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Lithium exposure in areas of the Western United States: Water and urinary levels in the Strong Heart Family Study

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BACKGROUND: Lithium production and processing is rapidly expanding, potentially increasing its environmental release. However, population-level exposure is poorly characterized in most countries.
OBJECTIVE: Our objective was to evaluate drinking water and urinary lithium levels in the Strong Heart Family Study, a longitudinal study conducted with tribal partners in Arizona, Oklahoma, and North Dakota and South Dakota.
METHODS: Lithium was measured in household tap water samples collected in 2022–2024 ($n = 673$) and spot urine samples collected in 2006–2009 and 2022–2024 ($n = 613$ paired samples). We examined within-person changes in urinary lithium, correlations between water and urinary lithium, and used mixed-effects models to estimate geometric mean ratios (GMRs) of urinary lithium in relation to study phase, water lithium, water source, and participant characteristics.
RESULTS: Median (interquartile range) water lithium was 35.6 (9.0, 54.1) µg/L. Water lithium exceeded the United States Geological Survey health-based screening level (10 µg/L) in 100% of Arizona, 93% of North Dakota/South Dakota, and 35% of Oklahoma samples. Median urinary lithium was 30.8 (17.4, 53.3) µg/g creatinine in 2006–2009 and 31.2 (18.0, 56.0) in 2022-2024. The GMR comparing urinary lithium in 2022-2024 to 2006-2009 was 1.08 (1.02–1.14). Water lithium correlated with urinary lithium in 2006-2009 ($\rho = 0.61$) and 2022-2024 ($\rho = 0.59$). Each doubling of water lithium was associated with 22% higher urinary lithium before and 9% higher after adjustment for study site; all models adjusted for participant characteristics and water source. Water lithium explained 29% of variation in urinary lithium levels.
SIGNIFICANCE: Lithium in drinking water is a widespread and persistent source of human exposure across Tribal communities in the Western United States, with regional variation. Our findings also support the use of urinary lithium as a biomarker of environmental exposure.
IMPACT: Our study provides novel evidence of high levels of lithium in household drinking water (2022–2024) in Native American communities. We found that drinking water lithium in Arizona, North Dakota and South Dakota often exceeded the United States Geological Survey health-based screening level, urinary lithium levels remained stable over 15-years of follow-up, and household drinking water lithium explained a substantial proportion of variability in urinary lithium. Our findings improve lithium exposure estimations among Strong Heart Family Study communities and support the need for further environmental monitoring and risk evaluation, particularly as lithium extraction and processing accelerate to meet energy demands.

Keywords: Lithium; Drinking Water; Urine Biomarker; Exposure; American Indians; Strong Heart Study

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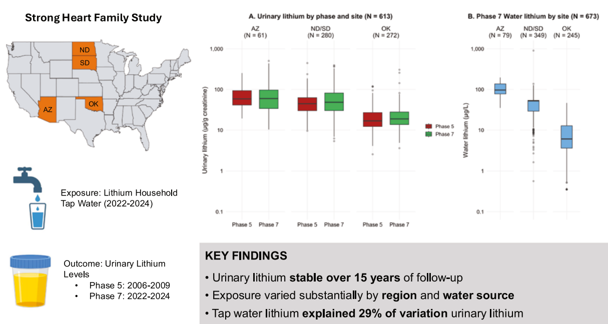
Graphical Abstract



INTRODUCTION

Lithium is a critical metal for the renewable energy transition [1]. Its demand has skyrocketed and is projected to increase over 600% by 2050 due to the efficiency, versatility, and scalability of lithium-ion batteries [2, 3]. Lithium resources are present in geological formations across the United States (US), including on and near Tribal lands [4]. As lithium extraction expands, concerns have emerged about environmental releases, exposure and potential health effects in nearby communities, including Indigenous communities in the US.

In 2022, the US Environmental Protection Agency (EPA) added lithium to the Final Fifth Contaminant Candidate List to evaluate whether a health-based drinking water standard should be developed [5]. Evidence on health effects remains mixed. Ecological studies have suggested potential neuropsychiatric benefits of lithium exposure [6–9]. However, epidemiologic studies of trace lithium have been largely inconclusive and epidemiologic studies of therapeutic lithium doses have documented adverse health effects including renal, thyroid, and parathyroid dysfunction [5, 10–16]. Lithium occurs naturally in surface water and groundwater through weathering of rock formations and interaction with lithium-rich brines [17]. Concentrations in surface water are typically low (1-10 µg/L), but in groundwater they can exceed 500 µg/L [17]. Although lithium is not currently regulated in public water systems, the US Geological Survey (USGS) established a non-enforceable health-based screening level of 10 µg/L [18]. Nationally, about 45% of public-supply wells and 37% of domestic supply wells exceed 10 µg/L [19]. Despite its widespread occurrence in drinking water [18, 19], the contribution of waterborne lithium to overall human exposure remains unknown.

To address this gap, we evaluated longitudinal changes in urinary lithium levels and examined the relationship between household drinking water and urinary lithium levels in individuals followed as part of a prospective cohort study among American Indian communities in Arizona (AZ), Oklahoma (OK), and North Dakota and South Dakota (ND/SD). In addition, given limited evidence on lithium biomarkers, we also evaluated whether urinary lithium reflects drinking water lithium concentrations, to investigate urinary lithium's utility as a biomarker of environmental exposure. We hypothesized that urinary lithium levels would be higher among participants in the AZ and ND/SD study sites, regions where lithium-bearing deposits are located, and higher lithium levels have been reported in drinking water. Given limited research on determinants of urinary lithium, we evaluated the association with water sources and participant characteristics (sociodemographic, anthropometric, and lifestyle factors). These findings provide baseline data to characterize exposure patterns over time and to inform future investigations of the potential health outcomes of chronic lithium exposure.

