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Association of soil selenium, strontium, and magnesium concentrations with Parkinson's disease mortality rates in the United States

Hongbing Sun

Center for Healthcare Studies, GEMS Department, Rider University, New Jersey

email:hsun@rider.edu

ABSTRACT

Among the 41 soil elements analyzed from 4856 sites across the contiguous 48 states, average Parkinson's Disease (PD) mortality rates between 1999 and 2014 has the most significant positive correlation with the average soil strontium (Sr) concentrations (correlation r= 0.47, significance level p =0.00), and average PD mortality rates has the most significant inverse correlation with the average soil selenium (Se) concentrations (r= - 0.44, p =0.00). Multivariate regression models indicate that soil Sr and Se concentrations can explain 35.4% of spatial disparities of the state average PD mortality rates between 1999 and 2014 (R^2 = 0.354). When the five outlier states were removed from the model, concentrations of soil Sr and Se can explain 62.4% (R^2 =0.624) of the spatial disparities of PD mortality rates of the 43 remaining states. The results also indicate that high soil magnesium (Mg) concentrations suppressed the growth rate of the PD mortality rates between 1999 and 2014 in the 48 states (r=-0.42, p=0.000). While both Se and Sr have been reported to affect the nervous system, this study is the first study that reported the statistically significant association between the PD mortality rates and soil concentrations of Se, Sr and Mg in the 48 states. Given that soil elemental concentration in a region is a broad indicator of the trace element intake from food, water and

air by people, implications of the results are that high soil Se and Mg concentrations helped reduce the PD mortality rates and benefited the PD patients in the 48 states.

Keywords: Selenium, magnesium, strontium, Parkinson's disease, mortality rate

1. Introduction

Parkinson's disease (PD) is the 14th leading underlying cause of death in the US with an average annual death of 21,063 between 1999 and 2014 according to the US Center for Diseases Control and Prevention (CDC)'s database and reports (Kenneth et al. 2011; Xu et al. 2013). Exposures to high concentrations of zinc (Zn), lead (Pb), mercury (Hg), and manganese (Mn) have been reported to increase the risk of PD in an area and in certain occupations such as farming, mining, and welding (Bellou et al. 2016; Elbaz and Tranchant 2007; Kieburtz and Wunderle 2013; Lai et al. 2002; McCormack et al. 2002; Weisskopf et al. 2010). Previous studies also suggested that life styles such as consumption of coffee, number of cigarettes smoked, and moderate exercise can reduce the incidences of PD (De Lau and Breteler 2006; Dick et al. 2007; Priyadarshi et al. 2001). However, causes of spatial disparities of PD mortality rates in the US have not been studied and reasons for the relatively high PD mortality rates in the western states are also not understood.

Hence, this study intends to examine whether the underlying soil elemental concentrations in a region are associated with the spatial disparity of PD mortality rates, and if so, to identify the soil elements that are associated with the high and low PD mortality rates in the 48 states. It has been long accepted that soil elemental concentration can be a broad indicator of the trace element intakes from food, water and air by people in a region (Abrahams 2002; Kabata-Pendias and Mukherjee 2007; Oliver 1997). Certain elements such as calcium (Ca), magnesium (Mg), and selenium (Se) are very important in health and excess or deficiency of these elements can exerts a tremendous influence on all body functions (Prashanth et al. 2015).

PD mortality rates are used in this study, instead of the incidence and prevalence rates, because PD mortality rates are available for the general population in the 48 states while PD incidences and prevalence rates are only available for limited subpopulation groups.

2. Method

2.1. Data collection

The PD mortality rates between 1999 and 2014 were obtained from the CDC's WONDER database (http://wonder.cdc.gov) using the code G20 following the Tenth Revision of the International Classification of Diseases. Average annual PD mortality rates were aggregated by state. Mortality rates in the CDC database were from the death certificates of 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 various populations to a single standard population (Anderson and Rosenberg 1998). US populations of 2007 corresponding to the required gender and race were selected as standard populations to calculate the average annual PD mortality rates of the respective gender and race between 1999 and 2014 for this study.

