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Associations of Spatial Disparities of Alzheimer's Disease Mortality Rates with Soil Selenium and Sulfur Concentrations and Four Common Risk Factors in the United States

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Abstract.
Background: Associations between environmental factors and spatial disparity of mortality rates of Alzheimer's disease (AD) in the US are not well understood.
Objective: To find associations between 41 trace elements, four common risk factors, and AD mortality rates in the 48 contiguous states.
Methods: Isopleth maps of AD mortality rates of the 48 states and associated factors were examined. Correlations between state average AD mortality rates and concentrations of 41 soil elements, wine consumption, percentage of current smokers, obesity, and diagnosed diabetes of the 48 states between 1999 and 2014 were analyzed.
Results: Among 41 elements, soil selenium concentrations have the most significant inverse correlations with AD mortality rates. Rate ratio (RR) of the 6 states with the lowest product of soil selenium and sulfur concentrations is 53% higher than the 6 states with the highest soil selenium sulfur product in the 48 states (RR = 1.53, CI95% 1.51–1.54). Soil tin concentrations have the most significant inverse correlation with AD mortality growth rates between 1999 and 2014, followed by soil sulfur concentrations. Percentages of obesity, diagnosed diabetes, smoking, and wine consumption per capita also correlate significantly with AD mortality growth rates.
Conclusions: High soil selenium and sulfur concentrations and wine consumption are associated with low AD mortality rates. Given that average soil selenium and sulfur concentrations are indicators of their intakes from food, water, and air by people in a region, long-term exposure to high soil selenium and sulfur concentrations might be beneficial to AD mortality rate reduction in a region.

Keywords: Alzheimer's disease, soil selenium, spatial disparity, sulfur, tin

INTRODUCTION

Alzheimer's disease (AD) is one of the leading underlying causes of death in the US with an average annual death of 71,301 between 1999 and 2014 according to the US Centers for Diseases Control and Prevention (CDC) database (https://wonder.cdc.gov/). There is also the continued increase of AD mortality rates as life expectancy increases [1]. While genetic factors such as mutations in amyloid precursor protein and presenilins 1 and 2 may have limited contributions to overall AD prevalence in a region, more recent studies have recognized that allele ε4 of apolipoprotein (APOE ε4) may have a much more

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profound influence on the risk of common sporadic, late-onset type of AD [2–5]. In addition, increased levels of cholesterol, midlife hypertension, diabetes, alcohol consumption, smoking, head injury, cognitive and physical activities are also recognized to play important roles in AD progress as people age [6–10]. Vitamins C and E, and selenium have been reported to be important in reducing oxidative stress and in inhibiting progresses of neurodegenerative diseases as well [11–17].

However, it is also clear there are spatial disparities of AD mortality rates in the US that cannot simply be explained by the demographic related factors [18, 19]. Significant contributions to AD prevalence by soil elements were rarely mentioned in most review articles [20]. Concentrations of soil elements have long been considered as broad indicators of the trace element intake from food, water, and air by people in a region [21, 22]. This ecological study intends to examine the spatial patterns of AD mortality rates and quantify their associations with concentrations of soil elements and other risk factors in the 48 contiguous states. Four traditional risk factors including percentage of diagnosed diabetes, obesity, current smokers, and alcohol consumption per capita will be examined as well. The reason that AD mortality rates are used, instead of incidence and prevalence rates, is because only AD mortality rates of general population in the 48 states are available. Selections of the four risk factors are because of the availability of their state-level data and their potential contributions to spatial disparities of AD mortality rates.

METHODS

Data collection

AD mortality rates between 1999 and 2014 were obtained from the CDC database using code G30 following the Tenth Revision of the International Classification of Diseases. Average annual AD mortality rates were aggregated by state. Mortality rates in the CDC database were from death certificates of the US residents and each death certificate identifies a single underlying cause of death and demographic data. The underlying cause of death in the CDC database is defined as "the disease or injury which initiated the train of events leading directly to death". Age-adjusted rates in the CDC database were calculated by applying the age-specific rates of the standard population of 2007 which is the median year between 1999 and 2014 [23].

