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Association Between Groundwater Lithium and the Diagnosis of Bipolar Disorder and Dementia in the United States

Lithium, a naturally occurring trace element in groundwater, is a cornerstone therapy for bipolar disorder and may have a role in the treatment of dementia.[1] Kessing et al[2] found an inverse association between lithium in drinking water and dementia in Denmark. In the United States, lithium exposure has also been associated with lower rates of mental health disorders.[3] However, mental health diagnosis rates vary substantially with local health care resources and demographics,[4] potentially confounding the relationship with groundwater lithium concentrations. We examined the association between groundwater lithium and diagnoses of bipolar disorder and dementia in the United States, adjusting for local health care resources and demographics.

Methods | *Data Sources, Study Population, and Outcomes*. Groundwater lithium concentrations were collected by the US Geological Survey[5] from more than 3000 drinking water wells from 1992 to 2003. Lithium concentrations vary widely in the United States because of diverse climates and geological compositions of aquifers.[5] Diagnoses were identified from the inpatient hospital, long-term care, and other therapy claims files in the following sources: Truven Health MarketScan Commercial Claims and Encounters (CCAE) database (2003-2010), a claims database for privately insured patients; Truven Health MarketScan Medicare Supplemental database (2003-2010), a claims database for Medicare recipients with employer-sponsored supplemental insurance; and Medicaid Analytic eXtract (MAX) (2011-2012). As confirmed with the University of Chicago institutional review board, the secondary analysis of deidentified data was exempt from informed consent. Primary outcomes were the prevalence of bipolar disorder and dementia. To prevent spurious causal inference from inadequate adjustment for confounders, we repeated our analysis for 3 "negative control" outcomes that have no known link to groundwater lithium (major depressive disorder, myocardial infarction, and prostate cancer).

County-level health care resources and demographics were collected from the Health Resources & Services Administration (HRSA) 2010 Area Health Resources Files (AHRF).[6] The ARHF county-level data were assembled from the American Medical Association, the American Hospital Association, and the American Community Survey by the HRSA. The ARHF is designed to measure geographic variation in "factors that may impact health status and health care in the United States."[6] From the ARHF, we extracted the number of hospital beds, primary care physicians per 100 000 persons, psychiatrists per 100 000 persons, and median household income for each county. County-level demographics included census population, median age, education, race, and ethnicity. Counties in the top and bottom deciles of census population were trimmed from the data set.

Table. Groundwater Lithium and County-Level Diagnosis Rates, Health Care Resources, Demographics, and Relative Risk of High Lithium Exposure[a]

Variable	Low Lithium (n = 3 822 894)[b]	High Lithium (n = 404 662)[c]	P Value	Relative Risk of High Lithium Exposure (95% CI)[d]		
				Model 1 Unadjusted[e]	Model 2 Health Care Resources Adjustment[f]	Model 3 Health Care Resources Plus Demographics Adjustment[g]
Mental Health Disorders						
Bipolar disorder[h]	208	93	<.001	0.46 (0.45-0.48)	0.66 (0.54-0.80)	0.95 (0.75-1.21)
Dementia[h]	48	34	<.001	0.66 (0.62-0.69)	0.97 (0.85-1.10)	1.02 (0.85-1.23)
Major depressive disorder[h]	843	708	<.001	0.86 (0.85-0.87)	0.95 (0.86-1.06)	1.12 (0.96-1.29)
Medical Diagnoses						
Myocardial infarction[h]	56	47	<.001	0.84 (0.80-0.88)	0.92 (0.81-1.04)	0.93 (0.76-1.14)
Prostate cancer[h]	53	41	<.001	0.74 (0.70-0.78)	0.86 (0.72-1.03)	1.10 (0.86-1.42)
County-Level Health Care Resources						
Mean hospital beds	232.8	108.4	.04	NA	NA	NA
Mean primary care physicians per 100 000 persons	61.2	41.9	.001	NA	NA	NA
Mean psychiatrists per 100 000 persons	5.1	1.8	.03	NA	NA	NA
≥1 Psychiatrist in county, %	58.5	28.1	.002	NA	NA	NA
Median household income, $	46 723	40 987	.001	NA	NA	NA
County-Level Characteristics						
Census population	77 601	29 202	.006	NA	NA	NA
Median age, y	40.7	35.4	<.001	NA	NA	NA
High school education, %	86.2	77.1	<.001	NA	NA	NA
Black race, %	7.3	2.7	.03	NA	NA	NA
Hispanic ethnicity, %	5.4	36.9	<.001	NA	NA	NA
Mean lithium exposure, µg/L	6.0	141.3	<.001	NA	NA	NA

Abbreviation: NA, not applicable.

