A Correlation Study on Soil Selenium Content and Diabetes Mellitus in Contiguous United States

Yang-Chih Tsao

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A Correlation Study on Soil Selenium Content and Diabetes Mellitus in Contiguous United States

By

Yang-Chih Tsao

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2017
A Correlation Study on Soil Selenium Content and Diabetes Mellitus in Contiguous United States

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Selenium, the essential trace element, is well known as its antioxidant function, antiviral properties, and its anti-inflammatory function to human health. The relationships between selenium status and diabetes mellitus have been widely studied, but the consistency of results is lacking. This study used diagnosed diabetes incidence from year 2004 to 2012 and soil selenium content by counties within 48 contiguous states in the U.S. with Generalized Linear Mixed Model- R-Side as the major statistical method to determine whether there is a significant correlation or not. Results showed that the diagnosed diabetes population had been increased from 2004 to 2012 for all 48 states. The South region showed the highest increased rate whereas the Northeast region showed the least. Also, Kentucky, Louisiana, Maryland, and Massachusetts are the four states showed the significant correlation between soil selenium content and diabetes incidence. However, improved analytical methods and data are needed for further research.
DEDICATION

To my parents, Yen-Chien Tsao and Ching-Hui Yu, my grandmother, and all my beloved families who have been there for me from the day one. Thank you for all of the love, support, encouragement, and dedication.
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CHAPTER I
INTRODUCTION

According to World Health Organization, the number of people worldwide with diabetes has risen from 108 million since 1980 to 422 million in 2014. The global prevalence of diabetes among adults age 18 and above has risen from 4.7 percent to 8.5 percent from 1980 to 2014 (1). Diabetes is also being projected that it will be the 7th leading cause of death in 2030 (2). Nationally, diabetes affected 29.1 million Americans in 2012. In 2012, approximately 21 million people were diagnosed in the United States with diabetes while an additional 8.1 million had the disease but were not diagnosed (3).

Diabetes, or often referred to as Diabetes Mellitus, is a group of metabolic diseases in which is characterized by hyperglycemia, or high level of blood glucose, resulting from defects in insulin secretion, insulin action, or both (4). The disease is classified as Type 1, Type 2, or Gestational Diabetes Mellitus. Type 1 Diabetes Mellitus, previously referred to as “insulin-dependent diabetes,” accounts for only 5-10 percent persons of with diabetes. Type 2 Diabetes Mellitus, or previously referred to as “non-insulin-dependent diabetes,” accounts for up to 95 percent of diagnosed cases and is associated with insulin resistance within the muscle, liver, and adipose cells. Gestational Diabetes Mellitus is a form of glucose intolerance during the pregnancy. Additionally, there are other types of diabetes such as, specific genetic defects and diseases caused diabetes as well (4,5).
Although the causes of Diabetes Mellitus are incompletely understood, it has been widely accepted that both environmental and genetic factors play an important role. The environmental factors are described as availability of food, body weight and fat distribution, physical inactivity, viral infection, and stress level (6,7). Gender, age, family history, and ethnicity also have a marked influence type 2 diabetes, in particular (7,8). Nearly 90 percent of persons with type 2 diabetes’ have insulin resistance, and the elevated levels of metabolic substrates contribute to the diabetes phenotype (8). Glucotoxicity, lipotoxicity, inflammation, and oxidative stress are linked to insulin resistance and further to other metabolic diseases later in life (8-11).

Oxidative stress may result in elevated free fatty acid levels, and it is positively correlated with both insulin resistance and beta-cell dysfunction (8). It can be defined as a state of imbalance between antioxidant defenses and the production of highly reactive molecular species, which leads to tissue damage (12). Oxidative stress results from both increased content of reactive nitrogen species and reactive oxygen species, and the formation of reactive oxygen species directly affect hyperglycemia; on the other hand, high levels of free fatty acid also result in reactive oxygen species formation (12). Evans et al. proposed that elevations in glucose and free fatty acid levels contribute to the generation of reactive oxygen species and oxidative stress, which play a key role in causing insulin resistance and beta-cell dysfunction depends on the ability to activate stress-sensitive signaling pathways (8).

Selenium (Se), the essential trace element, is well known as its antioxidant function, antiviral properties, and its anti-inflammatory function to human health. There are twenty-five selenoproteins that functions as a part of selenium in human (30). The
contents of selenium in food vary according to the soluble of selenium in soil and the capacity of plants to take in. Thus, crops are ideal indicator to show geographic patterns of variation in selenium content locally (26). As a dietary antioxidant, selenium has been widely studied for its relationship with chronic diseases, such as, thyroid disorders, cardiovascular disease, cancer prevention, and diabetes mellitus. However, the specific function of several selenoproteins remains unknown (30). Selenium is linked to a large variety of human health disorders both directly and indirectly, but the consistency of results are still lacking.