Concentrations of 41 elements in the top 5 cm of soil from 4,856 sites collected between 2007 and 2010 across the 48 states were obtained from a US Geological Survey (USGS) report [24]. The 4,856 sites were all at least 50–200 meters away from roads, buildings, or structures and 5 kilometers away from the downwind direction of major industrial activities to minimize the local anthropogenic pollutions in soil [24]. Selection of 41 out of the 44 elements in the USGS database is because three of the 44 elements in the database (silver, caesium, and tellurium) have concentrations less than their respective detection limits in more than 2/3 of the soil sample sites. The 41 elements include aluminum, arsenic, barium, beryllium, bismuth, calcium, cadmium, cerium, cobalt, chromium, copper, iron, gallium, mercury, indium, potassium, lanthanum, lithium, magnesium, manganese, molybdenum, sodium, niobium, nickel, phosphorus, lead, rubidium, sulfur, antimony, scandium, selenium, tin, strontium, thorium, titanium, thallium, uranium, vanadium, tungsten, yttrium, and zinc which encompass most of the elements that have potential influences on people's health. In the US, more than 80% of food supplies could be from a region of 50-mile radius except a few east coast states based upon a recent estimation [25]. 58.8% of the total population and nearly half (47–50%) of the population aged 55 and older were residents of the same states where they were born in according to the 2010 US census survey [26]. Hence, averaged soil elemental concentration can generally be considered as an indicator or a proxy of the long-term trace element intake by people in a region [21, 22].

State average wine consumption by people 14 years and older, in gallons of ethanol per capita between 1999 and 2013 for the 48 states were obtained from the database of National Institute on Alcohol Abuse and Alcoholism. State average percentages of current smokers, and self-reported diagnosed diabetes and obesity among US adults between 1999 and 2014 surveyed by the Behavioral Risk Factor Surveillance System were obtained from CDC for the 48 states. A responder's self-reported weight and height were used to calculate body mass index (BMI): weight in kilograms divided by the square of height in meters. A BMI greater than or equal to 30 was considered to be obese. A person has diagnosed diabetes when he (or she) reported ever being told by a health professional that he had diabetes. "Current smokers" are defined as persons who reported smoking at least 100 cigarettes during their lifetime and who, at the time they participated in the survey, reported smoking every day or some days.

Statistical analyses

GIS isopleth maps

An isopleth map of average AD mortality rates of the 48 states between 1999 and 2014 was plotted using the inverse distance weighted interpolation method. Isopleth map instead of choropleth map in this study was to reduce the effect of a sharp state boundary for improved visualization of regional patterns. Isopleth maps of concentrations of two elements selenium and sulfur in the top 5 cm of soil were plotted (Fig. 1). In addition, isopleth maps of the four risk factors, obesity, diabetes, wine consumption, and current smokers, were plotted as well (Fig. 2). Examination of isopleth maps allows both a quick visual and a statistical comparison of the spatial patterns of AD mortality rates, soil elemental concentrations, and the four risk factors. Aggregated state average data allow the study to reduce the noise effect of local variations, overcome data discontinuity at county levels, and extract major meaningful relationships between AD mortality rates, soil elemental concentrations, and the four risk factors in the 48 states. Because state level, instead of individual, data was analyzed, this study is an ecological study.

Correlations between AD mortality rates and soil elemental concentrations

Pearson correlation coefficients and their significance levels were calculated for the state average AD mortality rates between 1999 and 2014 and the state average soil elemental concentrations of the top 5 cm of soil in the 48 states. Because skewnesses of concentrations of some elements (arsenic, bismuth, calcium, cobalt, chromium, copper, iron, mercury, magnesium, molybdenum, sodium, nickel, lead, sulfur, antimony, scandium, selenium, tin, strontium, titanium, vanadium, uranium, tungsten) in the top 5 cm of soil are larger than the two standard errors of their skewnesses, nonparametric Kendall's Tau-b correlation coefficients were calculated as well. Pearson and Kendall's tau-b correlations between state average AD mortality rates, percentage of current smokers, diagnosed diabetes, obesity, and wine

