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The Geographic Distribution of Trace Elements in the Environment: The REGARDS Study

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Abstract

Background—Research on trace elements and the effects of their ingestion on human health is often seen in scientific literature. However, little research has been done on the distribution of trace elements in the environment and their impact on health. This paper examines what characteristics among participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study are associated with levels of environmental exposure to arsenic, magnesium, mercury, and selenium.

Methods—Demographic information from REGARDS participants was combined with trace element concentration data from the United States Geochemical Survey (USGS). Each trace element was characterized as either low (magnesium and selenium) or high (arsenic and mercury) exposure. Associations between demographic characteristics and trace element concentrations were analyzed with unadjusted and adjusted logistic regression models.

Results—Individuals who reside in the Stroke Belt have lower odds of high exposure (4th quartile) to arsenic (OR: 0.33, CI: 0.31, 0.35) and increased exposure to mercury (OR: 0.65, CI: 0.62, 0.70) than those living outside of these areas, while the odds of low exposure to trace element concentrations were increased for magnesium (OR: 5.48, CI: 5.05, 5.95) and selenium (OR: 2.37, CI: 2.22, 2.54).

Conclusions—We found an association between levels of trace elements in the environment and geographic region of residence, among other factors. Future studies are needed to further examine this association and determine whether or not these differences may be related to geographic variation in disease.

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Competing interests

The authors declare that they have no competing interests

Authors' contributions

NJR performed data analysis and drafted the manuscript. KH participated in study design and review and approval of the manuscript. SJ was involved in interpretation of data and manuscript preparation. LAM participated in study design, interpretation of data and manuscript preparation.

Keywords

Trace elements; REGARDS study; stroke

Introduction

Stroke is a widely studied cardiovascular disease and continues to be the focus of numerous epidemiological studies and randomized clinical trials. Though in recent years the stroke mortality rate has fallen by 22.8%, this disease continues to be a major health concern in the US, with still close to 800,000 people experiencing strokes each year; over 600,000 suffering from first events and the remaining experiencing recurrent strokes[1]. Since 1920, the stroke mortality rate has differed by geographic area in the US, with the highest mortality rate concentrated in the southeastern region of the US, often times labelled the Stroke Belt and including: Alabama, Arkansas, Georgia, Indiana, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia. The regional dissimilarities in stroke mortality have been studied for years and it has been hypothesized that variations in some stroke risk factors such as hypertension, socioeconomic status, and smoking, contribute to the differences in stroke mortality rate but researchers are still unclear as to why stroke mortality rates differ by region and why rates are especially high in the Stroke Belt [2]. One of the hypothesized causes of the stroke belt is environmental exposures including exposure to trace elements.

For the past several decades, trace elements and how they affect human health have been studied throughout the world. While some trace elements are beneficial to biological functions and processes, the intake of others can yield toxic results [3]. Studies have shown that specific trace elements have been linked to myocardial infraction [4, 5], atherosclerosis [6, 7], hypertension [8], and other cardiovascular related diseases. These elements are presumed to be associated with the risk of stroke but studies of this hypothesized association are limited. Since these trace elements have been linked to other cardiovascular diseases, it has been suggested that environmental factors, such as trace element distribution, can provide clues to help explain the regional differences that occur in stroke incidence and mortality.

Important to understanding the impact of trace elements on the regional variations in diseases, and stroke in particular, is to understand whether the distribution of trace elements differs regionally. In this paper, we will explore the geographic distribution of arsenic, magnesium, mercury and selenium among participants in the Reasons for Geographic and Racial differences in Stroke (REGARDS) Study.

Trace Elements

Arsenic—Arsenic (As) is a trace element that occurs naturally and can be found in both soil and water. Human exposure to arsenic occurs largely through the intake of food and drinking water, with seafood being the largest dietary source of arsenic. In addition to naturally occurring arsenic that can contaminate food sources, arsenic run-off from things such as mining; hazardous waste incinerators, wood preservatives, and herbicides and

insecticides can also cause contamination [9, 10]. The levels of contamination by these sources can differ by region due to certain areas housing more sources of pollution than others [10]. Though a certain level of arsenic can be tolerated by the human body, high levels of arsenic intake can be toxic and related to major health concerns [11]. Studies have shown that ingesting high levels of arsenic on a regular basis can cause certain types of skin, lung, bladder, and kidney cancer but this kind of causal relationship has not yet been found in studies of arsenic exposure and cardiovascular disease [10, 11]. There have been, however, studies that have shown associations between high levels of arsenic and some cardiovascular risk factors such as hypertension [12, 13], ischemic heart disease [14] and type 2 diabetes [15, 16].

Magnesium—Magnesium (Mg) is an important and essential micronutrient necessary for metabolic function in humans. Magnesium is typically ingested by humans as a result of their diets but it has also been associated with drinking water [17]. The level of hardness of water is determined mostly by the amount of calcium and magnesium in the water (the larger the amount of calcium and magnesium, the higher the degree of hardness), but also relies on a few other metals [18]. In several epidemiological studies, the degree of hardness of drinking water at different geographic locations has been shown to have an association with several cardiovascular diseases; some studies have also suggested that hardness of water is inversely associated with the incidence of some cardiovascular diseases [17, 19, 20].