This study used diagnosed diabetes incidence from year 2004 to 2012 and soil selenium content by counties in 48 contiguous states in the U.S. with Generalized Linear Mixed Model- R-Side as the major statistical method. Altitude and longitude, average household income, median age, and the gender ratio were also taken into considerations as other cofactors. The objective of this study was to determine if there is a significant correlation between soil selenium content and the incidence of diabetes among 48 contiguous states in the United States.
CHAPTER II
REVIEW OF LITERATURE

Prevalence of Diabetes

Global Prevalence

The number of people with diabetes is rising among the world. In 2016, World Health Organization issued a call for action on diabetes. The number of adults living with diabetes has almost quadrupled since 1980 to 422 million (1). The prevalence of diabetes among adults above age 18 has risen from 4.7 percent in 1980 to 8.5 percent in 2014, and it is estimated to be 4.4 percent in 2030 for all age-groups worldwide (1,14). It is also being projected as the 7th leading cause of death in 2030 (2). The dramatic increase is due to the rise of population growth, the change of living style, and the increase in obesity and overweight population (14). By 2030, it is estimated that the number of people with diabetes will be more than 82 million in persons aged 64 and older in developing countries and more than 48 million in developed countries. Middle Easter Crescent, sub-Saharan African, and India are estimated to have the greatest increases in diabetes population solely based upon the demographic change (14). In 2012 alone, 1.5 million deaths were caused directly by diabetes mellitus, and diabetes prevalence has risen faster in low- and middle-income countries over the past four decades (1).
National Prevalence

The economic and health burdens associated with diabetes mellitus have been widely addressed and are major public health concerns worldwide. Based on the National Diabetes Statistics Report, in year 2012, there were approximately 21 million American were diagnosed with diabetes, along with 8.1 million with undiagnosed diabetes (3). Also, there were 28.9 million adults with diabetes aged 20 and older amounted to 12.3 percent of the entire U.S. population (3). Most of the states in the South and East Coast are high in prevalence, and there is a dramatic increase in the prevalence of diabetes mellitus when comparing the trend in 2004 and 2012 (Figure 2.1 and 2.2).

![Figure 2.1 Prevalence of Diagnosed Diabetes Among US Adults, 2004](image)

Source: Centers for Disease Control and Prevention, 2016
The differences between age, gender, and ethnicity dominate the likelihood of developing diabetes mellitus. Among all the diabetes cases, there are approximately 11.2 million people with age 65 and older living with diabetes, which accounts for approximately 25.9 percent of the total population in the U.S. and just over one-fourth of the senior citizen population (3). Additionally, among the U.S. population over the age of 20 years, diabetes is more prevalent in the men with 15.5 million males having the disease compared to 13.4 million females. That is equivalent to 13.6 percent of the male population and 11.2 percent of the females have diabetes mellitus in the United States (3).
Ethnic differences in prevalence of type 2 diabetes are widely studied. A national survey from year 2010 to 2012 reported that 15.6 percent of American Indians/Alaska Natives, 13.2 percent of non-Hispanic black, 12.8 percent of Hispanic, 9.0 percent of Asian American, and 7.6 percent of non-Hispanic whites were diagnosed with diabetes mellitus (3). A 20-year follow up prospective cohort study by Shai et al. indicated that the risk of diabetes among females is significantly higher in Asians, Hispanics, and blacks when it compares to whites. Weight gain is particularly detrimental for Asian population (15). Lee et al. also concluded with a higher type 2 diabetes risk for Asian America while the BMI is lower than the white counterparts (55). Similarly, a randomized controlled clinical trial by Herman et al. in 2007 also concluded that the A1C level, which has been used as a clinical marker of chronic glycemia reflecting the average blood glucose levels for over 2- to 3- month period of time, are higher in Hispanics, Asians, American Indians, and blacks among whites (4,16). While there are many reasons stated for racial disparities in diabetes prevalence such as, socioeconomic, genetic/family histories, environmental, and physiological contributors; however, no scientific evidence up to date can support race alone as a risk factor of diabetes mellitus (15,16).

**Diabetes Belt**

Center of Disease Control and Prevention has defined a geographical region of the United States where is especially high in diagnosed diabetes prevalence as a “diabetes belt.” It consists with 644 counties in 15 mostly southern states. People live in the diabetes belt region more than likely to be non-Hispanic blacks with higher obesity rates, lower education levels, and less physical activity rates than other U.S. regions. (17). Counties were identified in the diabetes belt if at least 11 percent of the residents had
been diagnosed with diabetes, but other counties in other parts of the U.S. that with 11 percent or more of diagnosed diabetes were excluded since they are isolated and are not contiguous with other high diabetes rates counties (17). States with a portion of the counties in the diabetes belt are Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, and West Virginia. Mississippi is the only state that the entire state is included in the belt (Figure 2.3).

