Arsenic in Drinking Water and Stroke Hospitalizations in Michigan

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Background and Purpose—Mechanistic and human studies suggest a role for arsenic in ischemic stroke; however, risks from chronic, low-level exposures are uncertain and US studies are lacking. The objective was to investigate the association between low-level arsenic exposure in drinking water and ischemic stroke hospital admissions in Michigan.

Methods—Ischemic stroke hospital admissions among those aged ≥45 years were identified (1994 to 2006). Population-weighted average arsenic concentrations were estimated for each Michigan county (n = 83) and for zip codes in Genesee County (n = 27) where there is greater variation in arsenic concentrations. US Census data provided age- and sex-specific population counts and other county- and zip code-level variables (race, income), which were adjusted for in multilevel negative binomial regression models of arsenic and stroke admissions. Hospital admissions for duodenal ulcer and hernia, not hypothesized to be associated with arsenic, were also evaluated.

Results—Adjusted county-level analyses suggested a relationship between arsenic and ischemic stroke hospital admissions, although similar associations were observed for duodenal ulcer and hernia. In zip code-level analysis, arsenic was associated with an increased risk of stroke admission (relative risk, 1.03; 95% CI, 1.01 to 1.05 per μg/L increase in arsenic) after adjustment for confounders, and null or negative associations were found between arsenic and nonvascular outcomes.

Conclusions—Findings from this study suggest that exposure to even low levels of arsenic in drinking water may be associated with a higher risk of incident stroke. Given the ecological nature of the analysis, further epidemiological study with individual-level data on arsenic exposure and incident stroke is warranted. (Stroke. 2010;41:2499-2504.)

Key Words: arsenic ■ cerebrovascular disease ■ environment ■ stroke

Naturally occurring arsenic in groundwater is a global concern with 10s of millions of the world’s citizens exposed to elevated concentrations in their drinking water. Elevated levels of arsenic in drinking water are associated with a range of adverse health outcomes, including skin ailments, cancers, and Type 2 diabetes. Vascular diseases have also been associated with arsenic exposure, namely high blood pressure, coronary heart disease, peripheral arterial disease, and cerebrovascular disease. At concentrations >300 μg/L, health risks from arsenic are unequivocal; however, evaluating risks from chronic, low-level exposures (<100 μg/L) has generated much debate.

Mechanistic and human studies have suggested a role for arsenic in atherosclerosis, perhaps through decreases in the vascular matrix, disruption of endothelial integrity, and enhanced platelet aggregation. Roughly 85% of strokes in the United States are ischemic in nature with the primary underlying condition being atherosclerosis. However, only a few US studies of the association between arsenic and stroke have been conducted and results have been conflicting.

In regions with moderately elevated arsenic concentrations, studies have indicated increased cerebrovascular mortality with increasing arsenic exposure; no association of arsenic with stroke prevalence and mortality, and borderline decreased mortality with increasing arsenic exposure. Epidemiological investigations of cerebrovascular disease incidence and arsenic exposure in the United States have not been conducted. The objective of the current study was to investigate the association between low-level arsenic exposure in drinking water and hospital admissions for ischemic stroke in the state of Michigan.

Materials and Methods

The focus of this study was the 83 counties in the state of Michigan and the 27 zip codes of Genesee County in southeastern Michigan, where arsenic concentrations are elevated and display greater variability. Concentrations of arsenic ≥50 μg/L were first reported in Michigan groundwater in 1981. Since then, arsenic has been identified in unconsolidated and bedrock aquifers throughout southeastern Michigan with concentrations frequently exceeding the new maximum contaminant level (10 μg/L) set by the US Environmental
Protection Agency. Approximately 230,000 people in southeastern Michigan are exposed to arsenic >10 μg/L in their drinking water, making this one of the densest populated regions of moderately elevated arsenic exposure in the United States.

**Stroke, Duodenal Ulcer, and Hernia Hospital Admissions**

Ischemic stroke hospital admissions among those ≥45 years were identified from the Michigan Health & Hospital Association’s Michigan Inpatient Database using principal International Classification of Diseases, 9th Revision, Clinical Modification codes for ischemic (433 to 436 excluding 435) for the time period 1994 through 2006. Hospital admission for 2 nonvascular outcomes, duodenal ulcer (532.xx) and hernia (550–553), were also identified using principal International Classification of Diseases, 9th Revision, Clinical Modification codes to serve as comparison groups for examining specificity of arsenic–stroke findings. Given the nature of these administrative data, individuals could not be identified and thus, for a given outcome, the data may contain multiple events per person if an individual had >1 admission during the study time period. Additional fields included with the hospital admission data were age, race, sex, year of hospital discharge, and county and zip code of residence. Admissions with missing age, sex, or geographic identifiers were excluded (n=259).

