Environmental Exposures Lead to Premature Age-Related Diseases

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ABSTRACT

The Age-related diseases are diseases that occur with increasing frequency as aging increases. It covers many kinds of diseases which mostly happen in the elderly, such as the atherosclerosis, arthritis, osteoporosis, type-2 diabetes, stroke, chronic kidney disease, and cardiovascular disease. This paper aims to identify the relationship between the heavy metals and pesticide in blood and urine with age-related diseases. For arthritis, cardiovascular disease, stroke, chronic kidney disease, macular disease and atherosclerosis, the National Health and Nutrition Examination Survey (NHANES) can directly determine who has these specific diseases. However, for Alzheimer's and Parkinson's, these two diseases could not be directly seen through a single variable. The respondents who have these two diseases could be justified by other variables. For example, Alzheimer's could be defined based on the cognitive function datasets, and Parkinson's could also be defined by the prescription medicine datasets in the NHANES. The metals in blood and urine have been selected in 18 different kinds of metals, and the pesticide content in blood and urine have also been included in the NHANES. By calculating the P-value between the diseases and the heavy metals, it demonstrates that the concentrations of cadmium, mercury and many of the heavy metals are associated with many age-related diseases, not only one disease.

Keywords: Age-related diseases; National health and nutrition examination survey; NHANES; Heavy metals; Herbicide

ABBREVIATION

(URXDAZ) Daidzein (ng/mL); (URXDMA) O-Desmethylangolensin (O-DMA)(ng/mL); (URXEQU) Equol (ng/mL); (URXETD) Enterodiol (ng-mL); (URXETL) Enterolactone (ng/mL); (URXGNS) Genistein (ng/mL); (URXUCR) Creatinine, urine (mg/dl); (URXUAS) Urinary total Arsenic (ug/L); (URXUAB) Urinary Arsenobetaine (ug/L); (URXUMMA) Urinary Monomethylarsonic acid (ug/L); (URXUDMA) Urinary Dimethylarsinic acid (ug/L); (URXUHG) Mercury, urine (ng/mL); (URXUSB) Antimony, urine (ng/mL); (URXUCD) Cadmium, urine (ng/mL); (URXUCO) Cobalt, urine (ng/mL); (URXUCS) Cesium, urine (ng/mL); (URXUMO) Molybdenum, urine (ng/mL); (URXUPB) Lead, urine (ng/mL); (URXUTL) Thallium, urine (ng/mL); (URXUTU) Tungsten, urine (ng/mL): (URXUUR) Uranium, urine (ng/mL); (LBXBCD) Cadmium (ug/L); (LBXBPB) Lead (ug/dL); (LBXTHG) Mercury, total (ug/L); (URXCOTT) Total Cotinine, urine (ng/mL); (URXHCTT) Total Hydroxycotinine, urine (ng/mL); (URXANBT) Anabasine, urine (ng/mL); (URXCOXT) Cotinine-n-oxide, urine (ng/mL); (URXNICT) Nicotine, urine (ng/mL); (URXNNCT) Nornicotine, urine (ng/mL); (URXNOXT) Nicotine-1 N-oxide, urine (ng/mL); (URDTNE2) TNE-2 (nmol/mL); (URDTNE3) TNE-3 (nmol/mL); (URDTNE6) TNE-6 (nmol/mL); (URX1TB) 2, 4, 5-trichlorophenol (ug/L); (URX14D) 2, 5-dichlorophenol (ug/L); (URXDCB) 2, 4-di-

chlorophenol (ug/L); (URX3TB) 2, 4, 6-trichlorophenol (ug/L); (LBCTCD) 2, 3, 7, 8-Tetrachloro-p-dioxn (tcdd) (fg/g); (LBCTCD-LA) 2, 3, 7, 8-tcdd lipid adjusted (pg/g); (URX24D) 2, 4-D (ug/L); (URX25T) 2, 4, 5-T (ug/L); (URXUBA) Barium, urine (ng/mL)