Mercury—Mercury (Hg) is a heavy metal found in the environment due to human and natural causes. Mercury can be released into soil and water through sources such as wastewater treatment plants, mining, and the burning of fossil fuels. Mercury can also be found in dental amalgam fillings, batteries, glass thermometers, fluorescent light bulbs and other household items [21, 22]. However, the highest source of mercury ingestion by humans is through the consumption of contaminated seafood [21]. High levels of mercury consumption in humans and from inhalation from wildfires could lead to potential health concerns [23]. There are some areas of the country that are particularly susceptible to higher levels of mercury contamination due to large forested areas with a great number of wetlands and low levels of productivity among surface waters. These areas are often labelled as “biological Hg hotspots” and typically lead to fish in those areas having greater Hg levels [21]. Regular consumption of these contaminated fish can lead to mercury poisoning and possibly some cardiovascular diseases that have been suggested to have associations with high levels of mercury intake [24, 25].

Selenium—Selenium (Se) is a trace element that occurs naturally in the Earth’s crust and is mostly found in soil and rocks. Selenium can also be found in dietary sources such as cereals, grains, and vegetables, as well as environmental sources like anti-dandruff shampoo, plumbing brasses and hazardous waste sites [26]. In human health, selenium plays a major role in particular enzyme functions in the body and largely enters the body through selenium-containing foods [26, 27]. Though some foods naturally have small amounts of selenium, most plants absorb selenium from the soil in which they were grown and animals get their selenium through the plants that they digest [26]. Therefore, selenium in the environment and the amount that people ingest, will have regional variations due to the

differences in the environments where plants are grown and what animals are fed. Many have suggested an association of low levels of selenium with certain cardiovascular diseases but studies performed investigating this relationship have yielded inconclusive results [28].

In this paper, we will assess whether environmental levels of arsenic, magnesium, selenium and mercury differ across regions, a necessary first step to examining whether they can mediate regional differences in stroke.

Methods

Study Participants

The REGARDS study is a longitudinal cohort study involving 30,239 black and white participants aged 45 and older across the contiguous 48 United States, and is aimed at identifying the causes of increased stroke mortality in the Stroke Belt and among blacks. Participants were selected randomly from a nationwide commercial listing (Genesys, Inc) and then contacted through mail and telephone to be invited to participate in the study. Once an individual was successfully enrolled and eligibility status confirmed, demographic and medical risk factor information from each participant was collected via telephone, and subsequently an in-home examination was performed to collect data on physical measurements, as well as to obtain blood and urine samples. Specimens were sent to the central laboratory at the University of Vermont for processing and assaying. After the initial in-home visit, participants are contacted in 6-months intervals to collect follow up information on potential stroke events, among others. All REGARDS participants provided written informed consent, and Institutional Review Board approval was obtained at all participating institutions [29].

Each participant was assigned a 5-digit FIPS code based on the county and state of his/her residence, as determined via geocoding. Measurements of arsenic, magnesium, mercury, and selenium, described in more detail below, were then matched to participants via the FIPS code. Concentrations of these elements were collected from soil and water sediment measurements obtained from the USGS National Geochemical Survey (NGS) for all of the FIPS codes assigned to participants in the REGARDS study.

Geochemical Information

Samples included in the NGS database were collected from a variety of different sources and documentation specifying information such as date of collection and the origins of the samples can be found on the NGS website (<http://mrddata.usgs.gov/geochem/doc/home.htm>). Multiple analytical techniques were used to measure the levels of these elements in the original data but because some techniques supplied few measurements for areas where REGARDS participants reside, only two techniques were used for this analysis: atomic absorption (AA) was used to measure the concentrations of arsenic, mercury, and selenium while inductively coupled plasma spectrometry was used to measure magnesium concentration [30, 31]. Arsenic, mercury, and selenium measurements are expressed in terms of parts per million (ppm) and magnesium measurements are expressed in terms of percentage by weight (wt%). The median level of arsenic, magnesium, mercury, and

selenium were collected by taking the midpoint of all measurements within each county. The median was obtained in lieu of the mean due to levels of contamination present that could or could not be related to the levels of these elements in the soil and water. When the data was collected, researchers included information on the contamination of variables and contaminated measurements from FIPS in the REGARDS dataset that had “moderate” or “heavy” degrees of contamination were excluded from the data (N=67 different observations from the NGS dataset).

Covariates

For the purposes of this study, only certain demographic information will be studied for each participant. Age, sex, and race are all based on self-report. Education was defined in four levels: Less than high school, high school graduate, some of college, and college graduate or above. Annual household income was defined by five levels: Less than \$20,000, between \$20,000 and \$34,999, between \$35,000 and \$74,999, \$75,000 and above, and those who refused to answer this question. Geographic area was described by three different variables. Region was categorized as those who lived in the Stroke Belt and those who did not. Urban group was defined by census tract and was split into three levels: rural (< 25% urban), mixed (25–75% urban), and urban (> 75% urban) based on census data. The rural-urban commuting area (RUCA) codes, which measure “population density, urbanization, and daily commuting” (Cromartie, 2011), were defined by seven groups: isolated rural, other small rural, small rural core, other large rural, large rural core, urban core, and other urban. Atmospheric particulate matter with aerodynamic diameter $\leq 2.5\mu\text{m}$ ($\text{PM}_{2.5}$) denotes the concentration of particulate matter of this size that is present in the air for a given FIPS code [32]. This data was collected using remote sensing technology in collaboration with National Aeronautic and Space Administration [33].

Statistical Analysis

We assessed the relationship between each factor and each element univariately initially. Due to the distributions of each of the four element concentrations being highly skewed, the elements were each dichotomized at the median value. Each element was also dichotomized according to low (measurement is in the 1st quartile) or high exposure (measurement is in the 4th quartile), depending on whether or not an element is considered toxic or if a deficiency of the element could result in health risks. Univariate analyses then used logistic regression models to determine the likelihood of being above (or below) the median, and similarly above (or below) the 4th (1st) quartile. Further analyses then examined those factors that were significant in univariate models to determine whether they were still significantly associated with the elements after multivariable adjustment.