Figure 2.3 Areas of Diabetes Belt

Source: Centers for Disease Control and Prevention, CDC Identifies Diabetes Belt
Diabetes Mellitus

Diabetes, or often referred to as Diabetes Mellitus, is a group of metabolic dysfunctions characterized by a defect in either insulin secretion/ action alone or together at the same time (4). There are three main types of Diabetes Mellitus, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, or Gestational Diabetes Mellitus. Type 2 Diabetes Mellitus is much more common than the other types, and it accounts for 90 to 95 percent of all the diagnosed cases (4,5).

Insulin is the body hormone that plays the major role of glucose homeostasis along with glucagon which are produced by the pancreas. Pancreas has two functional components, the exocrine cells and endocrine cells. Exocrine cells produce enzymes to help with digestions where endocrine cell is composed of small islands of cells called “islets of Langerhans,” which release insulin and glucagon into the blood stream. There are many types of hormone producing cells in the islets of Langerhans, but beta-cells are the major cells to produce insulin and amylin (8,12). After a meal, there is an increase of glucose in the blood stream which results in glucose entering the beta-cell through Glut2 transporter. The glucose in the beta-cell is then metabolize through glycolysis and TCA cycle in the cytoplasm and mitochondria, then it produces ATP. Increased ATP triggers a depolarization cascade within the beta-cell and results in insulin release. When insulin is secreted into the blood stream, it then targets other bodily cells and binds to the insulin cell receptor to stimulate the uptake of glucose and decrease blood glucose level by insulin signal transduction pathway. Insulin regulates the storage of glucose. It promotes the conversion of glucose to pyruvate then to acetyl CoA by glycolysis and then to triacylglycerols, which it can be stored into the adipose tissues. Insulin also promotes the
uptake of amino acids from the blood stream to the liver and stimulates protein synthesis. Additionally, insulin promotes the storage of fat into the skeletal muscles as fatty acids and the synthesis of triacylglycerols in the liver (12).

Once a person has been diagnosed with diabetes mellitus, it indicates that there is too much glucose in the bloodstream, and it is not being delivered into the body cells properly regardless of the type of diabetes. Although the exact etiologies of Type 2 diabetes are not known; in most cases, it is resulted from progressive defection in insulin secretion which is associated with insulin resistance and beta cells dysfunction (18). Once the body cells become resistant to the insulin and the pancreas is unable to produce enough insulin to overcome this resistance, this leads to hyperglycemia, or the increase of excessive glucose in the bloodstream. While endogenous insulin levels may be normal, depressed insulin levels are not able to adequately overcome the insulin resistance of the cells (18). Increased hepatic glucose production coupled with diminished glucose uptake and utilization and resulted in insulin resistance occurring mainly in cells of muscle, liver, and adipose (19).

Glucotoxicity, lipotoxicity, inflammation, and oxidative stress are linked to insulin resistance and further to other metabolic diseases later in life (8-11). Oxidative stress is thought to play an important role in the onset and progression of diabetes. Many of the risk factors that contribute to diabetes, such as, obesity, increased age, and unhealthy lifestyle are all underwrite to an oxidative environment which may affect insulin sensitivity by impairing insulin function and glucose tolerance (20). Reactive oxygen species (ROS), such as superoxide anion, hydrogen peroxide, and hydroxyl radical are formed by the partial reduction of oxygen, and it is associated with cellular
responses in several physiological processes in moderate amounts. However, excessive accumulation of ROS can lead to cellular damage of lipids, membranes, proteins, and DNA (21). Prolonged overproduction of ROS produce oxidative stresses and is shown to be caused by hyperglycemia, UV radiation, and increased intake of free fatty acids (12,22). Rains et al. stated that evidence studies indicated that people with diabetes tend to have a more oxidative internal environment and an increased oxidative stress marker, such as membrane lipid peroxidation when it compared to the normal healthy subjects (22). Similarly, Rosen et al. reviewed in the article that both increased oxidative stress and antioxidant depletion affect the insulin-mediated phosphatidylinositol 3-kinase (PI3K) and GLUT 4 translocation impairment which can lead to defective glucose uptake (12). However, there is also evidence research argued that ROS enhanced insulin sensitivity (23).

**Risk Factors for Diabetes Mellitus**

The differences between age, gender, and ethnicity dominate the likelihood of developing diabetes mellitus. A person with a history of impaired fasting glucose or impaired glucose tolerance has an increased risk of developing Type 2 diabetes mellitus later in life (24).

**Age and Gender**

Regardless of the gender, both males and females with age 45 and above have the higher chance to develop type 2 diabetes mellitus; although it is now occurring more frequently in a relatively younger age and even in one’s childhood (24). This may be attributed to the fact that decreasing in physical activity, increasing the likelihood of
weight gain, and loss of muscle mass (4). Additionally, family history also increases the possibility of becoming diabetic if the immediate family has it (24).

