR, 1.46; 95% CI, 1.35-1.59). Using probabilistic bias adjustments, the study team presents a range of effect estimates after accounting for a presumed unmeasured confounder that is positively associated with the exposure group and the outcome (eTable 2 in the Supplement). The adjusted effect estimate for lithium becomes null only when the unmeasured confounder is strongly associated with ASD (eg, OR, 5) and nearly 2 times more common in the exposed than the unexposed group.

Discussion

In this population-based study of ASD in Denmark, we found that estimated maternal exposure to higher levels of residential lithium in drinking water during pregnancy was associated with a moderate increase in ASD risk in the offspring while adjusting for several sociodemographic and neighborhood factors, including air pollution. Although we cannot rule out confounding due to un-

Table 3. Autism Spectrum Disorder (ASD) According to Lithium (Li) Levels in Maternal Residential Drinking Water During Pregnancy in Denmark, Stratified by Child's Sex and Birth Year

Prenatal Li, μg/L[a]	No. Participants with ASD	No. Control participants	OR (95% CI) Adjusted[b]	OR (95% CI) Adjusted[c]
Stratified by child's sex				
Male				
Per IQR increase (9.4 μg/L)	7009	34 749	1.21 (1.15-1.28)	1.20 (1.14-1.27)
Q1 (≤7.4)	1376	8794	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	1758	8634	1.25 (1.15-1.35)	1.28 (1.18-1.39)
Q3 (12.7-16.8)	1646	8334	1.19 (1.09-1.30)	1.22 (1.11-1.33)
Q4 (>16.8)	2229	8987	1.46 (1.34-1.59)	1.45 (1.32-1.58)
Female				
Per IQR increase (9.4 μg/L)	1833	9115	1.34 (1.21-1.49)	1.32 (1.18-1.47)
Q1 (≤7.4)	342	2339	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	427	2297	1.16 (0.99-1.36)	1.20 (1.01-1.41)
Q3 (12.7-16.8)	443	2137	1.31 (1.10-1.55)	1.32 (1.11-1.58)
Q4 (>16.8)	621	2342	1.58 (1.34-1.87)	1.53 (1.28-1.82)
Stratified by child's birth year				
Years 2000-2003				
Per IQR increase (9.4 μg/L)	4728	23 407	1.30 (1.22-1.39)	1.29 (1.20-1.38)
Q1 (≤7.4)	934	6017	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	1240	5930	1.31 (1.19-1.44)	1.33 (1.21-1.47)
Q3 (12.7-16.8)	1022	5540	1.16 (1.04-1.29)	1.18 (1.05-1.31)
Q4 (>16.8)	1532	5920	1.59 (1.43-1.76)	1.57 (1.41-1.75)
Years 2004-2007				
Per IQR increase (9.4 μg/L)	2943	14 650	1.19 (1.09-1.29)	1.16 (1.07-1.27)
Q1 (≤7.4)	568	3660	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	703	3643	1.17 (1.03-1.32)	1.18 (1.03-1.34)
Q3 (12.7-16.8)	728	3523	1.22 (1.07-1.39)	1.21 (1.06-1.39)
Q4 (>16.8)	944	3824	1.41 (1.24-1.60)	1.37 (1.20-1.57)
Years 2008-2013				
Per IQR increase (9.4 μg/L)	1171	5807	1.15 (1.00-1.31)	1.12 (0.97-1.29)
Q1 (≤7.4)	216	1456	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	242	1358	1.08 (0.87-1.33)	1.12 (0.90-1.39)
Q3 (12.7-16.8)	339	1408	1.41 (1.14-1.75)	1.45 (1.16-1.81)
Q4 (>16.8)	374	1585	1.30 (1.04-1.61)	1.25 (0.99-1.57)

Abbreviations: OR, odds ratio; Q, quarter.

[a] Lithium quartiles: Q1, less than or equal to 7.4; Q2, 7.4 to 12.7; Q3, 12.7 to 16.8; Q4, more than 16.8 μg/L.

[b] Model adjusted for child's sex (in birth year stratified analyses), the exact birth year (in both sex or birth-year categories stratified analyses), maternal age, location of birth, neighborhood community employment ratio and housing index, and maternal smoking during pregnancy.

[c] Additionally adjusted for ambient air pollution (NO_2, $PM_{2.5}$) during pregnancy based on model b.

measured factors in our analyses, a single uncontrolled confounding factor is unlikely to explain away our findings unless it is strongly associated with ASD and lithium exposure. Overall, our study suggests that naturally occurring lithium in drinking water may be a novel environmental risk factor for ASD development that requires further scrutiny.

Research that examines health effects associated with low-dose exposure to lithium from drinking water sources has received increased attention,[16,44,45] including recent studies of adults' mental health conducted in Denmark that were based on the same waterworks lithium measurements employed in this study.[18,21,38] Concerns about exposure to therapeutic

Table 4. Autism Spectrum Disorders (ASDs) According to Lithium (Li) Levels in Maternal Residential Drinking Water During Pregnancy in Denmark, by ASD Subtypes