[a] Comparison of unadjusted rates was performed with χ^2 test; the mean covariate comparisons were performed with t test.

[b] Lithium concentration 40 µg/L or less (in 142 counties).

[c] Lithium concentration exceeding 40 µg/L (in 32 counties).

[d] Calculated for mental health disorders and medical diagnoses only. Relative risk of bipolar disorder, dementia, major depressive disorder, myocardial infarction, and prostate cancer by exposure to high lithium (>40 µg/L) with and without adjustment for county-level health care resources and demographics.

[e] Model 1: fixed-effects Poisson regression model, ignoring county-level clustering and county covariates.

[f] Model 2: mixed-effects Poisson regression model with inverse probability of treatment weighting (IPTW) used to balance county-level health care resources (hospital beds per population, primary care physicians per population, psychiatrists per population, and household income) between the high-lithium and low-lithium groups. Balancing after IPTW was good, with standardized differences less than 10%, except for minor residual imbalance of the variables primary care physicians and psychiatrists per population (10.8% and 17.7%, respectively). These variables were added as covariates to control for the residual imbalance. The model was also adjusted for sex and payer.

[g] Model 3: model 2 plus county-level demographics (census population, education, black race, and Hispanic ethnicity) included as covariates.

[h] Rate per 10 000 persons.

Statistical Analysis. We fit a mixed-effects Poisson regression model with inverse probability of treatment weighting (IPTW), where treatment was defined as lithium exposure exceeding 40 µg/L (a natural break in the lithium distribution).[7,8] Weights were based on county-level health care resources, designed to give the low-lithium counties the same distribution of health care resources as the high-lithium counties. We also controlled for sex, payer, and county-level demographics. As a sensitivity analysis, we also examined the association of lithium as a continuous variable (restricted cubic spline with 5 knots), controlling for county-level demographics and health care resources.

Results | Claims data for 4 227 556 adults living in 174 counties were analyzed, including 3 046 331 with private insurance, 261 461 with

Medicare Supplemental, and 919 764 with Medicaid. Among them, 404 662 patients (9.6%) lived in 1 of 32 counties with high lithium (>40 µg/L). The mean and median lithium concentrations were 27.4 µg/L and 11.1 µg/L, respectively (IQR, 3.7-23.6 µg/L).

Unadjusted prevalence rates for all outcomes were significantly lower in high-lithium counties. However, high-lithium counties had fewer physicians and health care resources and had smaller, younger, less educated, and more Hispanic populations (**Table**).

After adjustment for county-level demographics and health care resources, high lithium did not confer any significant benefit for bipolar disorder, dementia, or the negative controls major depressive disorder, myocardial infarction, or prostate cancer. The **Figure** shows the lack of any association across the entire lithium distribution.

Figure. Relative Risk of Bipolar Disorder and Dementia by County Lithium Concentration, Modeled as a Restricted Cubic Spline and Adjusted for County Covariates
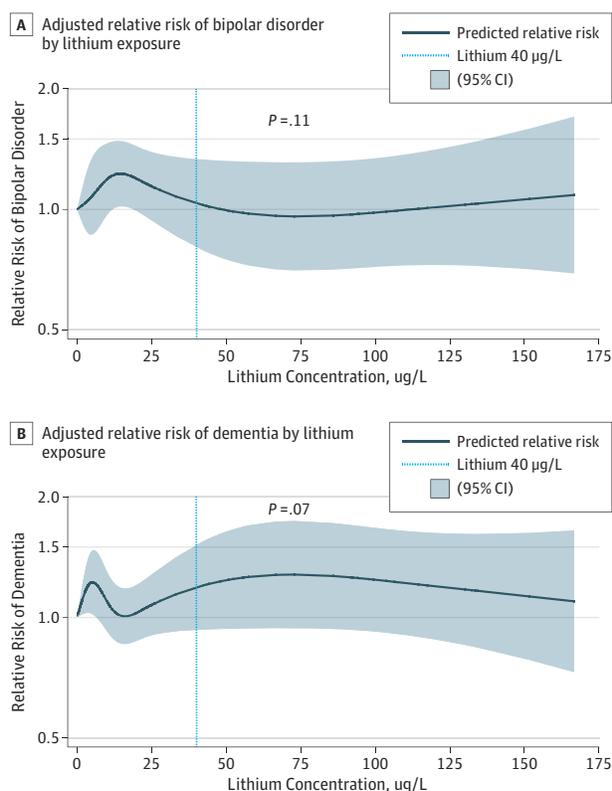
A, After adjustment for local health resources and demographics, the relative risk is not significantly different from 1 at almost all concentrations of lithium, and the joint test of the lithium spline terms is nonsignificant. B, Similarly, there is no significant association between lithium exposure and the relative risk of dementia after adjustment.