**Overweight and Obesity**

Based on the definition from Centers for Disease Control and Prevention, people with a BMI of at least 25.0 kg/m\(^2\) but less than 30.0 kg/m\(^2\) are being classified as overweight or with a BMI of 30.0 kg/m\(^2\) and above for being obese are at a greater risk for developing Type 2 diabetes (4). A high-density lipoprotein (HDL) cholesterol value of less than 35 mg/dL, a low-density lipoprotein (LDL) value greater than 100 mg/dL, a triglyceride level greater than 250 mg/dL, and hypertensive blood pressure of 140/90 mm Hg or higher are all associated with an increased risk of developing diabetes (Table 1) (24).

<table>
<thead>
<tr>
<th>High-Density Lipoprotein Cholesterol</th>
<th>&gt;40 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Density Lipoprotein Cholesterol</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>&lt;120/80 mm Hg</td>
</tr>
</tbody>
</table>


**Racial/Ethnic Minorities**

It is unclear why certain ethnic groups (African Americans, Hispanic Americans, Native Americans, Asian Americans, and Pacific Islanders) historically are at a higher risk for developing Type 2 diabetes compared to Caucasians (15,24). Shai et al. even
concluded that weight gain is particularly detrimental for Asians. The differences in racial/ethnic prevalence of diabetes may simply occur due to the differences in socioeconomic status was proposed by Singnorello et al (25).

**Selenium**

Selenium (Se) is the essential micronutrient first discovered by Berzelius in 1817 as a by-product of sulfuric acid (26). This trace element is generally recognized by its antioxidant and anti-inflammatory function additionally with the antiviral properties to human health. Sea food and organ meats are rich in selenium; other sources include muscle meats, cereals and other grains, and dairy products. Brazil nuts are the richest natural food source with a mean concentration up to 83 micrograms per gram, whereas the Recommended Dietary Allowance for adults for both genders is 55 micrograms daily. Based on National Health and Nutrition Examination Survey in 2014, the average daily selenium intake in the US is about 112.3 micrograms from food for aged 2 and above. Males have slightly higher serum selenium level than females, and Caucasian have higher level than African Americans. Hence, the typical American diet provide sufficient levels selenium (27,28).

The content of selenium in plant-based foods solely depends on the amount of selenium in soil and the capacity of plants to take in; therefore, it varies widely according to geographic locations (26). Selenium exists in two forms which are the organic selenomethionine and selenocysteine and the inorganic selenite and selenite, and most selenium is stored in animal and human tissues as selenomethionine (29). Jejunum and ileum are where mainly the absorption of selenium occurs through transcellular diffusion in mammals, and the liver regulates the whole-body selenium distribution (26,30). Both
serum selenium level and plasma selenium concentration are the most commonly used measures for selenium status. The concentration in blood and urine indicates recent selenium intake; on the other hand, the analyses of hair or nail selenium content shows the long-term status over months or years (29).

Selenium attributes its nutritional functions through 25 selenoproteins in human, which are a group of proteins that contain the 21st amino acid, selenocysteine. Most selenoproteins involve with antioxidant activities, thyroid hormones regulation, selenium transportation and storage, reduction of oxidized proteins and membranes, cellular redox regulation, and DNA synthesis. However contrary, the specific function of several selenoproteins remain unknown (30).

Glutathione peroxidases (GPxs) are a family of enzymes with antioxidant functions. They are recognized for catalyzing the reduction of hydrogen peroxide and organic hydroperoxides, hence protecting cells from oxidative damage (29,30). Additionally, the role of GPx4 is to be believed in male fertility and sperm maturation (29). Thioredoxin reductases (TrxRs) play a central role in the regulation of gene expression by redox control of transcription factors which indirectly regulates cellular activities such as cell proliferation, cell death, and immune-response activation. Thioredoxin reductase are also being proposed to act as a cellular redox sensor which regulate the cell signaling in response to elevated levels of reactive oxygen species (30). Moreover, TrxR2 is essential for heart development and heart function (29).

The iodothyronine deiodinases (DIOs) are associated with thyroid hormone metabolism. All DIOs participate in thyroid hormone metabolism by catalyzing the activation or inactivation of tetraiodothyroxine (T4) and triiodothyronine (T3), and
regulate various metabolic processes, such as lipid metabolism, thermogenesis, and the growth of brain (29,30). Autoimmune diseases such as Hashimoto thyroiditis and Graves disease caused by either hypo- or hyperthyroidism have been reported as decreased thyroid hormone metabolism due to insufficient DIOs and increased oxidative damage in the thyroid tissue as the low level of GPx. Additionally, Selenoprotein S (SelS) is proposed as a possible link to type 2 diabetes and has been characterized in controlling the inflammatory response (29).