MATERIALS AND METHODS

Study population

The Strong Heart Study (SHS) and its kinship-based extension the Strong Heart Family Study (SHFS) are participatory-based prospective cohort studies of cardiovascular disease and its risk factors in American Indian adults [20]. The SHFS began with a pilot phase in 1998-1999 (Phase 3) by recruiting family members of the original SHS study participants [20]. During study visits, centrally-trained staff administered standardized questionnaires, performed a physical examination, and collected urine samples [20]. For this analysis, we measured urinary lithium in urine samples collected during Phase 5 (2006–2009) and Phase 7 (2022–2024). We additionally measured lithium in tap water samples that were collected from participant homes during Phase 7. The study protocol was approved by institutional review boards (IRBs), participating tribal communities, and the respective area Indian Health Service IRBs. All participants provided informed consent.

Urinary lithium measurement

Morning spot urine was collected and aliquoted in 1 mL vials, shipped on dry ice, and stored at -80 °C at the Medstar Health Research Institute in Hyattsville, MD (Phase 5) or at Columbia's Trace Metals Core Laboratory (Phase 7). Urine samples were prepared by mixing 0.1 mL of urine with 50 µL of an internal standard solution (500 µg/L Ga, Y, Rh, Ir) in 15 mL metal-free polypropylene tubes and diluting to 5 mL with 2% HNO_3 and 500 µg/L gold. Urinary lithium levels were measured using triple quadrupole inductively coupled plasma mass spectrometry (QQQ-ICP-MS; Agilent 8900) as part of a multi-element analytical panel that included Li, V, Mn, Co, Ni, Cu, Zn, As, Se, Sr, Mo, Cd, Sb, Cs, Ba, W, Tl, Pb, and U. Quality control was performed using certified urine reference materials from the Quebec Multi-Element External Quality Assessment Scheme (QM-U-Q2413, QM-U-Q2414, QM-U-Q2415) and Seronorm L1 (LOT: 1706877, Sero, Billing, Norway). Accuracy of lithium analysis based on certified urine reference materials is summarized in Supplemental Table 1. All urinary lithium levels were above the limit of detection (0.11 µg/L). Lithium urine levels were normalized to creatinine (µg Li/g creatinine) to account for hydration status.

Water lithium measurement

Water lithium concentrations were measured in samples collected from household taps of SHFS Phase 7 participants ($n = 673$). Participants received a sampling kit with two prelabeled 20-mL polypropylene vials, nitrile or polypropylene gloves, and written instructions. Following the protocol, participants wore gloves, rinsed each vial three times with tap water, filled the vials completely, closed them tightly, and placed them in a sealed plastic bag. Samples were returned via pre-paid envelop or dropped off at the local study sites, where samples were stored unrefrigerated until shipment to the Columbia University Lamont Doherty Earth Observatory where they were refrigerated until analysis. Water samples were acidified to 1% HNO_3 and left to equilibrate for several days prior to analysis, then diluted ten-fold in 1% HNO_3 containing 5 µg/L indium as an internal standard (200 µL sample with 1800 µL diluent). Water lithium was measured using magnetic sector ICP-MS (Element 2; Thermo Fisher) at Lamont Doherty Earth Observatory as part of a multi-element panel (Li, Be, B, Rb, Mo, Ag, Cd, Sn, Sb, Cs, Ba, La, Tl, Pb, Bi, U, Mg, Al, P, S, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Sr, Na, K, As, Se) [21]. For quality

Table 1. Median (Interquartile Range) Urinary Lithium Levels (μg/g creatinine) in Phase 5 (2006–2009) and Phase 7 (2022–2024) of the Strong Heart Family Study (SHFS) by Participants Characteristics.

			Urinary Lithium (μg/g creatinine)[a]	
Characteristic	**Variable**	***N* (%)[a]**	**Phase 5**	**Phase 7**
Overall		613 (100)	30.8 (17.4, 53.3)	31.2 (18.0, 56.0)
Sex	Female	419 (68.4)	31.5 (17.0, 55.0)	31.3 (18.4, 55.6)
	Male	194 (31.6)	30.2 (17.6, 51.7)	30.5 (17.0, 59.9)
Age, years	<55	254 (41.4)	31.2 (19.5, 50.4)	31.3 (17.6, 54.1)
	55-65	176 (28.7)	37.0 (17.7, 56.3)	32.0 (18.7, 64.8)
	>65	183 (29.9)	28.7 (15.6, 55.6)	30.0 (18.9, 51.4)
Study Site	*AZ*	61 (10.0)	59.3 (41.6, 93.4)	60.3 (34.0, 96.6)
	ND/SD	280 (45.7)	44.8 (30.0, 63.5)	48.7 (30.2, 81.3)
	OK	272 (44.4)	17.0 (12.3, 26.9)	19.0 (13.8, 27.8)
Education	≤12 Years	320 (52.2)	34.7 (18.9, 56.4)	31.8 (18.4, 55.8)
	>12 Years	293 (47.8)	28.1 (16.0, 47.0)	30.3 (17.9, 59.6)
Smoking Status	Never	270 (44)	26.2 (15.5, 47.6)	27.2 (15.7, 47.7)
	Former	180 (29.4)	35.8 (20.2, 60.7)	35.6 (20.3, 56.6)
	Current	163 (26.6)	34.2 (20.6, 54.9)	33.2 (20.6, 66.5)
BMI, kg/m^2	<25	75 (12.2)	44.4 (25.5, 63.3)	39.6 (21.4, 81.8)
	25–30	153 (25)	29.7 (16.0, 50.8)	31.3 (19.2, 53.2)
	>30	385 (62.8)	30.0 (16.9, 51.8)	30.4 (17.5, 54.1)
Water Source [b]	Community Water System	513 (83.7)	31.5 (17.6, 53.0)	31.3 (18.0, 59.6)
	Drilled or Dug Well	44 (7.2)	30.4 (15.6, 53.6)	30.5 (18.0, 53.5)
	Bottled Water	317 (51.7)	25.3 (15.0, 45.8)	25.5 (15.3, 42.7)
	Other [c]	17 (2.8)	32.3 (18.8, 52.1)	36.9 (20.6, 85.1)
Water Lithium, μg/L [d](N = 425)	Tertile 1 (< 10.25)	142	15.9 (11.5, 24.9)	17.7 (12.7, 26.5)
	Tertile 2 (10.25-52.92)	142	32.1 (21.7, 50.3)	31.1 (18.4, 48.2)
	Tertile 3 (≥52.92)	141	50.2 (35.4, 78.2)	60.1 (35.8, 95.2)