Concentrations of 41 elements in the top 5 cm of soil from 4856 sites were obtained from a US Geological Survey (USGS)'s report (Smith et al. 2014). USGS soil samples were collected between 2007 and 2010 and chemical and mineralogical analyses were completed in 2013. The selection of 41 out of the 44 elements (See footnote of Table 1 for the list of elements) from the USGS database in this paper is because three of the 44 elements in the database (Ag, Cs and Te) have concentrations less than their respective detection limits in more than 2/3 of the soil sample sites. The top 5 cm of soil is a section of a soil profile with which people most often come into contact during their daily activities. It is also the soil section that has the most effect on the elemental concentrations of the water and food that people consume. Mineral weight percentage data analyzed were from the "soil A horizon" in the same USGS report (Smith et al. 2014). Soil A horizon, also known as the topsoil, is a soil mineral horizon formed at the ground surface or under the surface organic litter layer (Brady and Weil 2007). It is this mineral layer that directly controls the soil elemental concentrations of the top 5 cm (1.97 inches) of soil that were used in this study. All the 4856 soil sites sampled by the USGS were at least 200 meters away from a highway, 50 meters away from a rural road, and 100 meters away from a building or structure and 5 kilometers away from the downwind direction of major industrial activities to minimize the local anthropogenic pollutions in soil (Smith et al. 2014).

2.2. Statistical analysis

2.2.1 Spatial correlation of isopleth maps

An isopleth map of the average PD mortality rates of the 48 contiguous states between 1999 and 2014 was plotted using the inverse distance weighted (IDW) interpolation method to reduce the effect of a sharp state boundary for spatial analysis. Examination of the isopleth map allows both a quick visual and a statistical comparison of the spatial patterns between PD mortality rates, soil elemental concentrations, and mineralogical sources of soil elements.

Isopleth maps of concentrations of the two elements Sr and Se in the top 5 cm of soil, and an isopleth map of total feldspars were plotted as well. Selection of total mineral feldspars is because they are the primary mineral sources of alkaline earth (Sr, Ca, Mg, Ba) and alkali metals (Na, K) and aluminum (Al). Pearson correlation coefficients were calculated between the pairs of isopleth maps of the state average PD mortality rates, state average elemental concentrations, and feldspar weight percentage. State average elemental concentrations being used in the correlation calculations were to match the data type of the PD mortality rates grouped by states.

Aggregated state average data allows the study to reduce the noise effect of the local variations, overcome the data discontinuity of the PD mortality rates at county levels, and extract the major meaningful relationships between the PD mortality rates and soil elemental concentrations in the 48 states. Pearson correlations of isopleth maps were calculated using the Band Collection Statistics tool in ArcGIS (ESRI software).

2.2.2. Correlations between PD mortality rates and soil elemental concentrations and multivariate regression models

Pearson correlation coefficients and their significance levels were calculated for the state average PD mortality rates between 1999 and 2014 and the state average elemental concentrations of the top 5 cm of soil and feldspar weight percentage of the topsoil of the 48 states. Because the skewness of concentrations of some elements (Bi, W, Ni, Cr, Sb, Hg, S, Mo, Ti, Pb, Cu, Ca, As, V, Sc, Sn, Co, Sr, Fe, Mg, U, and Na) in the top 5 cm of soil are larger than the two standard errors of their skewness, the nonparametric Kendall's Tau-b correlation coefficients were calculated as well to corroborate the significance levels of the Pearson correlation coefficients.

For the step-wise multivariate linear regression models, PD mortality rates of the 48 states were used as the dependent variable, soil concentrations of Al, Ba, Ca, Hg, K, Mg, Na, Se and Sr were used as predictors because of their significant correlations with the PD mortality rates (see result section for details). The correlation coefficients and regression models were all calculated using SPSS software.