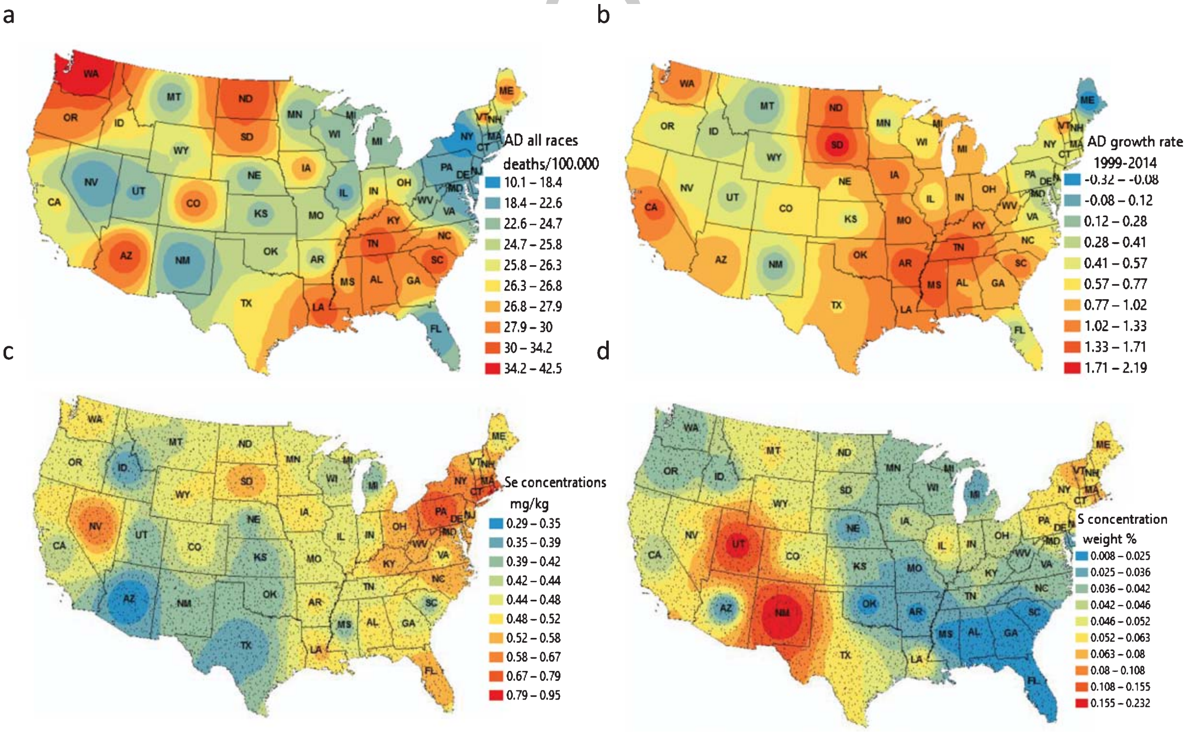

Fig. 1. Isopleth maps of state average (a) AD mortality rates of all races, (b) AD mortality growth rates of all races between 1999 and 2014, (c) soil selenium concentration, and (d) soil sulfur concentration. Fine dots in (c) and (d) indicate locations of soil samples.