[a]Urinary lithium levels among SHFS participants with measurements from both phases. Participant characteristics include sex, age, study site, education, smoking status, body mass index (BMI), self-reported water source, and water lithium tertiles (from household tap water samples). [b] Self-reported water source is not mutually exclusive. Participants could select more than one water source. [c] The self-reported water source "other" combined participants who answered spring ($n = 3$), hauling water ($n = 2$), other ($n = 12$). [d] Participants included in the "Water Lithium" section are those with urine measurements from both phases, as well as a Phase 7 tap water measurement. *AZ* Arizona, *ND/SD* North Dakota and South Dakota, *OK* Oklahoma.

control, certified water reference materials SRM 1643f from the National Institute for Standards and Technology was analyzed alongside study water samples. Accuracy of lithium in certified water reference materials is reported in Supplemental Table 1. For 18 samples (2.7%) with lithium measured below the limit of detection (LOD, 0.5 μg/L), we imputed the lithium concentration as LOD/√2.

Additional variables

Information on sociodemographic (age, sex, education, study site), anthropometric (body mass index [BMI] as measured weight, kg / measured height, m^2), and lifestyle (smoking status) characteristics was collected via standardized protocol. Phase 7 participants completed a self-reported questionnaire indicating from where they primarily obtain their drinking water. Response options included public/community water system, drilled or dug well, spring, hauled water, cistern, bottled water, other, or unknown. The questionnaire was not mutually exclusive, meaning participants could select all relevant options. Water sources were modeled as binary indicators and were weighted equally in analysis. Because only a small number of participants reported spring ($n = 3$), hauled water ($n = 2$), and other water use ($n = 12$), these categories were combined into a single "other" category.

Exclusion criteria

A total of 672 and 1001 participants had urinary lithium data in Phase 5 and Phase 7, respectively (Supplemental Fig. 1). After excluding participants missing covariates (BMI, education, smoking status) or urinary creatinine data, 647 Phase 5 participants and 968 Phase 7 participants had urinary lithium data available. A total of 613 participants had urinary lithium measured for both Phase 5 and Phase 7; 449 Phase 5 and 538 Phase 7 participants had urinary lithium and corresponding Phase 7 water lithium measurements; and 425 participants had all three measurements (Phase 5 urine, Phase 7 urine, and Phase 7 water). To maximize the sample size, we retained as many participants as possible for each statistical analysis based on urine comparisons or water-to-urine comparisons.

Statistical analysis

We used the median (interquartile range [IQR]) to summarize creatinine-adjusted urinary lithium levels overall and by participant characteristics for participants with paired urine samples from Phase 5 and Phase 7 ($n = 613$). Participant characteristics included sex, age, BMI, study site, education, smoking status, self-reported water source, and by tertiles of water lithium (subset with water data, $n = 425$).

Water and urinary lithium were right-skewed and natural-log-transformed for analysis. We calculated Spearman correlations between Phase 7 drinking water lithium and urinary lithium measured at Phase 5 and Phase 7 to evaluate how well urinary lithium reflected drinking water intake. To assess within-person change, we computed phase-specific geometric means, geometric mean ratios (GMRs) comparing Phase 7 to Phase 5, and intraclass correlation coefficients (ICC), overall and by study site.

To evaluate associations between drinking water lithium and urinary lithium, we fit linear mixed-effects models with natural-log-transformed urinary lithium as the outcome and a random intercept for participant to account for repeated measures. Drinking water lithium was included in models after a log2-transformation. The exponentiated regression coefficients were interpreted as GMRs of urinary lithium per doubling of water lithium. To assess potential departures from linearity, we additionally modeled water lithium in tertiles, comparing tertiles 2 and 3 to the lowest tertile. We also evaluated GMRs of urinary lithium levels comparing participants who reported drinking water from each specific source, versus those who did not report that source (public/community water system, drilled/dug well, bottled water, other). All models were progressively adjusted as: (1) unadjusted (Model 1); (2) adjusted for participant characteristics (sex, age, BMI, education, smoking status) (Model 2); and (3) additionally adjusted for study site (Model 3).

To estimate the proportion of variance in urinary lithium that could be explained by study site and other participant characteristics, we fit mixed-effects models with natural-log-transformed urinary lithium as the dependent variable and a random intercept for participant to account for repeated measures. The models were progressively adjusted as: (1) unadjusted (Model 1); (2) adjusted for bottled water use and participant characteristics except study site (Model 2); (3) further adjusted for drinking water lithium (Model 3); and (4) further adjusted for study site (Model 4). Differences in marginal R^2 across models were used to assess the variance explained by drinking water lithium, participant characteristics, bottled water use, and study site using the MuMIn package in R [22]. Because SHFS participants are related, we conducted a sensitivity analysis that included a random intercept for family and a nested random intercept for participant within family. Analyses were conducted in R version 4.4.2 [23].

RESULTS

Descriptive characteristics

For all participants, the median (IQR) was 35.6 (9.0, 54.1) µg/L for water lithium and 30.8 (17.4, 53.3) and 31.2 (18.0, 56.0) µg/g creatinine for Phase 5 and Phase 7 urinary lithium, respectively (Supplemental Table 2; Table 1). Urinary lithium levels tended to be higher among participants who had less than or equal to a high school education, reported current or former smoking, had a BMI of less than 25 kg/m^2, and those in the highest water lithium exposure tertile. Levels were broadly similar by sex and age, while modest variation was observed across water source categories (Table 1).