2.2.3. Correlation between growth rates of PD mortality rates and soil elemental concentrations

Slopes of the regression lines of the PD mortality rates of the 48 states vs. years were calculated between 1999 and 2014. Regression slope of the PD mortality rates between 1999 and 2014 reflects the growth or decrease rate of the PD mortality rates during this period. Correlations between the growth rate of each state and concentrations of the 41 elements were calculated. Isopleth maps of the growth rate (regression slopes) and magnesium/aluminum (Mg/Al) ratios of the 48 states were plotted and the correlation between the two isopleth maps was calculated as well.

3. Results

315,951 deaths were attributed to PD as the underlying cause of death in the 48 contiguous states in the CDC database between 1999 and 2014. Of the 315,951 deaths, 298,774 were reported among whites, 132,453 were reported among female, and 183,218 were reported among male. District of Columbia (DC) was excluded from the statistics of the 48 states because DC's data were suppressed in multiple years in the CDC database. White constitutes 94.6% of the total mortalities reported in the 48 states during this period and the age-adjusted PD mortality rate of male is 1.38 times that of female.

3.1. Spatial similarity between isopleth maps of PD mortality rates and soil elemental distribution

PD mortality rates are apparently higher in the western US than in the eastern US (Figure 1a). Utah has the highest average age adjusted PD mortality rates of 9.6 deaths/100,000 people, while New York (State) has the lowest average age adjusted PD mortality rates of 4.2 deaths/100,000 people between 1999 and 2014. The western regions are dominated by the Aridisol (soil formed in the arid region) with relatively high feldspar content and high Sr and low Se soil concentrations (Figure 1a, c, d). Spatial correlations (r) between isopleth maps of PD mortality rates and Sr, Se, Hg, and feldspars are 0.60, -0.41,-0.28 and 0.62 respectively with significance levels p=0.00 for all.

Growth rates of PD mortality rates in the Isopleth map is apparently higher in the eastern US than in western US (Figure 1b). Nebraska has the highest PD mortality growth rate of 29.4% between 1999 and 2014 while Washington has the lowest PD mortality growth rate of 7% during this period (Figure 1b). Increase of the average PD mortality rates of the US over time (Figure 2a) was reported to be primarily related to the increased average life expectancy (Kieburtz and Wunderle 2013; Priyadarshi et al. 2001). Isopleth maps of growth rates of PD mortality rates (regression slope) between 1999 and 2014 correlate significantly and inversely with that of the soil concentration ratios of Mg/Al (r=-0.66, p=0.00) (Figure 1f).

3.2. Correlations of PD mortality rates and soil elemental concentrations

State average PD mortality rates have the most significant positive correlations with state average concentrations of four alkaline earth metals Sr, Ca, Mg and Ba (r=0.47, 0.46, 0.44, 0.36 and p=0.00, 0.00, 0.00, 0.01 respectively), two alkali metals Na and K (r=0.35, 0.33 and p=0.02,0.02) and Al (r=0.32, p=0.03) in the top 5 cm of soil (listed in a decreasing order of significance levels) (Table 1). Average soil Sr concentration also correlates significantly with the concentrations of Ba, Ca, Mg, Na, K, and Al (r=0.80, 0.79, 0.84, 0.88, 0.67, and 0.79 respectively, and all p=0.00), and the weight percentage of feldspar (r=0.84, p=0.00). The four alkaline and two alkali metals and Al are the main elemental compositions of calcium carbonate ($CaCO_3$) and feldspars ($NaAlSi_3O_8$ –$CaAl_2Si_2O_8$).

State average PD mortality rates have the most significant inverse (negative) correlations with state average concentration of Se (r=-0.44, p=0.0) and Hg (r=-0.39, p=0.01) in the top 5 cm of soil. Average soil Se concentration correlate significantly with that of Hg and Pb as well (r=0.71, 0.58 and both p=0.00).

Only marginal positive correlations exist between the PD mortality rates and concentrations of Cu, Fe, Zn, and Mn in the top 5 cm of soil. These metals have been reported to be associated with high incidences of PD for subpopulation groups in previous studies (Gorell et al. 1999; Willis et al. 2010; Wirdefeldt et al. 2011).