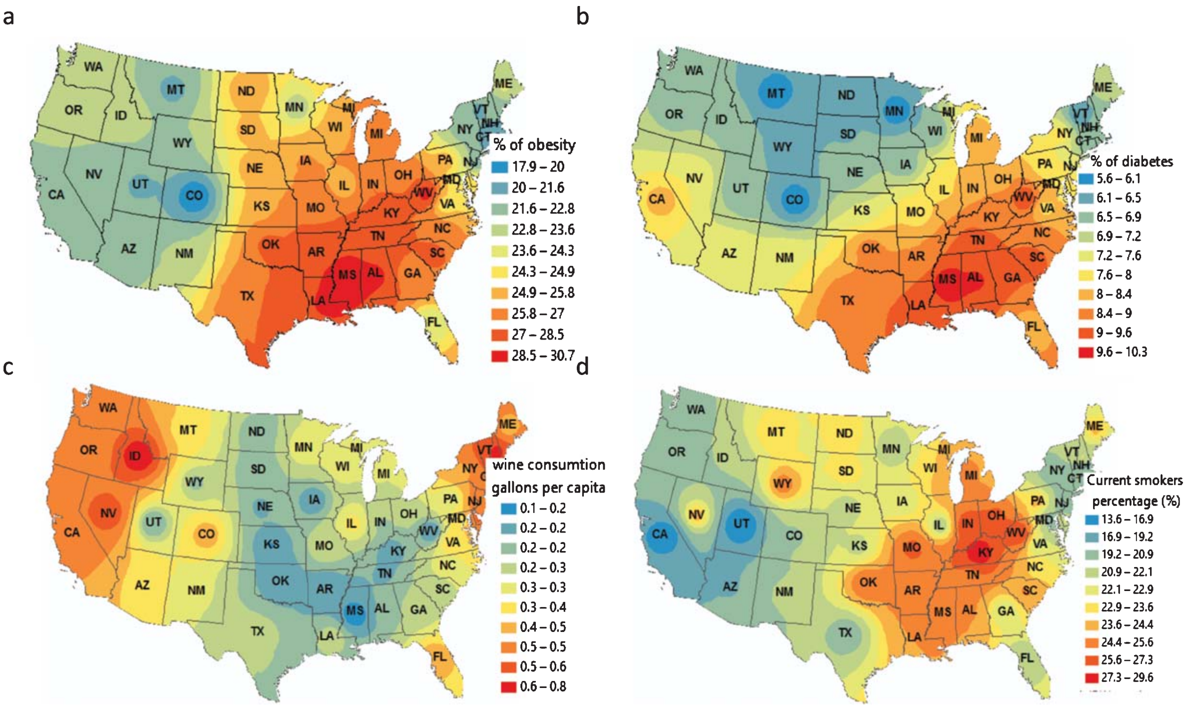

Fig. 2. Isopleth maps of the four risk factors: (a) state average percentage of obesity, (b) percentage of diagnosed diabetes, (c) annual wine consumption per capita in gallons of ethanol (1999 to 2013), and (d) percentage of current smokers between 1999 and 2014.

consumptions per capita between 1999 and 2014 (2013 for wine consumption) were calculated as well.

Even though this study is an exploratory-observational research in nature, cautions are still needed for propagation of Type I error in the multiple correlation results. For a more confirmatory reading, one might need to use the Bonferroni adjustment, i.e., a much lower p value ($<<0.05$) than 0.05 used in the current text to deem the correlation results statistically "significant".

Correlations between AD mortality growth rates and other factors

Slopes of the regression lines of AD mortality rates of each of the 48 states versus years were calculated between 1999 and 2014. Growth or reduction rate of AD mortality rates of each state discussed hereafter is referring to this regression slope of AD mortality rates between 1999 and 2014. Correlations between the growth or reduction rate of each state and concentrations of the 41 elements were calculated and they help reveal the elements that are most associated with AD mortality growth rates. Isopleth maps of the growth/reduction rates of the 48 states were plotted as well.

Step-wise multivariate regression models and rate ratios

For the stepwise multivariate linear regression models, state average AD mortality rates were used as dependent variables, state average soil selenium and sulfur concentrations, percentage of the current smokers, wine consumption per capita, and percentages of obesity and diabetes were used as predictors. Selection of multivariate linear regression model was because of the non-integer AD mortality rates obtained from CDC database. All correlations and regression models were calculated using the SPSS Statistics 24. Spatial autocorrelations of the model residuals were examined by Morgan's index.

Rate ratios (RR) were calculated using the age adjusted mortalities and their corresponding populations between 1999 and 2014 for two 8-state groups of the 48 states. The first 8-state groups with 6 states in each group were established by dividing the 48 states by 8 (to obtain the semi-quartile number of the 48) based on their soil selenium concentrations. The 6 states with the highest average soil selenium concentrations were placed in group #8 as the "control group" and the 6 states with the lowest average soil selenium concentrations were placed in group #1 as the "case group". Other states were placed in groups between 2 and 7 accordingly based on their soil selenium concentrations. The second 8-state groups with 6 states in each group were established following the same manner; however, here products (multiplication results) of state soil selenium and sulfur concentrations were used instead of only state soil selenium concentrations.

RESULTS

1,140,814 deaths were attributed to AD as the underlying cause of death in the 48 states in the CDC database between 1999 and 2014. Of the 1,140,814 deaths, 1,056,589 were reported among whites, 802,008 were reported among female, and 338,806 were reported among male. District of Columbia (DC) was excluded from statistics of the 48 states because of lack of DC's soil element concentration data in the USGS database. White constitutes 92.6% of the total mortalities reported in the 48 states, and age-adjusted AD mortality rate of female was 2.37 times that of male during this period.

Spatial disparities of AD mortality rates and soil elemental concentrations

AD mortality rates were apparently higher in the Southeastern US than in the Northeastern and Midwestern US (Fig. 1a). Washington State had the highest average age adjusted AD mortality rates of 42.5 deaths/100,000 people, while New York State had the lowest average age adjusted AD mortality rates of 10.1 deaths/100,000 people between 1999 and 2014.

Growth rates of AD mortality rates between 1999 and 2014 were apparently higher in North and South Dakota, Washington, and California and a few Southeastern states (Fig. 1b). South Dakota had the highest AD mortality growth rate of 219% between 1999 and 2014 (i.e., more than doubled) while AD mortality rate in Maine was actually reduced by 32.4% during the same period (Fig. 1b). Isopleth map of soil sulfur concentration has the most significant inverse correlation with isopleth map of AD mortality rates (Pearson correlation $r = -0.34$, $p = 0.00$), followed by that of selenium ($r = -0.287$, $p = 0.00$) using ArcGIS's Band Collection Statistic Tool. Isopleth map of AD mortality growth rates (regression slope) has the most significant correlation with isopleth map of obesity (positive $r = 0.627$, $p = 0.00$), and correlates significantly and inversely with isopleth map of sulfur concentration as well ($r = -0.446$, $p = 0.00$).