Results

Of the 30,239 participants in the REGARDS study, 30,172 had recorded FIPS county codes and were included in this analysis. For each trace element, some observations may have been excluded because the NGS database did not have measurements of that element for the given FIPS of the participant or because the participant had a missing value for a demographic variable, thus the sample size differs marginally by element. For the analysis, each element

included the following sample sizes: arsenic with 25,456 participants, magnesium with 25,537 participants, mercury with 24,624 participants, and selenium with 24,497 participants.

The average age of participants included in this study was 64.8 (9.4) years (Table 1), 42% were black, and 56% resided in the Stroke Belt. Table 2 provides the median, 25th, and 75th percentile information by each categorical demographic variable, for each trace element. The median values for mercury and selenium did not vary much across levels of the demographic variable. Arsenic differed more, with the largest difference between categories of the region, urban group, and RUCA variables. Those in the Nonbelt region had a median arsenic exposure almost twice as high as those in the Belt, and highest arsenic exposure levels were observed in urban areas. Similar differences were observed when examining levels of exposure to magnesium.

Arsenic

When considering exposure to arsenic above the 4th quartile (6.4 ppm), all factors, except age, PM_{2.5}, and race, were significant in the adjusted model. The odds of having high environmental exposure to arsenic are greater for those who have never been to college or those who did not complete college as compared to college graduates. Women were 9% less likely to live in areas with high arsenic exposure than men. Individuals in income groups making less than \$75,000 annually as well as those who refused to disclose income all have higher odds of high environmental arsenic exposure than those making \$75,000 or more. Those living in the Stroke Belt have 67% lower odds than others of being exposed to high levels of arsenic in their neighborhood. Those who live in Urban and mixed areas have higher odds of being exposed to high levels of environmental arsenic as compared to those from rural areas. RUCA category was significantly associated with odds of high levels of environmental exposure to arsenic; however, no clear trends emerged.

Magnesium

PM_{2.5}, race, region urban group and RUCA category were all significantly associated with environmental exposure to magnesium below the 1st quartile (0.0555% wt) in the adjusted model. The odds of having been exposed to magnesium below the 1st quartile decrease as PM_{2.5} increases (OR=0.94, CI: (0.92, 0.96)). Blacks had 8.6% higher odds than whites of low magnesium exposure. The odds of living in an area with low magnesium exposure for individuals who live in the Stroke Belt are 5.48 times the odds of that for those who live outside of the Stroke Belt. Again, those who live in urban areas had lower odds (OR=0.787, CI=(0.653, 0.949)) of low environmental exposure to magnesium than those who lived in rural areas, with similar trends observed for urbanicity described by RUCA.

Mercury

All of the same factors (education, income, race, region, urban group, and RUCA category) are significantly associated with mercury exposure above the 4th quartile (0.05 ppm) for both the unadjusted and the adjusted models, just as they were for environmental mercury exposure higher than the median and similar conclusions can be drawn (e.g. Blacks have higher odds of high exposure to mercury than whites, those in the Stroke Belt have lower

odds of high exposure to mercury than those who live outside of the Stroke belt, etc). The only difference in conclusions for the high mercury exposure outcome is observed when examining the RUCA category; high mercury exposure is no longer statistically significant when comparing other large rural areas to isolate rural areas. Additionally, $PM_{2.5}$ is significantly associated with high exposure to mercury with the odds decreasing as $PM_{2.5}$ increases (OR=0.98, CI: (0.968, 0.996)).

Selenium

For unadjusted analysis of exposure to selenium lower than the 1st quartile (0.25 ppm) outcome, the factors education, $PM_{2.5}$, race, region, and RUCA category variables were all significantly associated with the outcome, while for adjusted model all factors except the age and income variables were associated. Considering the adjusted model, women have 7.6% lower odds than men of living in areas with low exposure to selenium. Only those with a high school education or lower were significantly associated with the low environmental selenium exposure, having lower odds of low exposure to selenium than those completed college. For every one unit increase in $PM_{2.5}$, the odds of low exposure to environmental selenium increased by 3.3% (CI: 1.5%, 5.0%). The odds of low selenium exposure for individuals who live in the Stroke Belt are 2.4 times the odds of that for those who live outside of the Stroke Belt (CI: 2.2, 2.5). Both urban and mixed groups had lower odds of low selenium exposure as compared to the rural group. For RUCA category, the other small rural group had lower odds of having low selenium exposure as compared to the isolated rural group while the small rural core, large rural core, and urban core groups each had higher odds of low selenium exposure as compared to the isolate rural group (Table 6).

Discussion

This study observed a positive association with high environmental arsenic and both education and income but a negative association with education and income for high environmental mercury exposure in the adjusted models. The study also found a negative association with education and low environmental selenium. These findings are supported by previous studies on education and exposure to hazardous materials when it comes to arsenic but contradict previous studies on mercury exposure and education. Here, any level of education as compared to college graduates had higher odds of residing in areas with high arsenic exposure, though those odds did decrease as level of education increased. The same pattern was observed in income; lower income groups as compared to annual income of over \$75,000 had higher odds of high environmental exposure to arsenic, with these odds decreasing as income level increases. Also, participants with a high school education or less as compared to college graduates had lower odds of high exposure to mercury. The same is true of all income levels as compared to those making \$75,000 or more annually. Arsenic in the environment is often the result of not only wood preservatives and insecticides, but also hazardous waste incinerators. Mercury found in the environment is typically from coal mines, wastewater treatment plants, and like arsenic, waste incinerators [21, 22, 34]. Several studies have shown that areas where hazardous waste incinerators are located are typically areas of lower income residents and lower property values on housing, which both imply lower levels of education [35, 36], and should lead to higher levels of exposure to arsenic

and mercury in these areas. Selenium is mostly found in soil and affects people based on the animals and plants that they ingest. The sources of selenium from these plants and animals are often hard to track. Therefore, more research on selenium in serum and urine has must be done when looking at demographics than has been research on selenium in the environment and its effects by demographic variables.