Among the 44 elements analyzed for the top 5 cm of soil in Table 1, Mg has the most significant inverse (negative) correlation (r=-0.42, p=0.00) with the growth rates of PD mortality rates of the 48 states. The most significant positive correlation is between the uranium (U) concentrations and the PD mortality growth rates (r=0.32, p=0.03). Correlations between the growth rates of PD mortality rates and the Mg/Al and Mg/U concentration ratios are very significant as well (r=-0.48 and -0.58 respectively and both p=0.00).

3.3. Multivariate linear regression models

For the step-wise multivariate linear regression model with PD mortality rates as dependent variable, concentrations of Al, Ba, Ca, Hg, K, Mg and Na were excluded from the predictors because of their collinearities and only concentrations of Sr and Se were left as the predictors by the model. Concentrations of these two elements alone can explain 35.4% of spatial disparities of the state average PD mortality rates between 1999 and 2014 in the 48 states based on the R^2 (0.354) of the model. The unique contributions of Sr and Se to the spatial disparity from the regression model are 16.2% and 13.9% respectively based on their squared semi-partial correlations.

When the five outlier states (large states Nevada, California, New York, Pennsylvania, and a small state Delaware) were removed from the model, concentrations of these two elements Sr and Se can explain 62.4% (R^2 =0.624) of the spatial variations of PD mortality rates for the 43 remaining states (Figure 2b). Three large states CA, NY, and PA were the outliers in the regression model likely because of the significant racial variations in their populations and the large heterogeneities in the underlying soil geology of these states. DE as an outlier is likely because of the limited soil samples (only 2 samples) and a small population base. NV, another outlier as well, has the highest average Sr concentration in the top 5 cm of soil among the 48 contiguous states (351.32 mg/kg). In addition, pockets of high Sr concentrations (Figure 1c) in

NV may be related to ^{90}Sr introduced during the atmospheric nuclear weapons testing in the 1950s and 1960s (DHHS 2001; Simon et al. 2004).

4. Discussion

Results of the above correlations and multivariate regression models indicate a significant association between concentrations of soil elements and spatial disparity of the PD mortality rates in the 48 states.

4.1. Soil elements as facilitators of high PD mortality rates

Among the 48 soil elements analyzed from the 4856 sites across the US, elements in the top 5 cm of soil that have significant positive correlations with the PD mortality rates are the four alkaline earth metals (Ca, Sr, Mg, Ba), two alkali metals (Na, K), and Al (Table 1). The three elements among them that have been suspected of causing neural damage are Sr, Ba, and Al (Cordeiro et al. 2011; Bondy 2016). Sr^{2+} has been reported to change nerve signaling pathways by inhibiting the vesicular Ca^{2+}/H^{+} antiport and "activate transmitter release at concentrations one order of magnitude higher than Ca^{2+} does" (Cordeiro et al. 2011). Barium (Ba) has been associated with multiple sclerosis and other neurodegenerative disease, including the PD (Purdey 2004). Aluminum (Al) exposure has been reported to cause excess inflammatory activity within the brain in studies of Alzheimer's disease (Bondy 2016;).

It is difficult to speculate which element (or elements) is the main "culprit" behind the high PD mortality rates in the western US based simply on the correlation coefficients. In addition to the suspected neural damages from the three elements reported, there are also the relatively significant R^2 values in multivariate prediction models of the PD mortality rates based solely on Sr and Se concentrations in the top 5 cm of soil discussed above. Given the high degree of multicollinearity among the concentrations of Sr, Ba, and Al in the regression models, the author suspects that at least one of the three metals is likely to be associated with the high PD mortality rates.

Among the 41 soil elements, the only soil element that has a significant positive correlation with the growth rate of the PD mortality rates is uranium (U) (Table 2). Though it is not clear how U acts on the nervous system, U exposure has been linked to the increased incidences of lung cancers among the U miners in previous studies (Archer et al. 1973, Boffetta et al. 1998).