Water and urinary lithium levels varied by study site (Fig. 1, Table 1, Supplemental Table 2). Participants in AZ had the highest median lithium levels in both drinking water (96.7 µg/L) and urine (Phase 5: 59.3 µg/g creatinine; Phase 7: 60.3 µg/g creatinine). In OK, median lithium levels were lowest for water (6.1 µg/L) and urine (Phase 5: 34.7 µg/g creatinine; Phase 7: 31.8 µg/g creatinine). Participants in ND/SD had intermediate lithium levels (median in water: 52.5 µg/L; median in urine: Phase 5: 44.8 µg/g creatinine; Phase 7: 48.7 µg/g creatinine), with distributions of both urine and water measurements that included many of the values observed in AZ and OK. Consistent with these patterns, 100% of water samples from AZ, 93% from ND/SD (325 of 349), and 35% from OK (86 of 245) exceeded the USGS non-enforceable health-based screening level of 10 µg/L (Supplemental Table 2).

Most participants reported using a community water system (83.7%, Table 1), which was similar across study sites (80.3% in AZ, 84.6% in ND/SD, and 83.5% in OK) (Supplemental Fig. 2). Many participants in AZ (77.0%) and OK (73.2%) reported drinking bottled water, compared to only 25.4% in ND/SD. A single participant in AZ reported using a drilled/dug well, whereas 6.4% of participants in ND/SD and 9.2% in OK reported well use. For all water sources, urinary lithium levels were highest in AZ, intermediate in ND/SD, and lowest in OK (Supplemental Fig. 3).

Correlation between water and urinary lithium

Using Spearman correlations, we found that water lithium measured at Phase 7 (2022–2024) was positively correlated with urinary lithium levels at both study phases (2006–2009 and 2022–2024), with a slightly stronger correlation for Phase 5 ($\rho = 0.61$, $p < 0.001$) compared to Phase 7 ($\rho = 0.59$, $p < 0.001$) (Fig. 2). When stratified by study site, we found correlations between water and urinary lithium in ND/SD (Phase 5: $\rho = 0.31$; Phase 7: $\rho = 0.35$; both $p < 0.001$) and OK (Phase 5: $\rho = 0.20$, $p = 0.004$; Phase 7: $\rho = 0.27$, $p < 0.001$). Correlations in AZ were null (Supplemental Fig. 4).

Within-person change in urinary lithium over time

Among participants with paired urine measurements ($n = 613$), urinary lithium increased modestly over time, corresponding to an 8% increase from Phase 5 to Phase 7 (GMR = 1.08); 95% CI: 1.02–1.14 (Supplemental Table 3). When stratified by site, participants from ND/SD showed a significant increase in urinary lithium between phases (GMR = 1.10; 95% CI: 1.01–1.20), whereas changes in AZ and OK were not statistically significant (Fig. 3, Supplemental Table 3**)**. Individual-level trajectories showed substantial within-person variability (overall ICC 0.565), particularly in AZ and OK (ICC = 0.292 and 0.203, respectively), with both increases and decreases observed (Fig. 3, Supplemental Table 3).

Multivariable analysis of determinants of urinary lithium

After adjustment for participant characteristics (sex, age, BMI, education, smoking status), a doubling of water lithium was associated with 22% higher urinary lithium (GMR = 1.22, 95% CI: 1.19–1.25), which was attenuated to 9% higher (GMR = 1.09, 95% CI: 1.05–1.13) after adjustment for study site (Table 2**)**. Consistent exposure-response relationships were observed when water lithium was modeled as tertiles. When adjusted for participant characteristics, participants in the second and third tertiles of water lithium had 84% and 201% higher urinary lithium, respectively, compared with those in the lowest tertile, which was attenuated to 41% and 85% higher after adjustment for study site. Participants who reported using bottled water had 29% lower urinary lithium compared to those who did not report bottled water use (GMR = 0.71, 95% CI: 0.63–0.79) before adjustment for site, which was attenuated to 11% lower after adjusting for study site (GMR = 0.89, 95% CI: 0.80–0.99).

In models adjusted for age, sex, BMI, education, smoking status, and bottled water use, participants from the AZ and the ND/SD study sites had significantly higher urinary lithium levels compared with participants from OK (AZ vs. OK: GMR = 3.07, 95% CI: 2.61–3.60; ND/SD vs. OK: GMR = 2.21, 95% CI: 1.98–2.47) (Table 3). These differences persisted, although attenuated, after adjustment for water lithium (AZ vs. OK: GMR = 2.15, 95% CI: 1.73–2.67; ND/SD vs. OK: GMR = 1.75, 95% CI: 1.53-2.00).

Sex and education were not significantly associated with urinary lithium in any model, and smoking status was not associated with urinary lithium after adjusting for water lithium or study site (Table 3). After adjusting for study site, urinary lithium was 12% higher in participants aged 55–65 and 13% higher in those >65 compared to <55 years old. Participants with BMI > 30 kg/m^2 had lower urinary lithium levels compared to participants with BMI < 25 kg/m^2 across all models. In sensitivity analyses, adding family-level random intercept produced an estimated variance component of ~0, indicating minimal family clustering; therefore, we did not include family-level clustering in the final models (Supplemental Table 4).

Participant characteristics and bottled water use explained a small proportion of variability in urinary lithium (marginal $R^2 = 0.021$ and $R^2 = 0.054$, respectively) while for water lithium alone the marginal R^2 was 0.288 (Supplemental Table 5). The marginal R^2 for water lithium together with participant characteristics and bottled water was 0.313, which increased to 0.374 ($\Delta R^2 = 0.061$) with adjustment by study site.