Selenium is linked to a large variety of human health disorders both directly and indirectly. Most are due to the role of GPxs and TrxRs enzymes in the reduction of oxidative stress (29). Kashin-Beck disease and Keshan disease are the two confirmed diseases that are caused by severe selenium deficiency in soil selenium poor regions in China and Tibet; however, human selenium deficiency with obvious clinical signs is no longer common nowadays simply due to the wide-spread of food transportation across different areas and the availability of supplementation (31). Low selenium also results in poor immune function, cognitive decline, decreased male fertility, and higher risk of developing autoimmune thyroid diseases (32). In contrast, prolonged intake of high amount of selenium may result in selenosis, a chronic toxicity condition by showing hair and nail loss, garlic breath, and skin lesion symptoms (31). Although the relationships between selenium status and chronic disease condition have been widely studied, but the consistency of results are still lacking.

**Selenium and Diabetes Mellitus**

Evidence between selenium and diabetes mellitus causation is conflicting. The controversy was triggered by studies that were initially designed to study the benefits of
selenium with cancer prevention; however, an increase of newly diagnosed type 2
diabetes cases has been reported by several post-trials; therefore, the initial concern of the
disease risk has been raised (33,34).

**Selenium Induces Diabetes Mellitus**

A U-shaped link was discovered between serum selenium level and its benefits
regardless of the studies. To date, the positive association between serum selenium levels
and type 2 diabetes existed in populations with relatively low and already high serum
selenium levels has been proposed as the emerging conclusion (35,36). Overexpression
of GPx1 resulted in hyperglycemia, hyperinsulinemia, increased body fat, and elevated
plasma leptin was observed (37,38). Also, another study was conducted by the same
group proposed that selenium deficiency partially rescued the insulin resistance that
caused by the overexpression of GPx1 (39). In addition to insulin resistance, the level of
GPx1 also significantly affected dietary fat and polyunsaturated fatty acid intake based on
ethnicity (40). High levels of prolonged selenium supplementation also decreased insulin
sensitivity and higher liver triglyceride concentration addition to other findings (41).
However, clinical trials showed the positive correlation in relatively low and high
baseline selenium levels with gender specific (42,43).

**Selenium Increases Insulin Sensitivity**

Early studies indicated that selenate acted like the mechanism of insulin action
(44). High doses of sodium selenate stimulated glucose uptake by enhancing the
translocation of glucose transporters to the plasma membrane, and improved glucose
homeostasis in both type 1 and 2 diabetic animals either by intraperitoneal injection or
oral supplementation (45,46). Likewise, decreased insulin secretion due to impaired islet function and free radical scavenging systems was observed in animals with selenium deficiency status (35,47). Selenate supplementation also improved glucose tolerance in high fat diet-induced obese animals, which led to the possible role of selenate as to prevent obesity and its related diseases (48). In addition, overexpression of GPx4 decreased lipid peroxides and protected against the free fatty acid induced beta-cell dysfunctions. The possible therapeutic function of high GPx4 in obesity-associated type 2 diabetes with elevated free fatty acid levels was being proposed (49).

Both excessive supplementation and a deficiency of selenium can cause diabetogenic effects followed by a U-shaped and dose-dependent curve. It appears that supranutritional level, which is the intake level of selenium is above the recommended nutritional level, but does not exceed the toxicity level, of selenium may promote type 2 diabetes in an otherwise healthy subject. However, it appears that selenium may be beneficial for preventing further diabetes-related complications in diabetic subjects with suboptimal selenium status (50). The precise mechanistic link is unclear, but the result of reverse causation through behavioral changes after diagnosis or a result of pathophysiological changes that related to diabetes was being proposed (40,42). Excessive antioxidant resulted in increased free radical production which may lead to the overconsumption of chain-breaking antioxidants, elevated lipid peroxidation, and enhanced oxidative stress in the chronic hyperglycemia state; or simply the effect of different form of selenium supplementations was also being concluded (35,43).

Lastly, based on current knowledge, body selenium status should be the main consideration while determining the potential benefits or detriment before supplementing
selenium. In contrast, populations with diabetes mellitus are advised against further selenium supplementation. In order to minimize the current conflicting results of the practicality of selenium supplements and to further improve the understanding of its mechanisms, further human subject research is essential.
CHAPTER III