Correlations of AD mortality rates with soil elemental concentrations

Among the 41 soil elements analyzed, state average concentrations of selenium have the most significant inverse correlation with state average AD mortality rates of all races ($r = -0.343$, and $p = 0.018$). Among the 41 elements, soil tin concentration has the most significant inverse correlation ($r = -0.364$, $p = 0.011$) with AD mortality growth rates of the 48 states between 1999 and 2014, followed by soil sulfur concentration ($r = -0.308$, $p = 0.033$). When AD mortality rates and the concentration products of selenium and sulfur were correlated instead of selenium concentration alone, the correlation coefficient increased from 0.308 to 0.404. Because of skewed distributions of selenium and sulfur soil concentrations in the 48 states, when the non-parametric Kendall's Tau-b correlations were compared, soil sulfur concentrations have the most significant inverse correlations with both AD mortality rates and AD mortality growth rates of the 48 states between 1999 and 2014 ($r = -0.245$, -0.255, $p = 0.014$, 0.01 respectively, Table 1). Significant positive correlation exists only between soil vanadium concentrations and AD mortality rates for Pearson correlations (Table 1).

Correlation of AD mortality rates with the four risk factors

Among the four risk factors, wine consumption per capita, percentages of current smokers, obesity, and diagnosed diabetes, only percentage of obesity has significant positive correlation with AD mortality rates. Diagnosed diabetes and percentage of current smokers have positive but statistically insignificant correlation with AD mortality rates. Wine consumption per capita has inverse but statistically significant correlation only when non-parametric correlations were analyzed.

Wine consumption per capita correlates inversely and significantly, and percentages of obesity, diabetes, and current smokers correlate positively and significantly with AD mortality growth rates of the 48 states between 1999 and 2014.

R^2 of multivariate regression models, unique contributions, and rate ratios

The multivariate linear regression model based solely on state average soil concentrations of sele-

Table 1
Correlations of AD mortality rates, AD mortality growth rates, and concentrations of soil elements, wine consumption, percentages of smokers, diagnosed diabetes, and obesity

MR\Elem	Se	Pb	S	Hg	Sn	V	Wine	Smoker	Diabetes	Obesity
P. corr.	–0.343	–0.315	–0.287	–0.275	–0.185	0.317	–0.231	0.267	0.101	0.308
Sig.	0.018	0.029	0.048	0.059	0.207	0.028	0.115	0.066	0.496	0.033
K. corr.	–0.123	–0.156	**–0.245**	–0.087	–0.09	0.108	–0.199	0.209	0.108	0.264
Sig.	0.222	0.12	**0.014**	0.384	0.369	0.282	0.046	0.037	0.282	0.008
MGR\Elem	Sn	S	Pb	Be	Ca	Mn	Wine	Smoker	Diabetes	Obesity
P. corr.	–0.364	–0.308	–0.256	–0.226	–0.221	0.234	–0.417	0.317	0.364	0.51
Sig.	0.011	0.033	0.079	0.123	0.131	0.11	0.003	0.028	0.011	0
K. corr.	–0.195	**–0.255**	–0.112	–0.195	–0.184	0.14	–0.304	0.241	0.261	0.385
Sig.	0.051	**0.01**	0.263	0.051	0.064	0.16	0.002	0.016	0.009	0

MR, mortality rates; MGR, mortality growth rates; Elem, element list; P. corr., Pearson's correlation coefficients between AD mortality rates and risk factors and concentration of soil elements; K. corr., Kendall's Tau-b correlation coefficients; Sig., significance level of correlation coefficient, is considered significant with 95% confidence when Sig. value is less than 0.05. If Bonferoni adjustment for multiple tests is used, critical significant p values will need to be $<<0.05$; Wine, wine consumption per capita; Smoker, percentage of current smokers in a state; Diabetes, percentage of diagnosed diabetes reported in a state; Obesity, percentage of obesity calculated based on BMI in a state. Bold element sulfur is the element whose soil concentration has the most significant non-parametric correlation with AD mortality rates and AD mortality growth rates. Only the top 5 elements whose soil concentrations have highest inverse correlations and one element whose concentration has the highest positive correlation with the AD mortality rates are shown.