Differences between correlations of concentrations of soil elements and the PD mortality rates and the PD mortality growth rates in the 48 states (Table 1) are because states with high PD mortality rates are not the states with high PD mortality growth rates (Figure 1a,b).

4.2. Benefits of soil Se and Mg to PD patients

Among the 41 soil elements analyzed, state average concentrations of Se in the top 5 cm of soil has the most significant inverse correlation with the state average PD mortality rates ($r=-0.44$, $p=0.00$), followed by Hg ($r=-0.39$, $p=0.01$). Selenium (Se) has been broadly recognized an essential "antioxidant" trace element and has been reported to play an important role in the maintenance of optimal brain functions (Cardoso et al. 2015; Qureshi et al. 2006). Selenium is not an actual antioxidant itself but is as an integral component of selenoproteins (Steinbrenner et al. 2016). Decreased expression of several selenoproteins is associated with the pathologies of a few age-associated neurodisorders, including Parkinson's disease, Alzheimer's disease, and epilepsy (Chen and Berry 2003; Zhang et al. 2010; Zafar et al. 2013).

Magnesium (Mg) is the element among the 41 elements in the top 5 cm of soil analyzed that has the most significant inverse(negative) correlation with growth rates of the PD mortality rates between 1999 and 2014 (Table 2). The significant inverse correlation between growth rates of the PD mortality rates and Mg concentrations implies that high Mg concentrations in topsoil of a region may suppress growth rates of the PD mortality rates of that region. Recent studies based on the laboratory rat experiments reported that Mg deficit can result in loss of dopaminergic neurons and sufficient Mg supply can exert ameliorating effects in dopaminergic neurons involving the 1-methyl-4–phenylpyridinium toxicity (Hashimoto 2008; Hashimotot et al.. 2007; Oyanagi 2005; Shindo et al. 2015, 2016, Taniguchi et al., 2013). The results of this study, with human PD mortality data for the first time, support these findings of the beneficial effects of Se and Mg on PD.

Implication of the significant inverse correlation ($r=-0.39$, $p=0.01$) between the state average mortality rates and state average concentrations of soil Hg is not clear, though soil Hg concentrations are also significantly correlated with that of Se ($r=0.71$, $p=0.00$). If PD has a mold related initiation as suggested in a recent study (Inamdar et al. 2013), one possible explanation would be that accumulation of Hg in soil can act as a fungicide through its more toxic form of methylmercury (Barrett 2010; Wiener et al. 2003) and depress the long-term PD mortality rates of a region.

4.3. Limitations of the study

One weakness of the current study is that other confounding factors such as smoking, obesity, pesticide, population mobility and comorbidities can also affect the PD mortality rates of a region (Bellous et al. 2016). Another weakness is that PD mortality rates instead of PD incidence or prevalence rates were used. PD mortality rates might be influenced more by the social economic conditions than the PD incidences (Willis et al. 2010). In addition, associations between the elemental concentrations and the PD mortality rates are based mainly on the spatial correlations. However, given the significant benefit of Se and Mg to PD patients implicated in this study, researches using more sophisticated case-control designs are needed to substantiate the current results.

5. Conclusions

Results of this study indicate that there is a significant association between the spatial disparity of PD mortality rates and soil elemental concentrations, particularly concentrations of Sr and Se in the 48 US states. High PD mortality rates in the western states correlate with high soil concentrations of Sr, Ba, and Al. Regions of high soil Se concentration correlate to regions of low PD mortality rates. Regions of high soil Mg concentrations correlate to regions of low PD mortality growth rates. Multivariate linear regression models based solely on soil Sr and Se concentrations can explain 35.4% of the PD spatial mortality rates in the 48 US states. When the five outlier states (NV, NY, CA, PA, and DE) were removed, soil Sr and Se concentrations can explain 62.4% of the spatial variations of PD mortality rates in the remaining 43 states. Given that soil elemental concentration is a broad indicator of the element intake from food and water by people in a region, association of high soil Se and Mg concentrations with the low PD mortality indicates that Se and Mg may be beneficial to PD patients in the 48 states.