A CORRELATION STUDY ON SOIL SELENIUM CONTENT AND DIABETES MELLITUS IN CONTIGUOUS UNITED STATES

Abstract

Selenium, the essential trace element, is well known as its antioxidant function, antiviral properties, and its anti-inflammatory function to human health. The relationships between selenium status and diabetes mellitus have been widely studied, but results have been conflicting. This study used diagnosed diabetes incidence from year 2004 to 2012 and soil selenium content by counties in 48 contiguous states in the U.S. with Generalized Linear Mixed Model- R-Side as the major statistical method to determine whether there is a significant correlation or not. Results showed that the diagnosed diabetes population had been increased from 2004 to 2012 for all 48 states. The South region showed the highest increased rate whereas the Northeast region showed the least. Also, Kentucky, Louisiana, Maryland, and Massachusetts are the four states showed the significant correlation between soil selenium content and diabetes incidence. However, improved analytical methods and data are needed for further research.
**Introduction**

The high burdens of economic and health due to diabetes mellitus have been widely addressed and are major public health concerns worldwide. The dramatic increase is due to the rise of population growth, the change of living style, and the increase in obesity and overweight population (14). Although the causes of Diabetes Mellitus are incompletely understood, it has been widely accepted that both environmental and genetic factors play an important role (6,7). Additionally, glucotoxicity, lipotoxicity, inflammation, and oxidative stress are linked to insulin resistance and further to other metabolic diseases later in life (8-11).

Oxidative stress is thought to play an important role in the onset and progression of diabetes. Many of the risk factors that contribute to diabetes, such as, obesity, increased age, and unhealthy lifestyle are all underwrite to an oxidative environment which may affect insulin sensitivity by impairing insulin function and glucose tolerance (20). Evidence studies have shown an increased incidence of diabetes with a more oxidative internal environment and an elevated oxidative stress marker; on the other hand, another research argued that ROS enhanced insulin sensitivity (22,23).

Selenium (Se) is the essential trace element which generally being recognized by its antioxidant and anti-inflammatory function additionally with the antiviral properties to human health (26). Seafood and organ meats are rich in selenium; other sources include muscle meats, cereals and other grains, and dairy products (27). The content of selenium in plant-based foods solely depends on the amount of selenium in soil and the capacity of plants to take it up; therefore, it varies widely according to geographic locations (26). Selenium is linked to a large variety of human health disorders both directly and
indirectly. Kashin-Beck disease and Keshan disease are the two confirmed diseases that caused by severe selenium deficiency in soil selenium poor regions in China and Tibet; however, human selenium deficiency with obvious clinical signs is no longer common nowadays simply due to the wide-spread of food transportation across different areas and the availability of supplementation (31). Nonetheless, low selenium also results in poor immune function, cognitive decline, decreased male fertility, and higher risk of developing autoimmune thyroid diseases (32). Although the relationships between selenium status and chronic disease condition have been widely studied, but the consistency of results are still lacking.

**Objective**

To examine the possible correlation between county-level measures of soil selenium content and to use diagnosed diabetes incidence rate among 48 contiguous states in the United States from 2004 to 2012.

**Methods**

Data from Diagnosed Diabetes Incidence, 2004 to 2012 by counties from Centers for Disease Control and Prevention’s (CDC); mean average selenium concentration by counties, 2012 from U.S. Geological Survey (USGS); Estimated Resident Population for Counties from 2004 to 2012 from the Population Division, U.S. Census Bureau; and National Counties Gazetteer, Latitude and Longitude 2012 from U.S. Census Bureau were downloaded and compiled onto a Microsoft Excel spreadsheet. Overall, 3107 counties across the 48 contiguous states were used and analyzed; counties both in Alaska and Hawaii were excluded. All available data were used for analysis.
Other covariates such as the county-level mean household income, median age, and gender ratio from 2004 to 2012 were obtained from the Centers for Disease Control and Prevention (CDC). Data analyses were performed by using the statistical software (SAS, Version 9.4, SAS Institute, Cary, N.C.) to determine whether there was a significant association between soil selenium concentration and diabetes incidence by using the generalized linear mixed model- R-side as the major statistical method. The key feature of this model was to analyze the correlation between pairs of observations within a group typically decreases with increasing distance between observations. Both latitude and longitude were used in this study to determine the distance between counties; as the distance increased between counties, the significance of the correlation in soil selenium content and diabetes incidence decreased. Two different types were used to specify the covariance structure in this study. SP(EXP) was used as type 1 and SP(GAU) was used as type 2 in the statistical model. The level of significance was set at P-value less than 0.05 unless otherwise specified.