**Population and Demographic and Socioeconomic Data**

Year 2000 US Census data were the source for population counts and other county and zip code-level variables (median income and percent black).

**Arsenic Data**

Estimates of arsenic concentrations in Michigan drinking water were compiled from a Michigan Department of Environmental Quality arsenic database, which contains results from water samples collected and analyzed between 1983 and 2002. The database includes 32,942 analyses of water samples from the state of Michigan. These samples were analyzed using several methodologies including graphite furnace atomic absorption spectrometry (1983 to 1987, 1989 to 1995), inductively coupled plasma optical emission hydride generation (1987 to 1988), hydride flame (quartz tube atomic absorption spectrometry; 1989 to 1995), and inductively coupled plasma/mass spectrometry (1996 to the present); previous analyses have indicated that samples analyzed using different methods were highly correlated. Approximately 86% of the analyses were of private wells, and 14% came from municipal wells. Mean arsenic concentrations by county were calculated for private wells and public supplies. Areas served by municipal surface water receive their water from the Great Lakes; arsenic concentrations in municipal surface water supplies in Michigan averaged 0.30 μg/L. Population-weighted county- and zip code-level average arsenic concentrations were calculated by joining mean arsenic concentrations with Census 2000 population data and Michigan Department of Environmental Quality data on populations served by private well, municipal groundwater, and municipal surface water.

**Statistical Analysis**

Demographic characteristics and arsenic levels were summarized with means and SDs or medians and interquartile ranges (IQRs) for continuous variables and with frequencies and percents for categorical variables. Stroke counts were calculated by county (n=83), year (1994 to 2006), age group (45 to 59, 60 to 74, 75+), and sex (male, female). County-level population counts, sociodemographic variables (median income, percent black), and arsenic concentrations were then merged with the stroke count data to create the multilevel data set for analysis. The association between levels of arsenic in drinking water and counts of ischemic stroke admissions in Michigan counties was evaluated using a negative binomial regression model, which uses the log of population size as an offset and naturally accounts for overdispersion. An additional scale parameter was added to account for possible “residual” overdispersion. The association between arsenic and stroke was evaluated with and without adjusting for covariates; for example, age (modeled as indicator variables representing 60 to 74 and 75+ with 45 to 59 as the referent), sex (modeled as an indicator variable with male as the referent), median county-level income (modeled as a continuous variable), and percent black in the county (modeled as a continuous variable). A linear time trend in stroke admissions was also explored. Because the data within each county are correlated, a generalized estimating equations approach was taken to model within-county correlation. Four different working correlation structures, independent, compound symmetry, autoregressive, and unstructured, were tested and different levels of clustering by age group, sex, and year were considered. The quasi-likelihood under the independence model criterion was used to select the best working correlation structure determined to be the unstructured correlation structure for the unadjusted models and the compound symmetry correlation structure for the adjusted models. A secondary analysis following the same methods was conducted at the zip code-level focusing on Genesee County, a county with historically high arsenic levels, where >2800 measurements allowed for zip code-level population-weighted average arsenic estimates. A time trend was not explored in this secondary analysis because of small numbers in zip code-level yearly data. In the zip code-level analysis, additional models (unadjusted and adjusted) were constructed in which arsenic was modeled as a series of dummy variables based on the quintiles of the arsenic distribution with the lowest quintile serving as the referent. A test for trend was also performed by modeling arsenic as an ordinal variable ranging from 1 to 5 based on the quintiles of the distribution. These unadjusted and adjusted models were repeated considering 2 nonvascular outcomes, duodenal ulcers and hernias. These analyses were performed at both the county- and zip code-level. All data analyses were performed using the SAS PROC GENMOD procedure (SAS Institute Inc, Cary, NC). A 2-tailed probability value <0.05 was regarded as statistically significant.

**Results**

Demographic and socioeconomic data for the 83 Michigan counties and 27 Genesee County zip codes are included in Table 1. Based on information provided in the 2000 US

| Table 1. Demographic and Socioeconomic Characteristics in the 83 Counties in the State of Michigan and the 27 Zip Codes of Genesee County in Southeastern Michigan From the 2000 US Census |
|---------------------------------|------------------|-----------------|
| Counties in state of Michigan (n=83) | Median | IQR |
| Percent >65 years | 13.9 | (12.3–17.4) |
| Percent male | 49.6 | (49.2–50.4) |
| Percent black | 1.1 | (0.2–4.2) |
| Median income | 37,218 | (33,391–41,987) |
| Percent below poverty | 10.3 | (8.0–12.4) |
| Percent rural | 64.2 | (43.1–82.6) |
| Land area (square miles) | 724 | (576–1468) |
| Zip codes of Genesee County (n=27) | | |
| Percent >65 years | 10.5 | (8.3–12.0) |
| Percent male | 49.8 | (48.3–50.7) |
| Percent black | 3.4 | (1.1–18.4) |
| Median income | 45,568 | (35,311–55,915) |
| Percent below poverty | 6.5 | (3.8–9.8) |
| Percent rural | 49.8 | (5.1–100.0) |
| Land area (square miles) | 16.1 | (2.2–41.4) |
County-Level Analysis

There were 294,095 ischemic stroke admissions in Michigan over the study time period with complete data. Fifty-two percent (n = 151,962) of the admissions were in women. Fifty-eight percent (n = 249,639) of the admissions were in whites, 14% (n = 41,918) were in blacks, and the remaining 1% were in other race–ethnic groups. Median age of the admissions was 74 years (IQR, 65 to 81).