Race was negatively associated with low environmental exposure to selenium but positively associated with low exposure to magnesium. Gender was found to be negatively associated with high levels of arsenic exposure and low exposure to selenium. Due to magnesium being a nutrient that is most ingested in food, there has been limited research on magnesium found in the environment and how different demographic groups and regions are affected. Similarly, selenium is mostly found in soil and affects people based on the animals and plants that they ingest. The sources of selenium from these plants and animals are often hard to track. Therefore, more research on selenium in serum and urine has must be done when looking at demographics than has been research on selenium in the environment and its effects by demographic variables.

The study of geographic differences and stroke is one of the main aims of the REGARDS study. Here, one of the goals was to determine whether there were, in fact, geographic differences in trace element concentrations in areas where REGARDS participants reside. This comparison occurred on multiple levels. First, differences in urban, mixed, and rural areas were explored. Those in mixed and urban areas each had higher odds of high exposure to arsenic than those in rural areas. Comparisons of low exposure to selenium between mixed and urban areas to rural areas indicated negative associations. As with many of the demographic characteristics discussed previously in this study, there has been limited research on urban, mixed, and rural environments and environmental trace element concentrations that could exist in these areas.

Comparing trace element concentrations between participants who reside in the Stroke Belt and those who do not was one of the primary interests for this study. Here, those living in the Stroke belt had lower odds of high environmental arsenic exposure and high environmental mercury exposure than those living outside of this region. This goes along with studies by the USGS and others that suggest that western areas and states such as Michigan, Minnesota, South Dakota, Oklahoma, and Wisconsin and in the New England area had higher arsenic concentrations than areas in the South [37]. Additionally, those in the Stroke Belt have 5.5 times the odds of low exposure to magnesium and 2.4 times the odds of low exposure to selenium than those living outside of this region.

This study has several strengths. One strength is that the sample size here is very large, including over 30,000 participants in the REGARDS study. Another is that the study is very racially diverse. Most studies do not have high percentages of black participants but REGARDS did an excellent job of recruiting participants of that demographic. This study is also very geographically diverse. There were over 1,700 FIPS codes (similarly to zip codes) used in the conduct of this study. This provides for a very diverse study sample.

In addition to the strengths of this study, there were also weaknesses. The biggest weakness was the use of the USGS data to determine levels of the trace elements studied here. The range of dates of soil and water samples collected by the USGS is very vast. Some samples were collected as early as the 1970s and 80s while other samples were collected after the year 2000, which makes it difficult to determine if the same amounts of these trace elements were present at the time that the study participants resided in the area of their associated FIPS code, particularly since little data exist on how the level of these elements change over time. However, these are the only publically available data on trace element levels in the environment. Another weakness is that this a cross-sectional study, thus only associations can be observed to be statistically significant and causal inferences cannot be drawn based on the overall results. Lastly, studying only environmental exposure in these areas as they relate to the demographics studied here do not give a direct association with stroke.

Conclusions

Overall, we found that even after controlling for demographic and other characteristics, the distributions of arsenic, magnesium, mercury and selenium in the environment differ across regions. Future work will involve examining the four trace elements analyzed here in serum and urine samples from a smaller cohort of REGARDS participants to assess their association with stroke, as well as examining whether the geographic differences described herein can help mediate geographic differences in stroke.

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List of abbreviations

AA	Atomic absorption
As	Arsenic
Hg	Mercury
FIPS	Federal Information Processing Standard
Mg	Magnesium
NGS	National Geochemical Survey
PM	Particulate Matter
Ppm	Parts per million

RUCA	Rural-Urban Commuting Area Codes
Se	Selenium
OR	Odds ratio
REGARDS	Reasons for Geographic and Racial Differences in Stroke
USGS	United States Geochemical Survey