DISCUSSION

In this study of drinking water and urinary lithium levels across Tribal communities in the Western US, 73% of household water

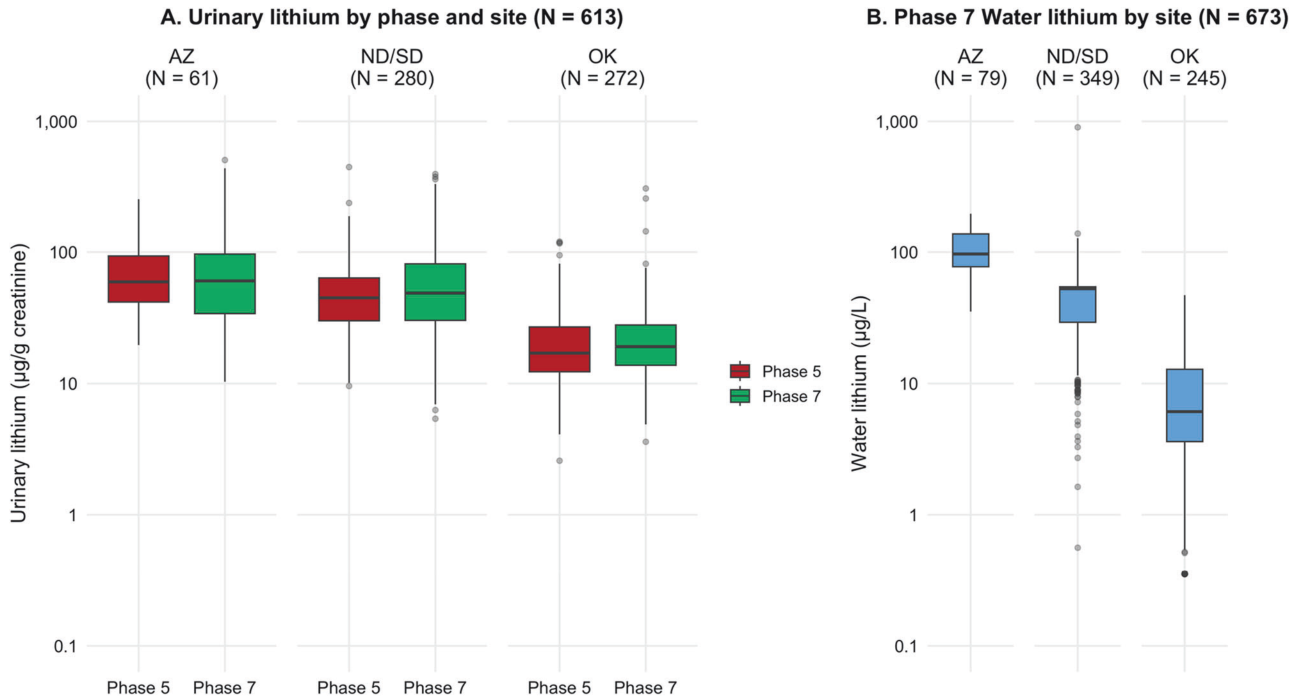


Fig. 1 Urinary and Water Lithium Levels Across Strong Heart Family Study (SHFS) Phases and Sites. Distribution of lithium levels in SHFS participant urine samples and household tap water by study site. Panel **A** shows creatinine-adjusted urinary lithium from Phase 5 (μg/g creatinine; red) and creatinine-adjusted urinary lithium from Phase 7 (μg/g creatinine; green) ($n = 613$). Panel **B** shows Phase 7 household tap water lithium (μg/L; blue) among all participants with a household tap water sample ($n = 673$). Boxes represent interquartile ranges (25^{th}–75^{th} percentile), horizontal lines denote medians, and whiskers indicate 1.5 × the interquartile range; points beyond whiskers are outliers. Lithium levels are plotted on a log10 scale for interpretability. *AZ* Arizona, *ND/SD* North Dakota and South Dakota, *OK* Oklahoma.

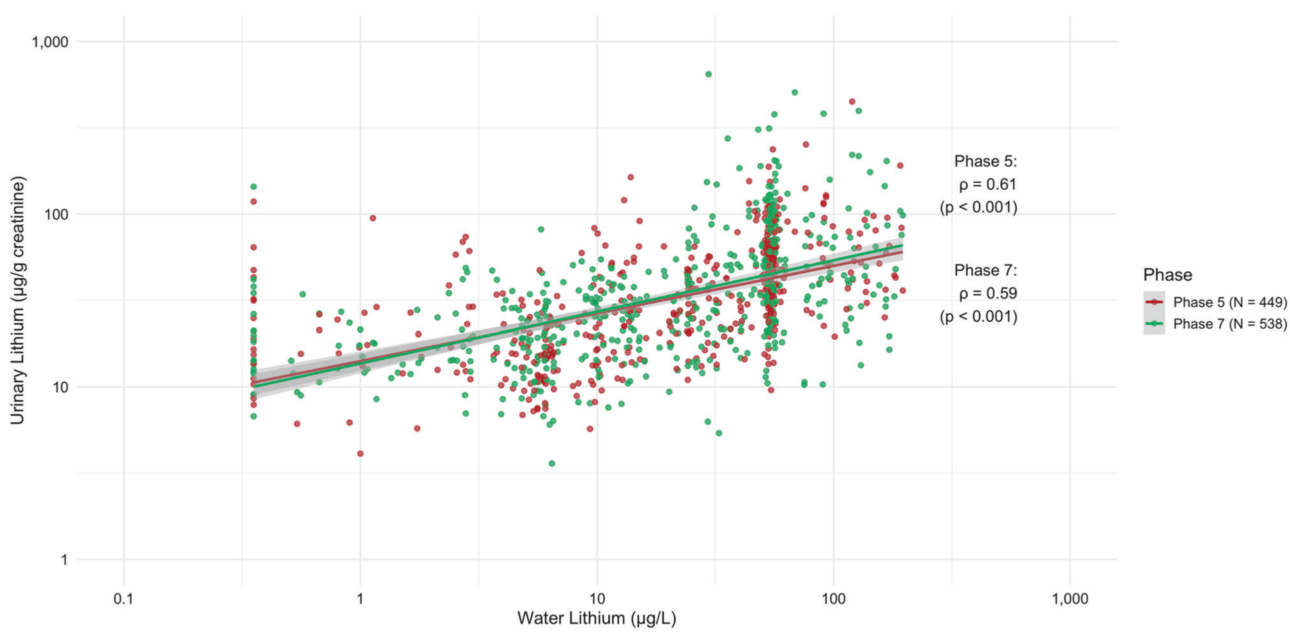


Fig. 2 Urinary Lithium vs. Water Lithium by Strong Heart Family Study (SHFS) Phase. Association between household tap water lithium and creatinine-adjusted urinary lithium by study phase. Scatterplots show individual participant measurements from Phase 5 (2006–2009; red, $n = 449$) and Phase 7 (2022–2024; green, $n = 538$). Lines represent fitted linear regressions with 95% confidence intervals for visualization. Both axes are displayed on a log10 scale for interpretability. Spearman correlation coefficients (ρ) and *p*-values are shown for each phase.