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Table 1. List of elements whose soil concentrations have significant correlations with PD mortality rates and PD mortality growth rates between 1999 and 2014

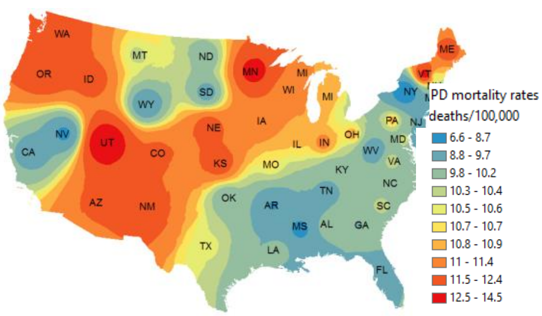
List of elements that have significant correlation with PD mortality rates											
Elements	Sr	Ca	Mg	Ba	Na	S	K	Al	Cu	*Hg*	*Se*
Correl.	0.47	0.46	0.44	0.36	0.35	0.34	0.33	0.32	0.28	-0.39	-0.44
Sig.	0	0	0	0.01	0.02	0.02	0.02	0.03	0.05	0.01	0

List of elements that have significant correlation with PD mortality growth rates									
Elements	U	*Sc*	*Fe*	*V*	*Sr*	*Ca*	*Na*	*Mg*	
Correl.	0.32	-0.28	-0.29	-0.29	-0.32	-0.32	-0.34	-0.42	
Sig.	0.03	0.05	0.05	0.04	0.03	0.03	0.02	0	

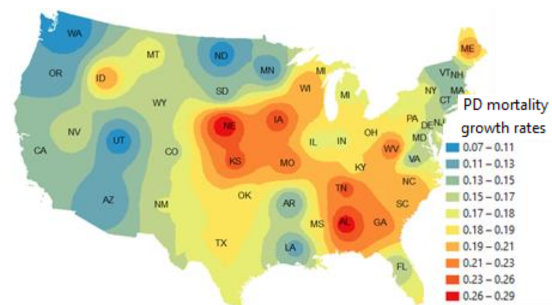
Note: Elements: Element name; Correl.: Pearson correlation coefficient, Sig.: Significance level (two tailed). Highlighted yellow cells indicate concentrations of the corresponding elements having significant correlations in both Pearson and Kendall's Tau-b tests (Sig. value <0.05). Elements are arranged in a decreasing order of correlation coefficients. Italic elements are the elements that have inverse correlation with PD mortality rates or PD mortality growth rates. The 41 elements analyzed are Al, As, Ba, Be, Bi, Ca, Cd, Ce, Co, Cr, Cu, Fe, Ga, Hg, In, K, La, Li, Mg, Mn, Mo, Na, Nb, Ni, P, Pb, Rb, S, Sb, Sc, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Y, and Zn.

Figure 1. a), Isopleth maps of the average PD mortality rates and b), growth rates of the PD mortality rates between 1999 and 2014, c), weight percent of feldspars in soil A horizon, d), Se and e), Sr concentrations in the top 5 cm of soil , e), Mg/Al concentration ratios in the top 5 cm of soil of the 48 contiguous states. Fine dots in maps c)-e) are locations of soil sample sites.