INTRODUCTION

With aging the human body becomes worse; the elderly have a higher probability of getting more diseases than the young. Atherosclerosis is a disease with erectile dysfunction, heart attack and strokes. People with stroke lack motor skills and have facial paralysis or numbness. People with macular degeneration might have blurred vision and partial loss of vision. Many age-related diseases have their own specific symptoms. Heavy metals are linked to many diseases. For cadmium, it is ingested by human from the contaminated foods and inhalation of air. The ingested cadmium is taken by gastrointestinal tract and lung and enters to the blood stream [1]. One research which uses the post-mortem brain tissues found that the brain which has Alzheimer's disease had higher concentration of cadmium than the comparing group which do not have this disease [2]. Moreover, not only Alzheimer's disease, but also cadmium could cause osteoarthritis by diminishing skeletal growth, which could result osteopenia [3]. Another harmful element like 2,3,7,8-Tetrachloro-p-dioxin (TCDD) which is mainly used in herbicide is also connected with many diseases. A research which had used the zebrafish to be the test group revealed that TCDD exposure could not only attack the liver, kidney, gut and pancreas but also it could influence the eyes by disrupting the angiogenesis and vessel pruning of vascular development [4,5]. These examples show that excessive concentration of heavy metals or harmful elements may cause many different diseases. However, in the NHANES, there are no numeric relationships suggesting that the same metal is associated with multiple diseases. Although there are many studies claiming that people with excessive heavy metals may have their own symptoms. There is little literature that can conclude that different heavy metals are associated with different diseases. To solve this problem, in this paper, the heavy metals from 2003-2004 to 2017-2018 and the survey sample of the nationally representative age-related diseases are selected. There are around 43 harmful elements including the heavy metals and herbicide and 10 aging-associated diseases. To get the relationship between these harmful elements and aging associated diseases, we use the P-value to calculate them. After the P-value between the heavy metals and diseases is calculated, the lower P-value is chosen to demonstrate the relationships between heavy metals and age-related diseases. After that, these diseases are collected to make a comparison.

MATERIALS AND METHODS

Data Source

The data used to calculate the P-value come from the National Health and Nutrition Examination Survey (NHANES) from 2003-2004 to 2017-2018. This data is sponsored by a division of the Centers for Disease Control of the National Center for Health Statistics. The NHANES includes the health and nutritional status of both the children and adults in the United States. And in this study, the persons aged 20-150 are included to examine the association between harmful elements and age-related diseases.

Study Design and Participant Sample

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Measures

This research aims to demonstrate that environmental exposures lead to premature age-related diseases, and the conclusion of this research presents a convincing result that metals and pesticides are associated with age-related diseases. For the judgment of the disease, two conditions needed to be estimated. One was the variable for the disease, which could be directly judged by the specific value. This variable description is as follows: doctors told the participants whether they had those diseases or not. In this question, the participants could answer "yes", "no", "I don't know" and "refuse". Those who responded with "I don't know" and "refuse" were not suitable for the measurement, so they were excluded. In the case that no doctors told the respondents, some diseases like the Parkinson's disease were judged by whether that respondent had taken a series of medicines or not and some diseases like Alzheimer's were judged by the cognitive functions in different modules in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST) [6]. For Parkinson's, 0 and 1 were set to discover whether the respondent suffered from it not [7]. In which, 0 represented that the male/female had not previously taken any medication for Parkinson's. As a result, they did not suffer from Parkinson's. Whereas, 1 represented the opposite meaning. For Alzheimer's, there were four modules to judge, and the values of the four modules could influence the results, so we did not set the obvious variable which indicated the person had Alzheimer's. In this case, any lower P-value between the harmful elements and the four modules indicated that a certain relationship between them was present. After data cleaning, the data for the persons who have age-related diseases and the data for these harmful elements are the parameters to calculate P-value by using R Studio.

Statistical Analysis

In this research, we set the P-value to evaluate the relationship between harmful elements and the age-related diseases. If the P<0.05, we can define that there is a relationship between them. However, if it is larger than 0.05, this disease is excluded.

RESULTS

In our research, more than 43 harmful elements are measured in the urine and blood of the respondents, as given in **Table 1**.

Some are the heavy metals, and others are from the pesticide or the herbicides like 2, 4-dichlorophenoxyacetic acid (2, 4-D) or 2, 4, 5-trichlorophen-oxyacetic acid (2, 4, 5-T). The age-related diseases are listed in **Tables 2 and 3** (**Figure 1**).

Table 1: The age-related diseases and their symptoms After all the data cleaning, we put the data into RStudio and calculate the P-value. Then, the data with P-value less than 0.05 are selected to be shown in Table 2.

