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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Kaufmann, Westlye.

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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 al2 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 Survey4 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 AHRF 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 de-
We fit a mixed-effects Poisson regression model within inverse probability of treatment weighting (IPTW), where treatment was defined as lithium exposure exceeding 40 μg/L (a natural break in the lithium distribution). 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.

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.

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

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

Abbreviation: NA, not applicable.

* Comparison of unadjusted rates was performed with χ² test; the mean covariate comparisons were performed with t test.

<sup>a</sup> Lithium concentration 40 μg/L or less (in 142 counties).

<sup>b</sup> Lithium concentration exceeding 40 μg/L (in 32 counties).

<sup>c</sup> 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.

<sup>d</sup> Model 1: fixed-effects Poisson regression model, ignoring county-level clustering and county covariates.

<sup>e</sup> 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.

<sup>f</sup> Model 3: model 2 plus county-level demographics (census population, education, black race, and Hispanic ethnicity) included as covariates.

<sup>h</sup> 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). 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.
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 highest 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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Study concept and design: Parker, Gao, Gibbons.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Parker, Gao, Gibbons.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: All authors.

Administrative, technical, or material support: Gorges, Zhang.

Study supervision: Gibbons.

Conflict of Interest Disclosures: None reported.

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Additional Information: This article was the product of a class project of the Statistical Applications course at The University of Chicago taught by Dr Gibbons from September 25 to December 9, 2017. The Truven Health MarketScan Commercial Claims and Encounters (CCAE) database contains individuals who are employees, their covered spouses and dependents, Consolidated Omnibus Budget Reconciliation Act of 1985 (COBRA) continuers, and non-Medicare retirees. There are approximately 99 million unique enrollee records in the CCAE database from 2003 to 2010. The Truven Health MarketScan Medicare Supplemental database contains individuals who are Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. There are approximately 75 million unique enrollee records in this database from 2003 to 2010. The Medicaid Analytic Extract (MAX) data are created by the Centers for Medicare & Medicaid Services (CMS) from data submitted through each state’s Medicaid Statistical Information System and then processed to provide uniform coding across states. Beneficiary enrollment status was determined using the person’s summary files and then used to exclude beneficiaries enrolled in comprehensive managed care plans and/or Medicare to ensure that full claims records were present. Diagnoses were identified from the inpatient hospital, long-term care, and other therapy claims files, and county diagnosis and population counts were pooled over the 2-year period (2011-2012). Because of CMS restrictions on minimum cell sizes, county-level sex cells with diagnosis or population counts less than 11 were omitted.

Additional Contribution: Prof Don Rubin, PhD (Department of Statistics, Harvard University), provided assistance with our statistical approach. No compensation was received for his contribution to the study.


COMMENT & RESPONSE

Untangling the Factors Contributing to Functional Outcome in Schizophrenia

To the Editor Galderisi et al1 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 outcomes 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 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 had 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-