Prenatal Li, μg/L[a]	No.		OR (95% CI)	
	Participants with ASD	Control participants	Adjusted[b]	Adjusted[c]
Autistic disorder				
Per IQR increase (9.4 μg/L)	3962	19 240	1.26 (1.18-1.36)	1.24 (1.15-1.34)
Q1 (≤7.4)	750	4833	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	969	4683	1.31 (1.18-1.46)	1.33 (1.19-1.48)
Q3 (12.7 16.8)	951	4549	1.34 (1.19-1.50)	1.34 (1.19-1.51)
Q4 (>16.8)	1292	5175	1.53 (1.36-1.71)	1.49 (1.32-1.68)
Asperger syndrome				
Per IQR increase (9.4 μg/L)	1580	7660	1.38 (1.23-1.55)	1.34 (1.19-1.51)
Q1 (≤7.4)	311	1968	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	358	1966	1.06 (0.90-1.26)	1.09 (0.91-1.30)
Q3 (12.7 16.8)	300	1843	0.90 (0.74-1.09)	0.90 (0.74-1.10)
Q4 (>16.8)	611	1883	1.73 (1.45-2.06)	1.63 (1.35-1.97)
Pervasive developmental disorder-not otherwise specified				
Per IQR increase (9.4 μg/L)	3075	14 937	1.08 (0.99-1.17)	1.09 (1.00-1.18)
Q1 (≤7.4)	650	3761	1 [Reference]	1 [Reference]
Q2 (7.4-12.7)	767	3754	1.11 (0.99-1.25)	1.16 (1.03-1.31)
Q3 (12.7 16.8)	774	3617	1.16 (1.02-1.32)	1.21 (1.06-1.39)
Q4 (>16.8)	884	3805	1.21 (1.07-1.38)	1.23 (1.07-1.41)

Abbreviation: OR, odd ratio; Q, quarter.

[a] Lithium quartiles: Q1, less than or equal to 7.4; Q2, 7.4 to 12.7; Q3, 12.7 to 16.8; Q4, more than 16.8 μg/L.

[b] Model adjusted for child's sex, birth year, maternal age, location of birth, neighborhood community employment ratio and housing index, and maternal smoking during pregnancy.

[c] Additionally adjusted for ambient air pollution (NO_2, $PM_{2.5}$) during pregnancy based on model b.

doses of lithium in pregnancy, including increased risks for miscarriage[26] and cardiac malformations in newborns, have been raised.[27] Only 1 prior study of 194 mother-child pairs recruited from the northern Argentinean Andes, a region with varying and high drinking water lithium concentrations (5 to 1600 μg/L), has focused on studying the effects of lithium from drinking water on fetal growth.[46] This study found increasing maternal blood and urinary lithium levels to be inversely associated with ultrasound-estimated fetal size (body, head, and femur) in the second trimester and also a decrease in birth length.[46] The study also reported that lithium levels detected in the drinking water correlated moderately well with the lithium biomarkers in whole blood and urine (r = 0.40-0.44; P < .001). Our study found the higher levels of prenatal lithium exposure in Denmark to be associated with childhood ASD risk, even though the exposure range and maximum of lithium detected in Danish drinking water supplies (0.6 to 30.7 μg/L) were much lower than in Argentina. These observations call for additional epidemiological studies to examine lithium-exposure related ASD risk, as well as adverse fetal development, including studies that address dose response and gestational timing of exposures.

Strengths and Limitations

Strengths of our study are that it is a large nationwide, population-based study of ASD and that the cases were identified from national registries.[31] This record-linkage study avoids any self-selection or recall bias. ASD diagnoses made in the Danish Psychiatric Central Registry are found to have high validity for epidemiologic research.[47] Complete maternal addresses were ascertained from the Danish Civil Registration System allowing residential environmental exposure assessments during pregnancy, a critical and relevant time window for ASD development.[31] Bottled water consumption is low in Denmark (ranks as the second lowest in Europe),[48] making it an ideal location to study potential health effect of lithium exposure from drinking tap water. The residential lithium level in drinking water is modeled based on lithium measurements of 151 waterworks from 2009 to 2010 and 2013, spatially covering all regions of Denmark.[18,21] We were able to adjust for several potential social-neighborhood confounding factors and also for ambient air pollution levels at maternal residential locations.[31]

Our study also has several limitations. First, this registry study lacks information on dietary and lifestyle factors, including habits of water consumption. This study did not measure the actual sources of water the mothers consumed and did not consider childhood exposure. However, there are no established lifestyle risk factors for autism, thus these are unlikely to confound the associations with environmental sources of lithium, of which study participants were generally unaware.[49] Potential confounders may include elements and natural compounds of drinking water sources that are geospatially correlated with lithium, especially if they are of the same geogenic origin as lithium. We have checked that lithium does not co-occur with zinc and nickel in our waterworks measurements. However, lithium may geographically correlate with iodine in groundwater (relatively higher in the eastern part of Denmark). Previously, a principle component analysis in a nationwide groundwater study has also revealed that elevated iodine levels were associated with elevated lithium.[50] Nevertheless, low-level intake of iodine may lead to thyroid deficiency and adversely affect neurodevelopment;[51,52] thus, residual confounding by iodine could potentially bias the effect estimates toward the null. Moreover, arsenic in some waterworks detected at above national and guideline values[53] could potentially induce adverse health effects, but these higher arsenic levels are mostly detected for rural communities and small towns in Denmark.[54] We also do not have data on maternal use of lithium medication, but the prevalence of such use is very low (less than 0.1%) and likely not associated with drinking water lithium content.[55] Based on our quantitative bias analysis, each of the potential confounding factors discussed are unlikely to be strongly enough associated with ASD and with lithium exposure such that this would nullify the observed associations. We focused on lithium from residential drinking water and not from other exposure sources, such as intake of water at workplaces or via diets. Thus, the cumulative effect of lithium exposure from multiple sources cannot be assessed in this study. Additionally, our results may not be transportable to populations exposed to higher lithium concentrations outside the range of our data.

Conclusions

In summary, we found that geospatial model-based and estimated maternal pregnancy exposure to lithium from naturally occurring drinking water sources in Denmark was associated with ASD risk in the offspring. This study suggests that naturally occurring lithium in drinking water may be a novel environmental risk factor for ASD development that requires further scrutiny.

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