nium and sulfur as predictors and AD mortality rates as dependent variable indicates that soil concentrations of two elements selenium and sulfur can explain 20.8% of spatial disparities of AD mortality rates between 1999 and 2014 ($R^2 = 0.208$) in the 48 states. Unique contributions of selenium and sulfur to the spatial disparity are 11.36% and 8.01%, respectively, based on their squared semi-partial correlations with AD mortality rates. Using state group #8 which has the highest average soil selenium concentration as the "control' and state group #1 which has the lowest average soil selenium concentration as the "case", rate ratios of state group #1 are 1.37 (95% confidence interval-CI95% 1.36, 1.37) for all races, 1.37 (CI95% 1.36, 1.38) for white and 1.38 (CI95% 1.37, 1.40) for non-Hispanic white, 1.38 (CI95% 1.36, 1.40) for male, and 1.37 (CI95% 1.36, 1.39) for female. In other words, average mortality rates of the 6 states with the lowest soil selenium concentrations is 37% higher than average mortality rates of the 6 states with the highest soil selenium concentrations for all races. Rate ratios of other groups to the "control" group #8 are between 1.05 and 1.39 (Fig. 3). When the 48 states were grouped by their products of state average soil selenium and sulfur concentrations, rate ratios of the 6 states ("case") with the lowest product of selenium and sulfur to the 6 states ("control") with the highest product of selenium and sulfur are 1.53 (CI95% 1.51 and 1.54) for all races, 1.55 (CI95%, 1.53, 1.56) for white, and 1.54 (CI95%, 1.53, 1.55) for non-Hispanic white, 1.51 (CI95% 1.49, 1.54) for male, and 1.50 (CI95%, 1.48, 1.52) for female.

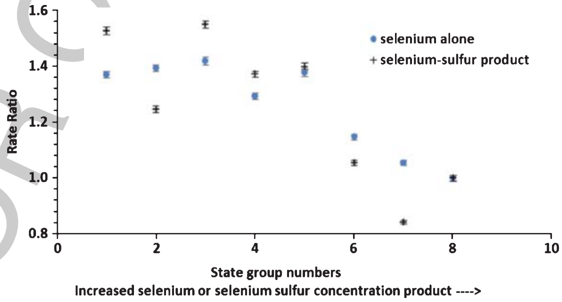

Fig. 3. Mortality rate ratios of the 48 states for all races versus soil selenium concentrations or product of soil selenium and sulfur concentrations. The 48 states were divided into 8 groups of 6 states each. Group #1 ("case") includes the 6 states that have the lowest soil selenium concentrations or selenium and sulfur concentration product while group #8 includes the 6 states that have the highest soil selenium concentrations or selenium and sulfur concentration product ("control"). 95% confidence intervals are shown by vertical bars.

When soil selenium and sulfur concentrations, wine consumption, percentage of current smokers, obesity, and diabetes were all used as predictors and AD mortality rates (all races) as dependent variable in the step-wise multivariate regression model, only selenium concentration and percentage of current smokers were left as predictors for the model with an R^2 of 0.209. Unique contributions of selenium concentrations and current smokers to the spatial variations of AD mortality rates are 13.62% and 9.18%, respectively. Moran's I indexes for spatial autocorrelations of residuals of this model and that of previous Se and S concentration model are 0. 093

($t = 1.041$, $p = 0.298$) and 0.157 ($t = 1.617$, $p = 0.106$), respectively, which imply an insignificant spatial autocorrelations of model residuals.

DISCUSSION

Results of significant correlations, multivariate regression models, and high rate ratios indicate important associations between spatial disparities of AD mortality rates and concentrations of selective soil elements and risk factors in the 48 states.

Factors associated with low AD mortality rates

Association of high soil selenium, sulfur, and tin concentrations with low AD mortality rates

The highest inverse correlations between AD mortality rates, AD mortality growth rates and soil selenium, sulfur and tin concentrations among the 41 elements analyzed in this study imply an association between high soil selenium, sulfur and tin concentrations and low AD mortality rates in a region.