Median arsenic level among the 83 counties was 1.83 µg/L (IQR, 0.94 to 3.75). Figure 1 displays the county-level average arsenic concentration and percent of the population black in the counties. Table 2 presents the unadjusted and adjusted associations between arsenic levels and ischemic stroke admissions from the county-level analysis. The unadjusted relative risk (RR) between arsenic levels and stroke admissions was 1.010 (95% CI, 1.006 to 1.014; P = 0.004) but not the test for trend based on the quintiles was significant (RR, 1.011; 95% CI, 1.002 to 1.019; P = 0.001).

At the county level, arsenic was associated with hernia admissions in both unadjusted (RR, 1.008; 95% CI, 1.003 to 1.013; P = 0.004) and adjusted models (RR, 1.011; 95% CI, 1.004 to 1.018; P = 0.004). Arsenic was also associated with duodenal ulcer admissions in the unadjusted model (RR, 1.010; 95% CI, 1.003 to 1.018; P = 0.009) but not the adjusted model (RR, 1.005; 95% CI, 0.999 to 1.012; P = 0.18).

Table 2. Association of Arsenic Levels (µg/L) With Ischemic Stroke Hospital Admissions in 83 Michigan Counties (1994 to 2006)*

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>Estimate (SE)</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>Arsenic level</td>
<td>0.010 (0.002)</td>
<td>(0.006 to 0.014)</td>
<td>1.010</td>
<td>(1.006 to 1.014)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Arsenic level</td>
<td>0.011 (0.004)</td>
<td>(0.002 to 0.019)</td>
<td>1.011</td>
<td>(1.002 to 1.019)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Age 60–74 (versus 45–59)</td>
<td>1.631 (0.037)</td>
<td>(1.559 to 1.703)</td>
<td>5.109</td>
<td>(4.756 to 5.489)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Age 75+ (versus 45–59)</td>
<td>2.503 (0.035)</td>
<td>(2.434 to 2.573)</td>
<td>12.220</td>
<td>(11.399 to 13.099)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Gender (female versus male)</td>
<td>-0.297 (0.009)</td>
<td>(-0.313 to -0.280)</td>
<td>0.743</td>
<td>(0.731 to 0.756)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Median income (per $1000)</td>
<td>-0.006 (0.002)</td>
<td>(-0.009 to -0.002)</td>
<td>0.994</td>
<td>(0.991 to 0.998)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Percent black</td>
<td>0.008 (0.002)</td>
<td>(0.004 to 0.011)</td>
<td>1.008</td>
<td>(1.004 to 1.011)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>Year</td>
<td>-0.002 (0.002)</td>
<td>(-0.005 to 0.001)</td>
<td>0.998</td>
<td>(0.995 to 1.001)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*RR represents risk of ischemic stroke admission for a 1-unit increase in continuous variables or for the comparison with the referent group for categorical variables.
and ischemic stroke admissions in adjusted analyses. Further-
association was observed between low-level arsenic exposure
as compared with the state as a whole, an
zip code-level analyses in Genesee County, where arsenic
result of unmeasured confounders and/or ecological bias. In
between arsenic and stroke at the county level could be the
findings are suggestive of an association between arsenic and
stroke that may only be apparent at more elevated levels of
arsenic such as those observed in Genesee County.

In this ecological study of Michigan counties, an association
between low-level arsenic exposure in drinking water and
hospital admissions for ischemic stroke was demonstrated
after adjusting for age and sex, the county-level factors of
median income and percent of black residents, and temporal
trends in stroke admissions. However, similar associations
were also observed for other nonvascular outcomes (duodenal
ulcer admissions in the unadjusted (RR, 0.987; 95% CI, 0.968
to 1.007; \(P=0.195\)) or adjusted models (RR, 0.995; 95% CI,
0.985 to 1.005; \(P=0.288\)). When arsenic was modeled as a
series of dummy variables based on quintiles, zip codes in the
third quintile had an elevated risk of hernia (RR,1.262; 95%
confidence interval (CI), 1.208 to 1.321) compared with zip
codes in the lowest quintile, although tests for trend for
these outcomes were not significant (Figure 2).