Discussion | Despite the substantial variation in groundwater lithium exposure in the United States, we found no significant association between groundwater lithium exposure and risk of bipolar disorder or dementia after adjustment for county-level demographics and health care resource. This indicates the purported association of high-lithium concentrations in drinking water with mental health disorders is driven by unaccounted variation in demographics, health care resources, and diagnosis practices.

Therapeutic lithium doses are orders of magnitude larger than groundwater lithium concentrations, making a true causal relationship between groundwater lithium and mental health biologically dubious. In our study, the high-lithium group was exposed to a mean of 141.3 µg/L in their water supply. This means that a patient would need to drink more than 1000 L of water a day to ingest the lowest reported effective therapeutic lithium dose of 150 mg.[1]

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COMMENT & RESPONSE

Untangling the Factors Contributing to Functional Outcome in Schizophrenia

To the Editor Galderisi et al[1] present the results of a network analysis of various psychopathological variables and functional outcome in a large sample of community-dwelling patients from Italy. Functional capacity was found to be the most central, and thus the most important, variable and to provide the connection between cognition and everyday outcomes. We appreciate this work but argue that important limitations require consideration.

First, the impact of social cognitive abilities in the presented network is likely underestimated owing to the used measures. A recent psychometric analysis, including a survey of experts,[2,3] failed to identify the Facial Emotion Identification Test as a best existing measure of facial emotion recognition and advises caution when using the Awareness of Social Inference Test owing to the limited ability of this measure to predict real-world outcomes. In contrast, other measures have shown consistent patterns of associations with functional outcome above and beyond neurocognition and symptom severity. Use of these measures may have resulted in a very different network.

Second, limited measurement also negatively affects the understanding of functional outcome. Functional capacity measured by the UPSA-B (ie, Brief University of California, San Diego Performance-Based Skills Assessment) explains predominantly work-related functional outcome. Being able to pay bills, use money, and use the phone to schedule an appointment with the physician are important skills, but these situations omit the social aspect of everyday interactions that are far more common. Thus, the absence of a measure of social skills capacity is a significant oversight. It is highly likely that social cognition is connected to real-world outcome through social skills rather than work-related functional capacity. While we do not debate the importance of functional capacity, we do argue that use of well-validated social cognitive measures and assessments of social skill would likely yield a more accurate understanding of the complex interplay between cognition and functional outcomes. Further, as social skill training has a larger direct impact on functional outcomes than functional skill training,[4,5] treatment efforts may be hindered by overemphasizing the improvement of detailed skills.

Finally, we note some concern related to the sample of participants. All participants were recruited from university hospitals in Italy, and no information is provided regarding sociocultural or ethnic background. Thus, the generalizability of these results to more diverse patients who may experience less supportive or more stressful day-to-day environments (eg, minority participants) is questionable.

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In Reply Hajduk and Pinkham argue that the understanding of the interplay between cognition and real-life functioning would have been more accurate in our study[1] if different social cognition tests and a measure of social capacity had been included. They base their comments on 2 studies by Pinkham et al.[2,3] In addition, they express some concern on participant recruitment and emphasis on targeting functional skills. We report hereafter our responses to their comments.

When we designed the study, the quoted articles were not available. The Awareness of Social Inference Test (TASIT) and Facial Emotion Identification Test (FEIT) were selected on the basis of available studies on validity and association with real-life functioning.[4] No consensus article or systematic review was available for social capacity measures, while this was the case for functional capacity measures included in our study.

In addition, the first Pinkham et al study[2] has several limitations including a low response rate to the survey and limited evidence supporting the choice of the measures. Direct comparison between FEIT psychometric properties and se-

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