References

- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Stroke SS. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation*. 2014; 129(3):e28. [PubMed: 24352519]
- Lanska DJ, Kuller LH. The geography of stroke mortality in the United States and the concept of a stroke belt. *Stroke*. 1995; 26(7):1145–1149. [PubMed: 7604404]
- Masironi R. Trace elements and cardiovascular diseases. *Bulletin of the World Health Organization*. 1969; 40(2):305. [PubMed: 4895656]
- D'Alonzo CA, Pell S. A study of trace metals in myocardial infarction. *Archives of Environmental Health: An International Journal*. 1963; 6(3):381–385.
- Hedge B, Griffith GC, Butt EM. Tissue and serum manganese levels in evaluation of heart muscle damage. A comparison with SGOT. *Proc. Soc. Exp. Biol. Med.* 1961; 107:734.
- Skoczyska A, Porba R, Steinmentz-Beck A, Martynowicz H, Affelska-Jercha A, Turczyn B, J drychowska I. The dependence between urinary mercury concentration and carotid arterial intima-media thickness in workers occupationally exposed to mercury vapour. *International journal of occupational medicine and environmental health*. 2009; 22(2):135–142. [PubMed: 19617193]
- Cheng TJ, Chu JJ, Chang CY, Tsai WC, Chen KJ, Guo HR. Atherosclerosis induced by arsenic in drinking water in rats through altering lipid metabolism. *Toxicology and applied pharmacology*. 2011; 256(2):146–153. [PubMed: 21851829]
- Schroeder HA. Cadmium as a factor in hypertension. *Journal of Chronic Diseases*. 1965; 18(7):647–656.
- Oppelt ET. Incineration of hazardous waste. *JAPCA*. 1987; 37(5):558–586. [PubMed: 3328776]
- Services, U.D.o.H.a.H. Toxicological profile for arsenic. 2007
- Srivastava S, Chen Y, Barchowsky A. Arsenic and cardiovascular disease. *Toxicological sciences*. 2009; 107(2):312–323. [PubMed: 19015167]
- Abhyankar LN, Jones MR, Guallar E, Navas-Acien A. Arsenic exposure and hypertension: a systematic review. *Environmental health perspectives*. 2011; 120(4):494–500. [PubMed: 22138666]
- Chen CJ, Hsueh YM, Lai MS, Shyu MP, Chen SY, Wu MM, Tai TY. Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension*. 1995; 25(1):53–60. [PubMed: 7843753]
- Chen CJ, Chiou HY, Chiang MH, Lin LJ, Tai TY. Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. *Arteriosclerosis, thrombosis, and vascular biology*. 1996; 16(4):504–510.
- Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL, Tai TY. Ingested inorganic arsenic and prevalence of diabetes mellitus. *American Journal of Epidemiology*. 1994; 139(5):484–492. [PubMed: 8154472]
- Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA*. 2008; 300(7):814–822. [PubMed: 18714061]
- Bo S, Pisu E. Role of dietary magnesium in cardiovascular disease prevention, insulin sensitivity and diabetes. *Current opinion in lipidology*. 2008; 19(1):50–56. [PubMed: 18196987]
- [USGS], U.G.S. Water Hardness and Alkalinity. 2013

19. Neri LC, Mandel JS, Hewitt D. Relation between mortality and water hardness in Canada. *The Lancet*. 1972; 1:931–934.
20. Rylander R, Bonevik H, Rubenowitz E. Magnesium and calcium in drinking water and cardiovascular mortality. *Scandinavian Journal of Work, Environment & Health*. 1991;91–94.
21. Driscoll CT, Han YJ, Chen CY, Evers DC, Lambert KF, Holsen TM, Munson RK. Mercury contamination in forest and freshwater ecosystems in the northeastern United States. *BioScience*. 2007; 57(1):17–28.
22. Services, U.D.o.H.a.H. Toxicological profile for mercury. 1999
23. [USEPA], U.E.P.A.. Mercury Study Report to Congress, vols 1–8. Washington (DC): Office of Air Quality Planning and Standards and Office of Research and Development; 1997. EPA-452/R-97–005
24. Salonen JT, Seppänen K, Nyyssönen K, Korpela H, Kauhanen J, Kantola M, Salonen R. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation*. 1995; 91(3):645–655. [PubMed: 7828289]
25. Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen TP, Korhonen MJ, Salonen JT. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. *Arteriosclerosis, thrombosis, and vascular biology*. 2005; 25(1):228–233.
26. Services, U.D.o.H.a.H. Toxicological profile for selenium. 2003
27. Stranges S, Marshall JR, Trevisan M, Natarajan R, Donahue RP, Combs GF, Reid ME. Effects of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial. *American journal of epidemiology*. 2006; 163(8):694–699. [PubMed: 16495471]
28. Alissa EM, Bahijri SM, Ferns GA. The controversy surrounding selenium and cardiovascular disease: a review of the evidence. *Medical Science Monitor*. 2003; 9(1):RA9–RA18. [PubMed: 12552253]
29. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Howard G. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology*. 2005; 25(3):135–143. [PubMed: 15990444]
30. Hageman PL, Brown ZA, Welsch E. Arsenic and selenium by flow injection or continuous flow-hydride generation-atomic absorption spectrometry. *US Geological Survey Open-File Report*. 2002:1–9.
31. Briggs PH. Chapter F: the determination of twentyseven elements in aqueous samples by inductively coupled plasma-atomic emission spectrometry. *Analytical Methods for Chemical Analysis of Geologic and Other Materials*. 2002
32. Abbey DE, Ostro BE, Petersen F, Burchette RJ. Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM_{2.5}) and other air pollutants. *Journal of Exposure Analysis and Environmental Epidemiology*. 1994; 5(2):137–159.
33. Al-Hamdan MZ, Crosson WL, Economou SA, Estes MG Jr, Estes SM, Hemmings SN, McClure LA. Environmental public health applications using remotely sensed data. *Geocarto international*. 2014; 29(1):85–98. [PubMed: 24910505]
34. (WHO), W.H.O.. Exposure to mercury: A major public health concern. Geneva: WHO; 2007.
35. Bullard RW, B. Environmental justice for all: community perspectives on health and research needs. *Toxicology and industrial health*. 1993; 9(5):821–841. [PubMed: 8184445]
36. Bryant BI, Mohai P. Race and the incidence of environmental hazards. 1992
37. Welch AH, Westjohn DB, Helsel DR, Wanty RB. Arsenic in ground water of the United States: occurrence and geochemistry. *Groundwater*. 2000; 38(4):589–604.