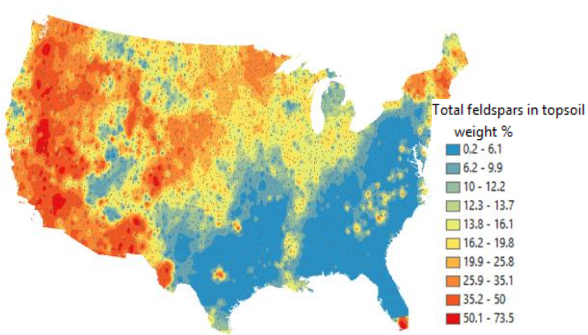
a). PD mortality rates



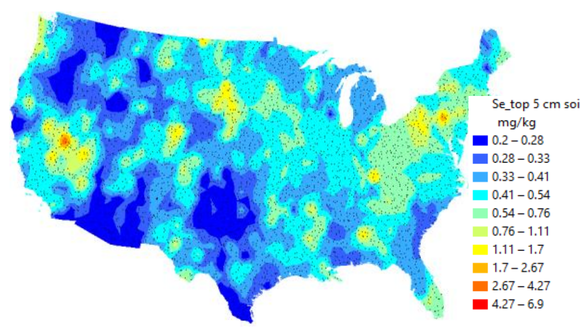
b). Grown rates of PD mortality rates



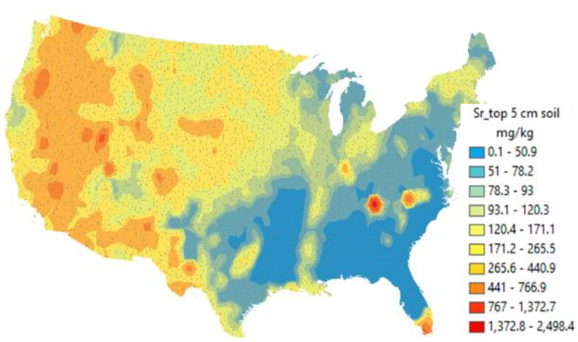
c). Feldspars in soil A horizon



d). Se concentrations in top 5cm of soil



e). Sr concentrations in top 5cm of soil



f). Mg/Al concentration ratios in top 5 cm of soil

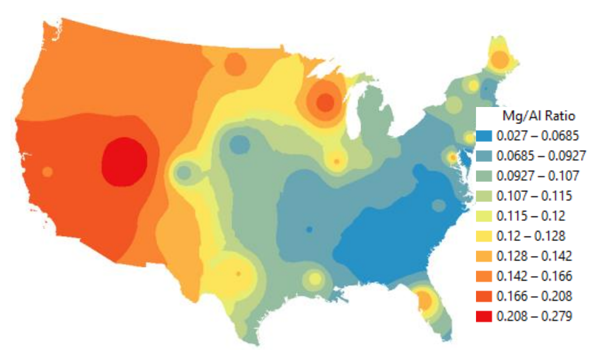
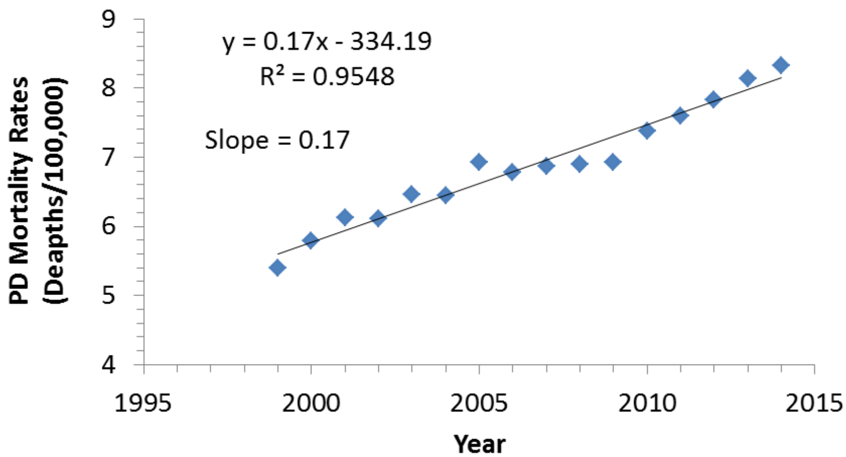


Figure 2. a). Regression plot of average PD mortality rates (deaths/100,000 people) of the 48 states between 1999 and 2014. Note slope (growth rate) of the regression line can be obtained from the plot. b). Predicted vs. observed state average PD mortality rates (deaths/100,000 people) between 1999 and 2014. R^2 of multivariate model (PD mortality rates as dependent, and soil Sr and Se concentrations as predictors) is 0.354. Adjusted R^2 of the multivariate model improved to 0.624 when the five outlier states NV, NY, CA, PA, and DE were removed.

a).



b).