samples exceeded the non-enforceable health-based screening level established by the USGS, and urinary lithium levels in the study participants remained persistent over a 15-year period. Based on marginal R^2 values from linear mixed-effects models, household drinking water lithium was the primary contributor to total lithium exposure, independent of sex, age, education, BMI, and smoking status, explaining 28.8% of the variability in urinary lithium levels. In contrast, drinking bottled water explained only 5.4% of the variability, and other participant characteristics collectively explained just 2.1%. Study site captured additional

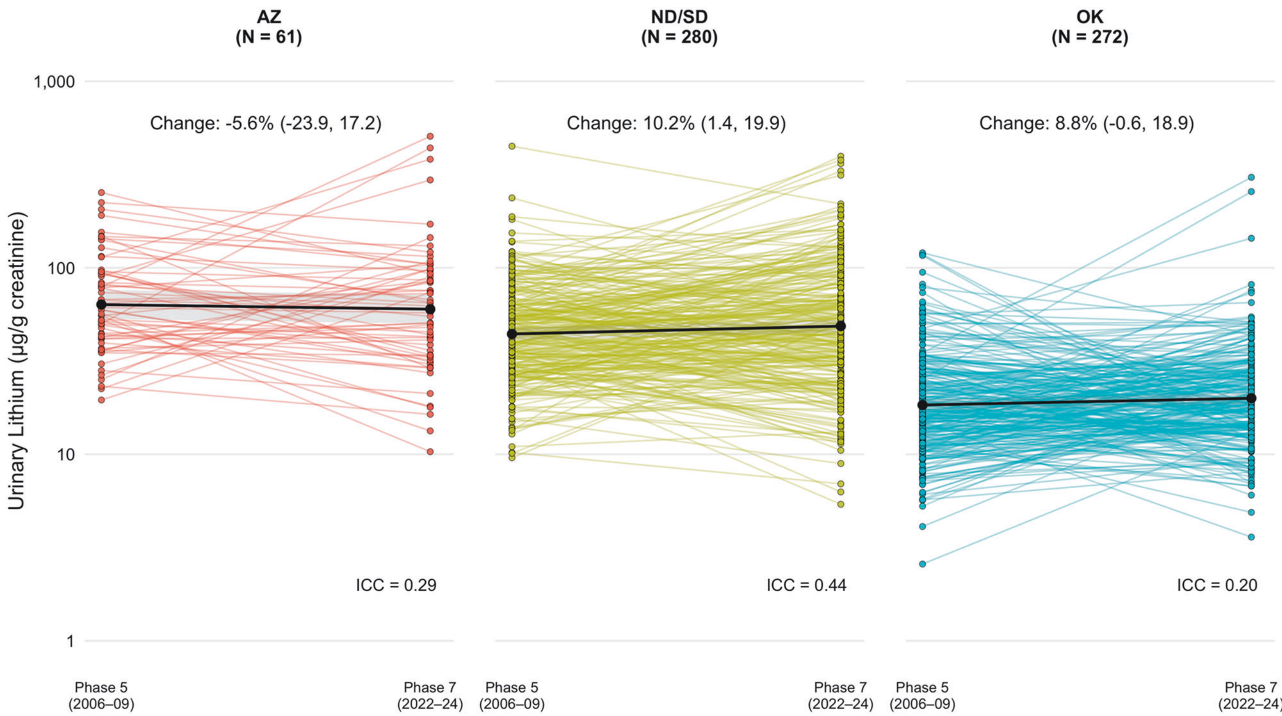


Fig. 3 Change in Urinary Lithium Over Time by Strong Heart Family Study (SHFS) Site. Longitudinal change in creatinine-adjusted urinary lithium levels between Phase 5 (2006–2009) and Phase 7 (2022–2024) of the SHFS by site. Colored lines for each study site represent within-person change. Points indicate measured urinary lithium levels (μg/g creatinine) displayed on a log10 scale for interpretability. Participants included in this figure are limited to those with urinary measurements from both phases ($n = 613$). Interclass Correlation (ICC) was calculated for each study site. The thick black lines represent the site-level percent change, based on geometric mean ratio derived estimates, with 95% confidence intervals (μg/g creatinine). Participant counts (N) are given for each site and phase. *AZ* Arizona, *ND/SD* North Dakota and South Dakota, *OK* Oklahoma.

Table 2. Geometric Mean Ratio (GMR, 95% Confidence Interval) of Urinary Lithium by Water Lithium and Water Source.

	Model 1	Model 2	Model 3
Water Lithium (μg/L)			
Per Doubling	1.22 (1.19–1.25)	1.22 (1.19–1.25)	1.09 (1.05–1.13)
Tertiles			
T1: ≤ 10.44	1.00 (ref)	1.00 (ref)	1.00 (ref)
T2: 10.44 - 53.05	1.88 (1.68–2.09)	1.84 (1.65–2.04)	1.41 (1.27–1.57)
T3: > 53.05	3.00 (2.70–3.34)	3.01 (2.70–3.35)	1.85 (1.58–2.17)
Water Source [a]			
Public/Community Water System	1.03 (0.84–1.27)	1.01 (0.83–1.24)	1.07 (0.91–1.24)
Drilled/Dug Well	1.11 (0.82–1.49)	1.07 (0.79–1.44)	1.23 (0.96–1.60)
Bottled Water	0.70 (0.62–0.78)	0.71 (0.63–0.79)	0.89 (0.80–0.99)
Other	1.14 (0.66–1.96)	1.14 (0.68–1.91)	0.91 (0.68–1.22)

GMR (95% Confidence Interval) of creatinine-adjusted urinary lithium levels by household tap water lithium concentration and self-reported water source of Strong Heart Family Study participants based on linear mixed-effects models with a random intercept for participant, incorporating urinary lithium measurements from Phase 5 and Phase 7 as repeated observations when available. Model 1 is unadjusted; Model 2 is adjusted for participant characteristics (sex, age, body mass index, education, and smoking status); Model 3 is adjusted for participant characteristics and additionally adjusted for study site. Drinking water lithium is modeled per doubling and by tertiles (T1–T3). [a] Self-reported water source compares the association with urinary lithium from utilizing that source vs. not utilizing that source. It is not mutually exclusive across sources. Participants could select more than one water source.

geographic differences, explaining 6.1% of the variability beyond water lithium, bottled water, and individual-level factors.