Table 1

Mean $\pm$ standard deviation and Correlations of Continuous Variables with Each of the Element Levels (N=26,352)

	Mean (SD)	Arsenic (As) N=	Magnesium (Mg)	Mercury (Hg)	Selenium (Se)
Age	64.8 $\pm$ 9.4	0.01 (p=0.09)	0.03 (p<0.0001)	0.01 (p=0.02)	0.01 (p=0.03)
PM 2.5	13.3 $\pm$ 1.9	-0.08 (p<0.0001)	-0.14 (p<0.0001)	-0.02 (p=0.0027)	-0.05 (p<0.0001)

Distribution of Arsenic, Magnesium, Mercury, and Selenium by Demographic Characteristics of REGARDS Study Participants [Median (25th quartile, 75th quartile)]

Table 2

	Arsenic (As) (ppm)		Magnesium (Mg) (wt%)		Mercury (Hg) (ppm)		Selenium (Se) (ppm)	
	N	Median(25 th , 75 th)	N	Median(25 th , 75 th)	N	Median(25 th , 75 th)	N	Median(25 th , 75 th)
Education								
Less than HS	3463	3.20 (2.10, 6.90)	3470	0.17 (0.05, 0.48)	3332	0.04 (0.03, 0.05)	3340	0.35 (0.25, 0.45)
HS Graduate	7278	3.45(2.10, 6.60)	7307	0.18 (0.05, 0.51)	7034	0.04 (0.03, 0.05)	6993	0.30 (0.25, 0.40)
Some College	7610	3.65 (2.10, 6.65)	7638	0.20 (0.06, 0.65)	7346	0.04 (0.03, 0.05)	7315	0.30 (0.25, 0.45)
College graduate or above	9833	3.70 (2.10, 6.35)	9853	0.21 (0.06, 0.65)	9545	0.04 (0.03, 0.05)	9471	0.30 (0.25, 0.40)
“Missing”	22	3.85 (2.35, 9.05)	22	0.44 (0.09, 0.96)	22	0.04 (0.03, 0.06)	22	0.35 (0.30, 0.50)
Gender								
Female	15509	3.40 (2.10, 6.35)	15554	0.18 (0.05, 0.57)	15012	0.04 (0.03, 0.05)	14928	0.30 (0.25, 0.40)
Male	12697	3.70 (2.10, 6.60)	12736	0.21 (0.06, 0.61)	12267	0.04 (0.03, 0.05)	12213	0.30 (0.25, 0.45)
Income								
Less than \$20k	5041	3.50 (2.10, 7.00)	5052	0.18 (0.05, 0.50)	4824	0.04 (0.03, 0.05)	4857	0.30 (0.25, 0.45)
\$20k–\$34k	6794	3.50 (2.10, 6.70)	6814	0.20 (0.06, 0.59)	6560	0.04 (0.03, 0.05)	6528	0.30 (0.25, 0.40)
\$35k–\$74k	8374	3.55 (2.10, 6.35)	8408	0.20 (0.06, 0.61)	8128	0.04 (0.03, 0.05)	8041	0.30 (0.25, 0.40)
\$75k and above	4515	3.70 (2.10, 6.20)	4525	0.22 (0.06, 0.69)	4408	0.04 (0.03, 0.05)	4369	0.30 (0.25, 0.40)
Refused	3482	3.4 (2.10, 6.40)	3491	0.18 (0.05, 0.57)	3359	0.04 (0.03, 0.05)	3346	0.30 (0.25, 0.45)
Region								
Belt & Buckle	16535	2.50 (1.80, 4.60)	16612	0.09 (0.04, 0.20)	16085	0.04 (0.03, 0.05)	15678	0.30 (0.20, 0.40)
Nonbelt	11671	5 (3.00, 8.10)	11678	0.65 (0.36, 1.19)	11194	0.05(0.03, 0.06)	11463	0.40 (0.30, 0.50)
Race								
Black	11164	3.90 (2.1, 7.0)	11191	0.20 (0.06, 0.81)	10767	0.05 (0.03, 0.05)	10830	0.30 (0.25, 0.50)
White	17042	3.30 (2.10, 6.30)	17099	0.20 (0.05, 0.53)	16512	0.04 (0.03, 0.05)	16311	0.30 (0.25, 0.40)
Urban Group								
Rural (25% Urban)	2903	2.40 (1.85, 4.20)	2905	0.10 (0.04, 0.30)	2809	0.04 (0.03, 0.05)	2765	0.30 (0.25, 0.40)
Mixed (25–75% Urban)	2938	2.65 (1.80, 4.60)	2941	0.08 (0.03, 0.29)	2845	0.04 (0.03, 0.05)	2816	0.30 (0.25, 0.40)
Urban (75% Urban)	19637	4.00 (2.20, 7.00)	19713	0.24 (0.08, 0.73)	18992	0.04 (0.03, 0.05)	18938	0.30 (0.25, 0.50)