Selenium is a major component of the glutathione peroxidase enzyme biologically, which removes peroxides, lipid hydroperoxides, and derivatives such as free radicals that are thought to impair cell membrane structure and function, promote atherosclerosis, and metabolically activate carcinogens [27–30]. Selenium has been considered to be important in the optimal brain functions and in impairing AD development by previous researchers [31–34]. Past studies of animal models have convincingly demonstrated the impact of selenium supplement on AD, although results of randomized controlled trials of impact of selenium on AD patients still need to be improved [33–41]. Increased rate ratios of AD mortalities in states with lower soil selenium concentrations (see above and Fig. 3) in this study support the beneficial effect of long-term exposure to high soil selenium on impairing AD development.

Though sulfur has not been widely analyzed in AD epidemiology studies, its antioxidant properties have been reported [42–44]. Several antioxidant mechanisms have been reported for sulfur, including scavenging of reactive oxygen species (such as superoxide, hydrogen peroxide, hydroxyl radical, peroxynitrite, and singlet oxygen) and metal binding [42, 45, 46]. Sulfur is a constituent of amino acids methionine, cysteine, and cystine and is supplied to humans mainly by the intake of methionine from plant and animal proteins [47]. Sulfur amino acid methionine controls the initiation of protein synthesis, and governs major metabolic and catalytic activities [47]. Sulfur amino acid deficiency has been found to depress brain glutathione concentration in animal models [48, 49]. Given that 90 to 98% of the sulfur in surface soils of temperate and humid regions is usually present in organic forms and sulfur is the 7th most abundant element measureable in human body, association of soil sulfur and AD may be more complicated than association of soil selenium and AD [47, 50].

Rate ratios of AD mortality for all races in the states of group #1 elevated from 1.37 to 1.53 when these states were changed from only low in soil selenium to low in both selenium and sulfur concentrations (Fig. 3). This 16% increase in rate ratios implies an increased risk when both soil selenium and sulfur concentrations are low and decreased risk when both soil selenium and sulfur concentrations are high. It may also imply a potential benefit for the traditional study of randomized selenium-AD-impact controlled trials if sulfur compound could be added in. Tin might be the third beneficial element associated with suppression of AD progress. Though the physiological mechanism of tin's association with suppression of AD progress was not reported before, tin compounds have been reported to be antioxidants and common reducing agents for conversions of nitro and oxime groups to amines [51–53]. Further study will be needed to verify this association given this is the first time that tin-AD relationship is reported.

Implication of the inverse correlations between state average mortality rates and soil concentrations of lead and mercury (Table 1) is not clear. Other studies have suggested binding of selenium to toxic metals such as mercury as one of the protection mechanisms of selenium in mitigating AD development [32, 54, 55]. Soil lead and mercury concentrations correlated more significantly with selenium concentrations ($r = 0.71$, 0.58 and $p = 0.00$, 0.00, respectively) than with AD mortality rates. High correlations between soil concentrations of selenium, lead, and mercury here might merely imply their similar soil environmental origin.

Wine consumption per capita and low AD mortality rates

Inverse correlations between wine consumption per capita and AD mortality rates and AD mortality growth rates between 1999 and 2014 imply that state average wine consumption per capita are associated with low AD mortality rates in a region. Previous studies have reported that moderate wine consumption, particularly red wines, are associated with better cognitive functions [57, 58].

Facilitators of high AD mortality rates

Among the 41 soil elements analyzed in the 48 states, only element vanadium has significant correlation with AD mortality rates of all races ($r = 0.317$, $p = 0.028$). Toxicity of vanadium has been reported before, but not extensively. Experimental results have shown that vanadium, as a transition metal element which occurs in various oxidative states, possesses the ability to produce reactive radicals, resulting in DNA damage, lipid peroxidation, depletion of protein sulfhydryls, and other effects [53]. This study is the first work that reports the association of AD mortality rates and high soil vanadium concentrations in a region.

For the four risk factors, percentage of obesity is the only factor that correlates significantly with AD mortality rates. Despite a close relationship between obesity and diabetes, percentage of diagnosed diabetes has positive but insignificant correlation with AD mortality rates. Though multiple population-based studies have shown that people with obesity and diabetes exhibit an increased risk of developing AD [59–62], recent research articles on autopsies of AD patients also reported non-associations between AD and diabetes [63, 64]. However, both obesity and diagnosed diabetes have significant correlations with AD mortality growth rates between 1999 and 2014 in this study.

Percentage of current smokers correlates marginally with AD mortality rates, but correlates significantly with AD mortality growth rates in this study. Previous studies of AD and smoking relation have been inconsistent with cross-sectional studies reporting an acceleration of AD development and case-control study reporting an impairment of AD development [65, 66].