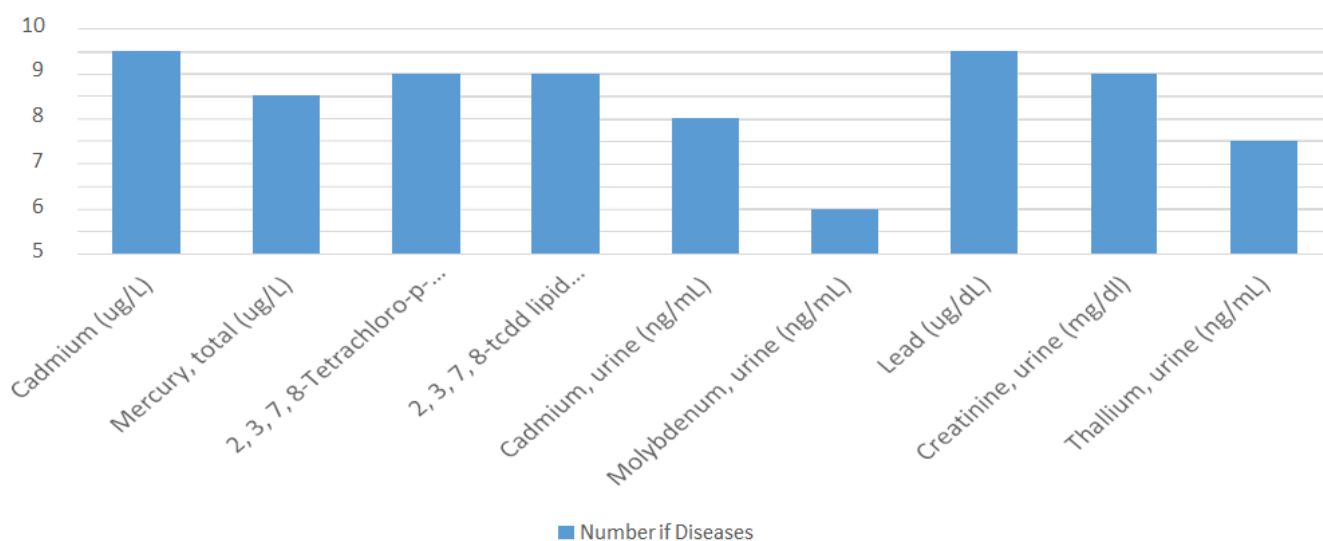| Age-related diseases	Symptoms
Stroke	Lack of motor skills, paralysis or numbness in face, arm, or leg, greater likelihood of seizure
Alzheimer's	Loss of memory, confusion, mood swings, mental decline, incoherent speech, lack of appetite, disorientation, inability to create new memories
Macular Degeneration	Blurred vision, partial loss of vision, straight lines become wavy, inability to see in dim lighting, seeing spots, new and abnormal blood vessels
Atherosclerosis	Erectile dysfunction, heart attack, mini-strokes (transient ischemic attacks), poor wound healing, or stroke
Arthritis	Pain (joints), stiffness, reduced range of motion, inflammation, difficulty in walking, muscle weakening, fatigue, redness
Osteoporosis	Brittle bones, lack of bone mass, frequent fractures, loss of height
Type-2 Diabetes	Increased thirst, blurred vision, hunger, fatigue, weight changes, frequent urination, poor wound healing
Parkinson's	Tremors, stiffness, lack of balance, amnesia/dementia, fatigue, poor sleep, stiff muscles, decreased motor skills, dizziness, confusion, slow movement, jaw stiffness, anxiety, distorted senses, weight loss, constipation, depression, neck
Chronic Kidney Disease	Fatigue, high blood pressure, loss of appetite, kidney damage, abnormal heart rhythm, fluid in the lungs, insufficient urine production, itching, kidney failure, severe unintentional weight loss, inflammation
Cardiovascular Disease (General)	Chest pain, chest tightness, shortness of breath. Pain, numbness, weakness or coldness in your legs or arms if the blood vessels in those parts of your body are narrowed. Pain in the neck, jaw, throat, upper abdomen or back.

Table 2: The age-related diseases associated with the harmful elements.

Harmful Elements	Age-related disease	P<0.05
Cadmium (ug/L)	Parkinson's	0.00232
Mercury, total (ug/L)	Parkinson's	0.00232
2, 4-dichlorophenol (ug/L)	Arthritis	0.024
2, 3, 7, 8-Tetrachloro-p-dioxn (tcdd) (fg/g)	Arthritis	<.001
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Arthritis	<.001
Cadmium, urine (ng/mL)	Arthritis	<.001
Cobalt, urine (ng/mL)	Arthritis	0.0003
Molybdenum, urine (ng/mL)	Arthritis	0.012
Mercury, urine (ng/mL)	Arthritis	0.028
Cadmium (ug/L)	Arthritis	<.001
Lead (ug/dL)	Arthritis	<.001
Mercury, total (ug/L)	Arthritis	<.001
Creatinine, urine (mg/dl)	Arthritis	<.001
2, 3, 7, 8-Tetrachloro-p-dioxn (tcdd) (fg/g)	Stroke	<.001
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Stroke	<.001
Cadmium, urine (ng/mL)	Stroke	<.001
Thallium, urine (ng/mL)	Stroke	<.001
Cadmium (ug/L)	Stroke	<.001
Lead (ug/dL)	Stroke	<.001