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	Arsenic (As) (ppm)		Magnesium (Mg) (wt%)		Mercury (Hg) (ppm)		Selenium (Se) (ppm)	
	N	Median(25 th , 75 th)	N	Median(25 th , 75 th)	N	Median(25 th , 75 th)	N	Median(25 th , 75 th)
“Missing”	2728	3.15 (2.05, 5.80)	2731	0.16 (0.04, 0.54)	2633	0.04 (0.03, 0.05)	2622	0.30 (0.25, 0.40)
RUCA Category								
Isolated Rural	605	2.20 (1.60, 3.80)	607	0.10 (0.03, 0.31)	578	0.04 (0.03, 0.05)	574	0.30 (0.25, 0.45)
Small Rural Core	1300	2.80 (1.90, 4.70)	1300	0.05 (0.03, 0.24)	1238	0.04 (0.03, 0.05)	1260	0.30 (0.25, 0.40)
Other Small Rural	298	2.40 (1.80, 4.60)	299	0.06 (0.03, 0.29)	289	0.04 (0.03, 0.05)	285	0.30 (0.30, 0.40)
Large Rural Core	2298	2.80 (1.90, 4.80)	2298	0.07 (0.03, 0.30)	2199	0.04 (0.03, 0.05)	2172	0.30 (0.25, 0.40)
Other Large Rural	802	2.25 (1.90, 4.15)	802	0.06 (0.04, 0.24)	786	0.04 (0.03, 0.05)	753	0.30 (0.25, 0.40)
Urban Core	18087	4.10 (2.20, 7.00)	18165	0.27 (0.09, 0.78)	17528	0.04 (0.03, 0.05)	17460	0.30 (0.25, 0.50)
Other Urban	2088	2.90 (2.05, 5.45)	2088	0.15 (0.04, 0.46)	2028	0.04 (0.03, 0.05)	2015	0.30 (0.30, 0.40)
“Missing”	2728	3.15 (2.05, 5.80)	2731	0.16 (0.04, 0.54)	2633	0.04 (0.03, 0.05)	2622	0.30 (0.25, 0.40)

Table 3

Unadjusted and Adjusted Arsenic Odds Ratios and 95% Confidence Intervals for Each Outcome

Arsenic (N=25,456)		
High Exposure (4 th quartile=6.4)		
Variable	Unadjusted Odds Ratio (95% C.I.)	Adjusted Odds Ratio (95% C.I.)
Age	1.00 (1.00, 1.00)	0.99 (0.99, 1.00)
Education (Ref=College Grad or Above)		
Less than HS	1.16 (1.06, 1.26)	1.20 (1.01, 1.34)
HS Graduate	1.12 (1.05, 1.20)	1.15 (1.06, 1.25)
Some College	1.10 (1.02, 1.17)	1.08 (1.00, 1.16)
Gender (Ref=Male)		
Female	0.92 (0.87, 0.97)	0.91 (0.86, 0.97)
Income (Ref= \$75k)		
Less than \$20k	1.29 (1.17, 1.41)	1.42 (1.26, 1.59)
\$20k–\$34k	1.25 (1.14, 1.36)	1.34 (1.20, 1.48)
\$35k–\$74k	1.12 (1.03, 1.22)	1.20 (1.09, 1.32)
Refused	1.13 (1.02, 1.26)	1.24 (1.10, 1.39)
PM_{2.5}	0.94 (0.92, 0.95)	1.01 (1.01, 1.03)
Race (Ref=White)		
Black	1.28 (1.21, 1.35)	1.01 (0.95, 1.08)
Region (Ref=Nonbelt)		
Belt and Buckle	0.31 (0.29, 0.33)	0.33 (0.31, 0.35)
Urban Group (Ref=Rural)		
Mixed (25–75% Urban)	0.97 (0.84, 1.12)	1.51 (1.23, 1.84)
Urban (75% Urban)	2.34 (2.11, 2.61)	3.07 (2.49, 3.77)
RUCA Category (Ref=Isolated Rural)		
Small Rural Core	1.43 (1.08, 1.89)	0.78 (0.55, 1.10)
Other Small Rural	1.45 (0.99, 2.13)	1.37 (0.93, 2.03)
Large Rural Core	1.65 (1.27, 2.14)	0.72 (0.52, 1.00)
Other Large Rural	1.34 (0.99, 1.81)	1.42 (1.04, 1.93)
Urban Core	2.80 (2.20, 3.56)	0.74 (0.54, 1.01)
Other Urban	1.79 (1.38, 2.32)	1.32 (1.000, 1.75)

**
Bold Odds Ratios and Confidence intervals signify statistical significance.

Table 4

Unadjusted and Adjusted Magnesium Odds Ratios and 95% Confidence Intervals for Each Outcome

Magnesium (N=25,537)		
Low Exposure (1 st quartile=0.0555)		
Variable	Unadjusted Odds Ratio (95% C.I.)	Adjusted Odds Ratio (95% C.I.)
Age	0.99 (0.99, 1.00)	1.00 (1.00, 1.01)
Education (Ref=College Grad or Above)		
Less than HS	1.39 (1.27, 1.51)	1.09 (0.98, 1.22)
HS Graduate	1.24 (1.15, 1.33)	1.05 (0.96, 1.14)
Some College	1.13 (1.05, 1.21)	1.08 (0.99, 1.17)
Gender (Ref=Male)		
Female	1.15 (1.09, 1.21)	1.05 (0.96, 1.14)
Income (Ref= \$75k)		
Less than \$20k	1.35 (1.23, 1.48)	1.02 (0.90, 1.15)
\$20k–\$34k	1.25 (1.15, 1.37)	1.09 (0.98, 1.22)
\$35k–\$74k	1.21 (1.11, 1.32)	1.10 (1.00, 1.23)
Refused	1.32 (1.19, 1.46)	1.09 (0.96, 1.24)
PM_{2.5}	1.07 (1.06, 1.09)	0.94 (0.92, 0.96)
Race (Ref=White)		
Black	0.86 (0.82, 0.91)	1.09 (1.01, 1.16)
Region (Ref=Nonbelt)		
Belt and Buckle	6.77 (6.30, 7.28)	5.48 (5.05, 5.95)
Urban Group (Ref=Rural)		
Mixed (25–75% Urban)	1.09 (0.98, 1.21)	1.13 (0.95, 1.35)
Urban (75% Urban)	0.37 (0.34, 0.41)	0.79 (0.65, 0.95)
RUCA Category (Ref=Isolated Rural)		
Small Rural Core	1.30 (1.07, 1.57)	1.20 (0.92, 1.56)
Other Small Rural	1.22 (0.93, 1.62)	1.21 (0.90, 1.62)
Large Rural Core	1.09 (0.91, 1.31)	1.13 (0.88, 1.46)
Other Large Rural	1.17 (0.95, 1.45)	1.06 (0.85, 1.32)
Urban Core	0.28 (0.24, 0.33)	0.46 (0.36, 0.59)
Other Urban	0.62 (0.51, 0.74)	0.65 (0.53, 0.79)

 Bold Odds Ratios and Confidence intervals signify statistical significance.