Results

The diagnosed diabetes population had been increased from 2004 to 2012 for all 48 states. The average increased diagnosed population was 2.2% from 2004 to 2012 for the West region (Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming) which Arizona had the highest overall increased diagnosed rate with 3.6% from 2004 to 2012 compared to Montana, the lowest overall increased diagnosed rate, 0.7% from 2004 to 2012 within the region (Figure 3.1). States in the South (Alabama, Arkansas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina,
Tennessee, Texas, Virginia, and West Virginia) showed a 2.4% average increased diagnosed diabetes population from 2004 to 2012. Arkansas had the highest diagnosed population rate as 3.5% from 2004 to 2012 whereas West Virginia had a 1.2% (Figure 3.2). States in the Midwest region (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin) showed a 2.17% average increased diagnosed diabetes population from 2004 to 2012. Within this region, Illinois had increased 2.9% from 2004 to 2012; South Dakota showed a lowest increased diagnosed population at 0.8% (Figure 3.3). Meanwhile, states in the Northeast region (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont) showed the lowest average increased diagnosed diabetes population from 2004 to 2012 among the entire U.S. at 1.71%. Connecticut showed an 2.4% increased diagnosed population from 2004 to 2012 as the highest increased rate in the region, and both Maine and Vermont showed an 1.2% increased diagnosed rate from 2004 to 2012 (Figure 3.4). Despite from the geographic locations, Arizona, Arkansas, Alabama, and Louisiana are the states that increased above 3% of the diagnosed population within the 8 year period; South Dakota and Montana showed an increased diagnosed diabetes population from 2004 to 2012 below 1%.

The significance of diabetes incidence and soil selenium concentration is showed by the results of California (model type 2; P= 0.01), Idaho (model type 2; P= 0.02), Utah (model type 2; P <0.001), and Washington (model type 1; P =0.03) in the West region. Illinois (model type 2; P= 0.03), Indiana (model type 2; P <0.001), Ohio (model type 1; P= 0.01), and South Dakota (model type 2; P= 0.02) showed that there is a significant correlation between soil selenium concentration and diabetes incidence. A significant
correlation is also being observed in Massachusetts (both model type 1 and 2; P= 0.03) and New Jersey (model type 2; P= 0.01). Additionally, the results of Florida (model type 1; P= 0.03), Kentucky (both model type 1 and 2; P= 0.01), Louisiana (both model type 1 and 2; P= 0.01), and Maryland (both model type 1 and 2; P= 0.03) also showed that there is a significant correlation between soil selenium concentration and diabetes incidence. Kentucky, Louisiana, Massachusetts, and Maryland are the 4 states that showed the significance correlation in both type 1 and 2 (Table 3.2 and Table 3.3). A negative association between soil selenium content and diabetes incidence was showed by the results for all the states in all the geographical regions (Figure 3.5)

Figure 3.1  Geographic Location: West (Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming)

When comparing the soil selenium concentration with diagnosed diabetes rate within all 48 states, either of the states with low soil selenium concentration (< 0.2 ppm) such as, Vermont (0.14 ppm) and New Hampshire (0.15 ppm), or states with high soil
selenium concentration (> 0.6 ppm) such as, South Dakota (0.8 ppm) and Colorado (0.7 ppm) did not present with a higher diabetes rate when it compared to states with higher diagnosed diabetes rates, such as Mississippi, Alabama, South Carolina, and West Virginia (Figure 3.5).

Average household income, gender ratio, and median age were also further taken into consideration as additional covariates. States of Arizona (P< 0.01), Indiana (P< 0.01), and New York (P= 0.03) showed that the diabetes incidence was negatively associated with soil selenium content when gender was included as a covariate. On the other hand, the results of Colorado (P< 0.01), North Dakota (P= 0.03), Washington (P< 0.01), West Virginia (P= 0.04), and Wyoming (P= 0.02) showed a negative association between diabetes incidence with soil selenium content along with adding the average household income as a covariate. Lastly, the results of including median age as a covariate showed that the diabetes incidence was negatively associated with soil selenium content for the states of Iowa (P< 0.01), Indiana (P< 0.01), Kentucky (P< 0.01), North Dakota (P< 0.01), South Dakota (P< 0.01), and West Virginia (P= 0.03). Kentucky is the only state showed that there was a negative association between soil selenium content and diabetes incidence with both model 1 and model 2 and after adding the covariate, median age. No results could be obtained from Arkansas, Connecticut, Delaware, Georgia, Maine, and Rhode Island after adding additional covariates.
Figure 3.2  Geographic Location: South (Alabama, Arkansas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia)

Figure 3.3  Geographic Location: Midwest (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin)
Figure 3.4  Geographic Location: Northeast (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont)

Table 3.2  Results from Model Type 1 Covariance Structure

<table>
<thead>
<tr>
<th>State</th>
<th>P Value</th>
<th>Soil Se (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLORIDA</td>
<td>0.03</td>
<td>0.19</td>
</tr>
<tr>
<td>KENTUCKY</td>
<td>0.01</td>
<td>0.29</td>
</tr>
<tr>
<td>LOUISIANA</td>
<td>&lt;0.001</td>
<td>0.37</td>
</tr>
<tr>
<td>MARYLAND</td>
<td>0.03</td>
<td>0.30</td>
</tr>
<tr>
<td>MASSACHUSETTS</td>
<td>0.02</td>
<td>0.19</td>
</tr>
<tr>
<td>OHIO</td>
<td>0.01</td>
<td>0.35</td>
</tr>
<tr>
<td>WASHINGTON</td>
<td>0.03</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 3.3  Results from Model Type 2 Covariance Structure