Lithium exposure varied across study sites, with higher water lithium and urinary lithium in AZ and ND/SD than in OK. These patterns are consistent with the geographic distribution of lithium-bearing geologic formations [24, 25]. In AZ, large pegmatites and claystone deposits are being developed for mining in the northwest region, and smaller deposits are under exploration in the southern and eastern regions [24]. In SD, elevated groundwater lithium may reflect localized pegmatite deposits in the Black Hills and lithium-rich volcanic ash beds interlayered within sandstone units of the Colorado Plateau and Northern Plains aquifers that have undergone alteration to clay minerals [3, 25, 26]. In ND, oilfield brines have also been reported to contain high lithium concentrations [3]. In contrast, OK has no known lithium deposits, although it has recently experienced

Table 3. Geometric Mean Ratio (GMR, 95% Confidence Interval) of Urinary Lithium by Participant Characteristics.

	Model 1	Model 2	Model 3	Model 4
Study Site				
AZ (vs. OK)	2.89 (2.46–3.40)	3.07 (2.61–3.60)	2.15 (1.73–2.67)	--
ND/SD (vs. OK)	2.37 (2.15–2.60)	2.21 (1.98–2.47)	1.75 (1.53–2.00)	--
Sex				
Male (vs. Female)	0.96 (0.85–1.10)	0.93 (0.82–1.05)	0.93 (0.84–1.03)	0.93 (0.85–1.03)
Age				
Age 55–65 (vs. <55)	1.08 (0.97–1.20)	1.08 (0.97–1.20)	1.09 (0.98–1.20)	1.12 (1.01–1.24)
Age >65 (vs. <55)	1.06 (0.95–1.18)	1.06 (0.95–1.19)	1.06 (0.96–1.18)	1.13 (1.02–1.25)
BMI				
BMI 25-30 (vs. <25)	0.91 (0.77–1.08)	0.90 (0.76–1.07)	0.91 (0.78–1.06)	0.93 (0.80–1.08)
BMI > 30 (vs. <25)	0.82 (0.70–0.97)	0.83 (0.70–0.98)	0.81 (0.70–0.93)	0.83 (0.72–0.95)
Education				
>12 vs. ≤12 years	0.96 (0.86–1.06)	0.95 (0.86–1.06)	0.98 (0.89–1.08)	0.98 (0.89–1.07)
Smoking Status				
Former (vs. Never)	1.18 (1.04–1.33)	1.15 (1.01–1.30)	1.08 (0.96–1.20)	1.07 (0.96–1.19)
Current (vs. Never)	1.19 (1.05–1.34)	1.16 (1.02–1.31)	1.08 (0.97–1.20)	1.09 (0.98–1.21)

GMR (95% Confidence Interval) of creatinine-adjusted urinary lithium by Strong Heart Family Study participant characteristics based on linear mixed-effects models with a random intercept for participant, incorporating urinary lithium measurements from Phase 5 and Phase 7 as repeated observations when available. Model 1 is unadjusted; Model 2 is adjusted for sex, age, body mass index (BMI), education, smoking status, and bottled water use (self-reported); Model 3 further adjusted for household tap water lithium; and Model 4 is further adjusted for study site. *AZ* Arizona, *ND/SD* North Dakota and South Dakota, *OK* Oklahoma.

growth in mineral processing infrastructure, including lithium processing facilities [27].

Study site remained a strong predictor of urinary lithium after adjustment for household water lithium which indicates that tap water does not fully explain geographic differences. Secondary drinking water sources beyond household water (e.g., places of work, school, relatives/neighbors' homes, worship, cultural activities) are likely important sources of lithium exposure that were not captured by the available data. Because models also adjusted for individual-level factors, differences between household water and urinary lithium across sites may reflect distinct exposure pathways.

In ND/SD, where most participants used public water systems (84.6%) and bottled water was less common (25.4%), median levels of urinary lithium (Phase 5: 44.8 µg/g creatinine; Phase 7: 48.7 µg/g creatinine) and water lithium (52.5 µg/L) are closely aligned, consistent with household water as the primary exposure source. In OK, median urinary lithium levels (Phase 5: 17 µg/g creatinine; Phase 7: 19.0 µg/g creatinine) were higher than expected given the relatively low water lithium concentrations (6.11 µg/L), suggesting additional sources of lithium exposure, such as diet or other environmental exposures. In AZ, where household water lithium concentrations were highest (96.7 µg/L), urinary lithium levels were not proportionally elevated (Phase 5: 59.3 µg/g creatinine; Phase 7: 60.3 µg/g creatinine), possibly reflecting greater reliance on alternative water sources, including bottled water. Importantly, bottled water cannot be assumed to consistently reduce exposure, as lithium concentrations in some brands can be high (> 1500 µg/L) [28]. It is possible that participants from more urbanized areas in AZ (located near Phoenix) may also consume a higher proportion of water outside the home compared with participants in highly rural areas of ND and SD. These differences are reflected in variation in the strength of correlations between water and urinary lithium across study sites. Together, these patterns show that regional context modifies the relationship between household water lithium and internal dose.