Effect of population migration and food transport on association of trace elements and AD mortality rates

According to an estimation in a recent study, at least 80% of food supplies in the US could have come from within a 50-mile food-shed radius for most US inhabitants in 2000 [25]. However, for states with large cities such as New York and other northeastern coastal states, their proportion of food reliance on regions of 50-mile radius, which is considered local, can be significantly small. For example, New York City could supply only 10% of its food from the 50-mile-radius region and the result is that New York State could only supply about 31% to 34% of its food need [25, 56]. Nationally, 58.8% of the total population and roughly 50% of population aged 55 and older resided in the state they were born according to 2010 US census survey [26]. However, proportions of migrant populations in some states were much higher than others. For example, Florida and Washington have only 35.2% and 46.9%, while Louisiana and Michigan have 78.8% and 76.6% of their total population surveyed in 2010 born in-state, respectively [26]. States with large proportions of their population born out of state and a large proportion of their food supply from a faraway region significantly, in author's opinion, lowered the correlation and regression R^2 of AD mortality rates and soil concentrations of selenium and sulfur in the 48 states. Removal of these outlier states, hence, can improve the significance of correlations between AD mortality rates and soil selenium and sulfur concentrations (Fig. 4).

Limitation of the study

One weakness of the current study is that many confounding factors such as hypertension, intake levels of antioxidants, comorbidities, etc., can also affect the spatial disparities of AD mortality rates of a region [4]. Current results were obtained from statistics of large datasets based upon averaged state values. Responses of an individual or a small group to the long-term exposure to selenium, sulfur, and risk factors can deviate significantly from the average responses of a large group, which is a common fallacy in ecological studies [67]. There might also

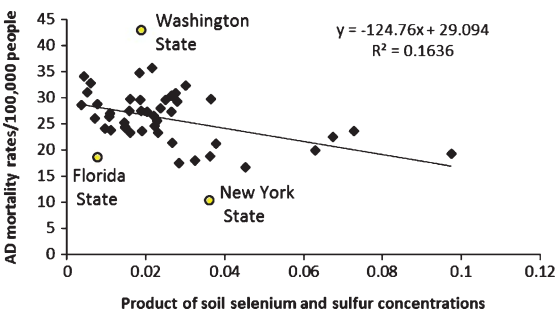

Fig. 4. Regression plot of state average AD mortality rates/100,000 people versus product of state average soil selenium and sulfur concentration. Note the three outliers, Florida, Washington, and New York, are shown in round markers. Removal of the three outlier states improved the regression R^2 from 0.1636 to 0.2342.

be a significant proportion of AD misdiagnoses in death certificates in the US [68]. Population migration and food transportation over long-distance could also distort the conclusions. Another weakness is that AD mortality rates instead of AD incidence or prevalence rates were used. AD mortality rates might be influenced more by social economic conditions than AD incidences. In addition, one also needs to be caution about the potential toxicity of high soil selenium concentration [69]. Given the promising potentials implicated by association of soil selenium, sulfur, and tin concentrations with low AD mortality rates, particularly by sulfur concentrations in this study, future randomized controlled trials may also need to examine whether addition of sulfur compounds could improve the result of traditional selenium-AD-impact studies.

Conclusions

Among the 41 elements analyzed, soil selenium concentrations have the most significant inverse correlation with AD mortality rates of the 48 states. Soil tin concentrations have the most significant inverse correlation with AD mortality growth rates of the 48 states between 1999 and 2014, followed by sulfur concentrations. When non-parametric correlations were calculated, soil sulfur concentrations have the most significant inverse correlation with both AD mortality rates and AD mortality growth rates of the 48 states. Multivariate linear regression models indicate that soil selenium and sulfur concentrations can explain 20.8% of the spatial variations of AD mortality rates in the 48 states. Rate ratio of top 6 (half quarter) of the 48 states with the lowest product of selenium and sulfur concentrations is 53% higher than the bottom 6 states with the highest product of soil selenium and sulfur concentrations (RR 1.53, CI95% 1.51 and 1.54). Soil sulfur and selenium concentrations can be a broad indicator of their elemental intakes from food, water, and air by people in a region. Given the significant association of soil selenium and sulfur concentrations with AD mortality rates shown in this study, it might be worth to examine whether addition of sulfur compound can improve the effect of selenium on AD development in future randomized controlled trials. This study also supports the association of low AD mortality rates and moderate wine consumption, and the association of high AD mortality rates and high percentage of obesity and smoking in a region.

DISCLOSURE STATEMENT

The author's disclosure is available online (http://j-alz.com/manuscript-disclosures/17-0059r3).

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