Table 5

Unadjusted and Adjusted Mercury Odds Ratios and 95% Confidence Intervals for Each Outcome

Mercury (N=24,624)		
High Exposure (4 th quartile=0.5)		
Variable	Unadjusted Odds Ratio (95% C.I.)	Adjusted Odds Ratio (95% C.I.)
Age	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)
Education (Ref=College Grad or Above)		
Less than HS	0.78 (0.72, 0.85)	0.84 (0.76, 0.92)
HS Graduate	0.74 (0.69, 0.79)	0.81 (0.75, 0.87)
Some College	0.87 (0.82, 0.93)	0.91 (0.85, 0.98)
Gender (Ref=Male)		
Female	0.999 (0.95, 1.05)	1.04 (0.99, 1.10)
Income (Ref= \$75k)		
Less than \$20k	0.69 (0.64, 0.76)	0.73 (0.66, 0.81)
\$20k–\$34k	0.75 (0.69, 0.81)	0.78 (0.71, 0.85)
\$35k–\$74k	0.79 (0.74, 0.85)	0.81 (0.74, 0.88)
Refused	0.81 (0.74, 0.89)	0.85 (0.76, 0.94)
PM_{2.5}	0.95 (0.94, 0.96)	0.98 (0.97, 1.00)
Race (Ref=White)		
Black	1.25 (1.19, 1.32)	1.24 (1.17, 1.32)
Region (Ref=Nonbelt)		
Belt and Buckle	0.57 (0.54, 0.60)	0.66 (0.62, 0.70)
Urban Group (Ref=Rural)		
Mixed (25–75% Urban)	1.42 (1.27, 1.58)	2.05 (1.73, 2.43)
Urban (75% Urban)	1.75 (1.60, 1.90)	1.70 (1.43, 2.03)
RUCA Category (Ref=Isolated Rural)		
Small Rural Core	0.77 (0.61, 0.97)	0.42 (0.32, 0.56)
Other Small Rural	0.98 (0.72, 1.35)	0.90 (0.65, 1.25)
Large Rural Core	0.99 (0.80, 1.21)	0.56 (0.43, 0.73)
Other Large Rural	1.25 (0.98, 1.58)	1.19 (0.94, 1.52)
Urban Core	2.01 (1.67, 2.42)	0.98 (0.76, 1.26)
Other Urban	1.44 (1.17, 1.76)	1.15 (0.93, 1.42)

Bold Odds Ratios and Confidence intervals signify statistical significance.

Table 6

Unadjusted and Adjusted Selenium Odds Ratios and 95% Confidence Intervals for Each Outcome

Selenium (N=24,497)		
Low Exposure (1 st quartile=0.25)		
Variable	Unadjusted Odds Ratio (95% C.I.)	Adjusted Odds Ratio (95% C.I.)
Age	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)
Education (Ref=College Grad or Above)		
Less than HS	0.95 (0.87, 1.04)	0.89 (0.80, 0.99)
HS Graduate	0.92 (0.86, 0.99)	0.90 (0.83, 0.98)
Some College	0.97 (0.91, 1.04)	0.95 (0.88, 1.03)
Gender (Ref=Male)		
Female	0.95 (0.90, 1.01)	0.92 (0.87, 0.98)
Income (Ref= \$75k)		
Less than \$20k	1.05 (0.95, 1.15)	1.09 (0.98, 1.23)
\$20k–\$34k	1.01 (0.92, 1.10)	1.02 (0.92, 1.13)
\$35k–\$74k	1.02 (0.94, 1.11)	1.01 (0.92, 1.11)
Refused	0.98 (0.89, 1.09)	1.01 (0.89, 1.13)
PM_{2.5}	1.09(1.08, 1.11)	1.03 (1.02, 1.05)
Race (Ref=White)		
Black	0.92 (0.87, 0.97)	0.90 (0.84, 0.96)
Region (Ref=Nonbelt)		
Belt and Buckle	2.22 (2.09, 2.35)	2.38 (2.22, 2.54)
Urban Group (Ref=Rural)		
Mixed (25–75% Urban)	0.95 (0.84, 1.07)	0.59 (0.48, 0.73)
Urban (75% Urban)	0.97 (0.89, 1.06)	0.63 (0.51, 0.79)
RUCA Category (Ref=Isolated Rural)		
Small Rural Core	0.90 (0.72, 1.13)	1.38 (1.02, 1.87)
Other Small Rural	0.62 (0.44, 0.88)	0.65 (0.46, 0.93)
Large Rural Core	1.02 (0.83, 1.25)	1.54 (1.15, 2.06)
Other Large Rural	1.03 (0.81, 1.31)	1.02 (0.80, 1.31)
Urban Core	0.96 (0.80, 1.16)	1.95 (1.47, 2.59)
Other Urban	0.80 (0.65, 0.98)	0.94 (0.75, 1.17)

Bold Odds Ratios and Confidence intervals signify statistical significance.