\[ \text{RR} \text{ represents risk of stroke admission for a 1-unit increase in continuous variables or for the comparison with the referent group for categorical variables.} \]

Discussion

In this ecological study of Michigan counties, an association
between low-level arsenic exposure in drinking water and
hospital admissions for ischemic stroke was demonstrated
after adjusting for age and sex, the county-level factors of
median income and percent of black residents, and temporal
trends in stroke admissions. However, similar associations
were also observed for other nonvascular outcomes (duodenal
ulcer and hernia) suggesting that the observed association
between arsenic and stroke at the county level could be the
result of unmeasured confounders and/or ecological bias. In
zip code-level analyses in Genesee County, where arsenic
concentrations are higher and there is greater variation in
arsenic exposure as compared with the state as a whole, an
association was observed between low-level arsenic exposure
and ischemic stroke admissions in adjusted analyses. Further-
more, in the zip code-level analyses, we found a significant
trend when arsenic was modeled based on quintiles of the
distribution and found null or negative associations between
arsenic and the nonvascular outcomes. Overall, the observed
findings are suggestive of an association between arsenic and
stroke that may only be apparent at more elevated levels of
arsenic such as those observed in Genesee County.

The discrepancy between the results of adjusted analyses at
the county- and zip code-level is not necessarily surprising
given the use of aggregated data in this ecological study.
Ecological bias in epidemiological studies can occur as a
result of using aggregated estimates of exposures and con-
founders in areas where there is considerable within-area
variability in these measures; the opportunity for this bias is
reduced in smaller area health studies such as those based on
zip codes. In our study, county-level aggregation resulted in
a narrower distribution of arsenic concentrations (IQR, 0.94
to 3.75) compared with the distribution based on the zip codes
of Genesee County (IQR, 2.00 to 12.80) suggesting that
ecological bias may have played a role in the county-level
analysis.

Importantly, although zip code-level adjusted analyses in
Genesee County revealed an association between arsenic and
stroke, unadjusted analyses failed to show even a nonsignif-
ificant elevation in stroke risk; this may be explained by
confounding. Genesee County is home to the urban city of
arsenic (median, 7.78 μg/L). Direct and indirect effects of arsenic exposure on ischemic stroke risk are biologically plausible further supporting the hypothesis that arsenic is associated with stroke. Arsenic may directly accelerate atherosclerosis by inducing endothelial dysfunction because arsenic disrupts endothelial monolayer integrity, increases production of reactive oxygen and nitrogen species contributing to cytotoxicity, increases inflammatory markers, and disrupts the intravascular matrix. Arsenic may also increase stroke risk through platelet-mediated effects because arsenic increases platelet aggregation and the formation of arterial thrombi. An increased prevalence of diabetes and hypertension in arsenic-exposed subjects may indirectly contribute to atherosclerosis. Inhibition of endothelial nitric oxide synthase and enhanced vasoconstriction by arsenic provide potential mechanistic links between arsenic exposure and hypertension, a strong risk factor for ischemic stroke.

Some limitations to this work warrant discussion. Common to ecological studies, this investigation did not contain individual-level data and therefore cannot be used to infer a causal relationship between arsenic and ischemic stroke. Due to the deidentified nature of these data, multiple events may have been recorded per person. In addition, there were not substantial changes in region-level exposure to shed light on temporal changes in arsenic exposure and stroke incidence. Investigating timing of exposure and disease risk was not possible using these simple ecological exposure estimates. Some confounding variables were crudely estimated using US Census data, introducing the possibility of residual confounding in these variables. Furthermore, unmeasured confounding is possible in any epidemiological study and may have been a factor in this study. In the county-level analysis, there was evidence of unmeasured confounding in that arsenic was associated with stroke but also with other nonhypothesized health outcomes (ie, duodenal ulcers and hernias). In contrast, we did not find an association between arsenic and the nonhypothesized health outcomes in the zip code-level analysis. There was some inconsistency in the dose–response findings with evidence of an effect in the third and fifth quintiles only; however, given the potential for error in estimating average exposure in each zip code, there is likely some noise in these risk estimates. The finding of a dose–response trend and increased risk in the third and fifth quintiles adds evidence to the possibility of a direct relationship between arsenic and stroke in a county with moderately elevated arsenic concentrations. Individual-level analyses may be a next step, including confirmed diagnosis of ischemic stroke, residential histories, and individual-level exposure reconstruction accounting for the possibility of latency effects.

**Summary**

Findings from this study suggest that exposure to even low levels of arsenic in drinking water may be associated with a higher risk of incident stroke. Given the ecological nature of the current analysis and reliance on stroke hospitalizations, this finding requires further epidemiological study with individual-level data on arsenic exposure and incident stroke.
as well as biological and sociodemographic stroke risk factors.

Disclosures

None.

References


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