<table>
<thead>
<tr>
<th>State</th>
<th>P Value</th>
<th>Soil Se (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALIFORNIA</td>
<td>0.01</td>
<td>0.27</td>
</tr>
<tr>
<td>IDAHO</td>
<td>0.02</td>
<td>0.25</td>
</tr>
<tr>
<td>ILLINOIS</td>
<td>0.03</td>
<td>0.38</td>
</tr>
<tr>
<td>INDIANA</td>
<td>&lt;0.001</td>
<td>0.51</td>
</tr>
<tr>
<td>KENTUCKY</td>
<td>&lt;0.001</td>
<td>0.29</td>
</tr>
<tr>
<td>LOUISIANA</td>
<td>0.01</td>
<td>0.37</td>
</tr>
<tr>
<td>MARYLAND</td>
<td>0.01</td>
<td>0.31</td>
</tr>
<tr>
<td>MASSACHUSETTS</td>
<td>0.03</td>
<td>0.19</td>
</tr>
<tr>
<td>NEW JERSEY</td>
<td>0.01</td>
<td>0.45</td>
</tr>
<tr>
<td>SOUTH DAKOTA</td>
<td>0.02</td>
<td>0.76</td>
</tr>
<tr>
<td>UTAH</td>
<td>&lt;0.001</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Figure 3.5  State Level Diabetes Rate and Soil Selenium Concentration

**Discussion**

This appears to be the first study to examine the possible correlation between soil selenium content and diabetes incidence at the county level in contiguous United States. On average, results showed that the diagnosed diabetes population had been increased from 2004 to 2012. States in the South had the highest increased diagnosed population rate within the 8 year period compared to other regions. Arkansas, Alabama, and Louisiana are all fall within the Diabetes Belt, where there are large numbers of Hispanics, African Americans, persons of a lower socioeconomic status, higher rates of obesity than other regions in the country was consistent with the results that Southern states had the highest diabetes rate whereas the Northeast had the lowest rate from this study (17,51).

The distribution of selenium in soil and the capacity of plants to take in are both directly and indirectly affect the content of selenium in all natural foods (26). Due to the
wide-spread of food transportation and the change of eating habits, it is very difficult for one to eat locally grown food only. That may explain the reason why the results of states that showed a significant correlation between soil selenium content and diabetes incidence were different from the states with either high (> 0.6 ppm) or low (< 0.4 ppm) selenium in soil (52). Likewise, plants grown in soil fortified with selenium will be enriched in selenium also enhance the production and quality by increasing antioxidant activity of the plants as well as increase plants growth which may result in crops with high selenium concentration while the soil itself is deficit (53).

Additionally, it is rather difficult to determine the possible link between health status with environmental condition since population are less dependent on their immediate environment for foodstuffs (54). Also, age, gender, obesity, and social-economic status are all important factors that affect the disease progression than a simple cause (4,24,25).

Even though the data used in the study did not distinguish between type 1 and type 2 diabetes, approximately 95% of all the cases among adults are type 2 which apply to the great majority of cases (4). Additionally, this study only covered a limited time period and analysis using more years of data may provide a better insight to associations between the disease and the environmental condition. The distribution and speciation of selenium in the local environment is determined by the prevailing geochemical and soil characteristics. At minimum, geographical areas where are characterized as selenium deficiency or toxicity predict potential health risks. However, it is hardly to conclude that the characteristic of soil itself as the only factor to be considered for the potential health risks.
Conclusion

In conclusion, based on the results from the study, soil selenium content is correlated with diabetes incidence. Furthermore, soil selenium content is negatively associated with diabetes incidence regardless alone or adding other covariates. Improved analytical methods and data are needed. Further research needs to be done in order to have a more accurately determine possible correlations. At minimum, this study can be a starting point for future studies and further serves as a reference when one is considering supplementing selenium.
REFERENCES


APPENDIX A

SAS CODE
PROC IMPORT OUT = DATAFILE
FILE = "D:\DATA\SAS datasets\Incidence\DATAFILE.csv"
DBMS = CSV
REPLACE;
RUN;

proc genmod data=DATAFILE;
   model rateper1000=Se;
run;

data DATAFILE;
   set DATAFILE;
   obs = _n_;
run;

proc glimmix data=DATAFILE;
   class obs;
   logn= log(Population);
   model cases=se logn Aveincome medianage Malesper100f / solution
      link=log dist=Poisson;
   random _residual_ / type=sp(gau)(Long Alt) subject=intercept;
run;