Lithium is not currently regulated by the EPA's Clean Water Act or Safe Drinking Water Act [29, 30], and few water treatment technologies effectively remove lithium [31, 32]. Only reverse osmosis consistently achieves high removal of lithium from water [31]. Water softening has limited effectiveness for lithium removal because ion exchange resins preferentially bind calcium, magnesium, or sodium [31]. Conventional water treatment processes like chlorination, adsorptive media, and biological treatment are not effective [31]. The lack of affordable options for water treatment for lithium underscores the need for increased public surveillance and potential regulatory attention to lithium at both the federal and Tribal levels, especially in light of increased mining and lithium-ion battery production, as well as limited access to household hazardous waste facilities for proper battery disposal in some Tribal communities [33].

We observed no decline in urinary lithium between SHFS phases. Stable urinary lithium suggests household water lithium has not meaningfully changed over the 15-year period, consistent with lithium's resistance to removal by most treatment methods. This interpretation is supported by the similar correlation coefficients between Phase 7 water lithium and urinary lithium measured in Phase 5 and Phase 7 ($\rho \approx 0.60$). In addition, the observed moderate-to-strong correlation between household drinking water lithium and urinary lithium supports the use of urine as a biomarker of environmental lithium exposure, though validation across exposure sources and populations is needed.

The public health impacts of lithium in drinking water remain uncertain. At therapeutic doses (600–1200 mg/day), lithium is used to treat bipolar disorder, and its long-term adverse effects on renal and endocrine systems are well documented [16, 34]. These doses are several orders of magnitude higher than typical environmental exposures observed through drinking water (µg/L range). Epidemiologic studies report mixed findings, with some evidence linking lithium in drinking water to thyroid dysfunction, impaired fetal development, and altered reproductive outcomes [10–15], while other studies, largely ecological designs, have suggested potential benefits, including lower suicide rates and reduced risks of neuropsychiatric and neurodegenerative outcomes [6–9]. To our knowledge, no epidemiological studies have examined cardiovascular outcomes related to environmental lithium exposure, although evidence from patients receiving therapeutic lithium suggests potential cardioprotective effects [35]. In the absence of a maximum contaminant limit or recommended dietary allowance for lithium, and given the wide range of reported health effects, high-quality individual-level studies are needed to clarify the risks of environmental lithium exposure and inform guidance on optimal intake.

Our analysis has several limitations. First, tap water was only measured at Phase 7 and may not capture short-term variability or historical changes in individual water sources. However, substantial long-term changes in lithium concentrations in community water systems and private wells are unlikely given lithium's conservative behavior in aqueous systems [3, 36]. Second, although participants could report using multiple water sources, lithium was measured only in household tap water. As a result, we were unable to fully characterize individual-level exposure among participants who consumed water from locations outside the home. Additionally, detailed information on water system source (e.g., groundwater vs. surface water) was not consistently available and could not be reliably assigned. Finally, although our mixed-effects models adjusted for key demographic and lifestyle factors, residual confounding is possible. Confounding due to therapeutic lithium intake is unlikely. Urinary lithium levels in SHFS were several orders of magnitude lower than those reported among patients receiving therapeutic lithium [37]. While dietary lithium intake was not assessed, diet is unlikely to fully explain between-site differences given similar consumption patterns across study regions for lithium-containing foods (grains, nuts, seeds, legumes, vegetables) [38, 39]. Although lithium concentrations in these foods may vary depending on agricultural soil, water, and dust conditions, most lithium-containing foods consumed by SHFS participants are obtained through regional or national supply chains rather than locally grown sources [40], which likely reduces systematic geographic differences in dietary lithium intake. Regional variation in environmental exposure from atmospheric dust (industrial or natural in origin) is also possible [17, 41]. Future studies should confirm the role of medications, diet, and atmospheric dust with a formal source contribution analysis.

CONCLUSION

This study demonstrates that lithium in drinking water is widespread across certain Tribal communities in the Western US and has represented a persistent source of human exposure over the past decades, although the health implications are unknown. By linking individually matched household water samples with biomonitoring data, we provide evidence that drinking water is an important contributor to internal lithium dose and document substantial regional variation, with the higher water and urine levels observed in AZ and ND/SD and lower levels in OK. Together, these findings establish a baseline for understanding environmental lithium exposure in US communities and underscore the value of integrating drinking water measurements with biomonitoring data to characterize long-term exposure patterns and related health effects, while also supporting the use of urinary lithium as a biomarker of environmental exposure.

DATA AVAILABILITY

The data were collected, analyzed, and reported under agreements made with the sovereign tribal nations that have partnered in this research, which precludes commonly accepted modes of data sharing. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Strong Heart Study Coordinating Center at https://strongheartstudy.org/. Requests will be reviewed by tribal research partners before data may be released. This policy is consistent with the "NIH Policy for Data Management and Sharing: Responsible Management and Sharing of American Indian/Alaska Native Participant Data. (1)"(1) NIH. Supplemental Information to the NIH Policy for Data Management and Sharing: Responsible Management and Sharing of American Indian/Alaska Native Participant Data. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-214.html.

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AUTHOR CONTRIBUTIONS

EB: Formal analysis, Writing – Original Draft, Visualization. KS,ANA: Conceptualization, Methodology, Resources, Funding Acquisition, Writing – Review & Editing, Supervision. AEN: Methodology, Writing - Review & Editing, Funding Acquisition. WLC: Formal Analysis; Writing – Review & Editing. AR,JG: Methodology, Writing - Review & Editing. AB,BCB,AK,TA,SNC,AMF, JGU, YZ: Investigation, Writing – Review & Editing, Funding Acquisition. WC: Data Curation, Project Administration, Investigation. AM,CI,SA: Investigation. TZ,MO: Investigation, Project Administration. RO: Investigation, Writing – Review & Editing, Project Administration.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The Strong Heart Study and its expansion, the Strong Heart Family Study, are participatory based studies working in partnership with tribal communities in the Southwest, the Northern plains, and the Southern Plains. The protocol was approved by institutional review boards (IRBs), participating tribal communities, and the respective area Indian Health Service IRBs. All participants provided informed consent. All methods were performed in accordance with the Declaration of Helsinki and the approved IRB protocols.

ADDITIONAL INFORMATION

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