Mercury, total (ug/L)	Stroke	<.001
Creatinine, urine (mg/dl)	Stroke	0.022
2, 3, 7, 8-Tetrachloro-p-dioxn (tcdd) (fg/g)	Cardiovascular	<.001
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Cardiovascular	<.001
Cadmium, urine (ng/mL)	Cardiovascular	<.0001
Thallium, urine (ng/mL)	Cardiovascular	0.008
Cadmium (ug/L)	Cardiovascular	<.001
Lead (ug/dL)	Cardiovascular	<.001
Mercury, total(ug/L)	Cardiovascular	<.001
Creatinine, urine(mg/dl)	Cardiovascular	<.001
2, 3, 7, 8-Tetrachloro-p- dioxn (tcdd) (fg/g)	Macular Degeneration	<.001
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Macular Degeneration	<.001
Lead (ug/dL)	Macular Degeneration	<.001
Creatinine, urine (mg/dl)	Macular Degeneration	0.009
2, 3, 7, 8-Tetrachloro-p-dioxn(tcdd)(fg/g)	Osteoporosis	<.001
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Osteoporosis	<.001
Cadmium (ug/L)	Osteoporosis	<.001
Lead (ug/dL)	Osteoporosis	<.001
Mercury, total (ug/L)	Osteoporosis	<.001
Antimony, urine (ng/mL)	Osteoporosis	0.036
Thallium, urine (ng/mL)	Osteoporosis	<.001
Urinary dimethylarsinic acid (ug/L)	Osteoporosis	0.032
Creatinine, urine (mg/dl)	Osteoporosis	<.001
2, 3, 7, 8-Tetrachloro-p-dioxn (tcdd) (fg/g)	Chronic Kidney Disease	0.002
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Chronic Kidney Disease	0.001
Uranium, urine (ng/mL)	Chronic Kidney Disease	0.045
Cadmium (ug/L)	Chronic Kidney Disease	<.001
Lead (ug/dL)	Chronic Kidney Disease	<.001
Mercury, total (ug/L)	Chronic Kidney Disease	<.001
Creatinine, urine (mg/dl)	Chronic Kidney Disease	0.017
Cadmium, urine (ng/mL)	Alzheimer's	0.018
Lead, urine (ng/mL)	Alzheimer's	0.048
Lead (ug/dL)	Alzheimer's	<.001
Cadmium (ug/L)	Alzheimer's	<.001
2, 3, 7, 8-Tetrachloro-p-dioxn (tcdd) (fg/g)	Diabetes	<.001
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Diabetes	<.001
O-Desmethylangolensin (O-DMA) (ng/mL)	Diabetes	0.031
Creatinine, urine (mg/dl)	Diabetes	<.001
Cadmium (ug/L)	Diabetes	<.001
Lead (ug/dL)	Diabetes	<.001
Mercury, total (ug/L)	Diabetes	<.001
Barium, urine (ng/mL)	Diabetes	<.001
Cadmium, urine (ng/mL)	Diabetes	<.001
Molybdenum, urine (ng/mL)	Diabetes	0.019
Thallium, urine (ng/mL)	Diabetes	<.001
2, 3, 7, 8-Tetrachloro-p-dioxn (tcdd) (fg/g)	Atherosclerosis	<.001
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Atherosclerosis	<.001
Cadmium, urine (ng/mL)	Atherosclerosis	<.001
Thallium, urine (ng/mL)	Atherosclerosis	0.033
Cadmium (ug/L)	Atherosclerosis	<.001
Lead (ug/dL)	Atherosclerosis	<.001
Creatinine, urine (mg/dl)	Atherosclerosis	0.048

Table 3: The harmful elements associated with different diseases.

Harmful Elements	Diseases	Number of Diseases
Cadmium (ug/L)	Parkinson's, Arthritis, Stroke, Cardiovascular, Osteoporosis, Chronic Kidney Disease, Alzheimer's, Diabetes, Atherosclerosis	9
Mercury, total (ug/L)	Parkinson's, Arthritis, Stroke, Cardiovascular, Osteoporosis, Chronic Kidney Disease, Diabetes Atherosclerosis	7
2, 3, 7, 8-Tetrachloro- p-dioxn (tcdd) (fg/g)	Arthritis, Stroke, Cardiovascular, Macular Degeneration, Osteoporosis, Chronic Kidney Disease, Diabetes,	8
2, 3, 7, 8-tcdd lipid adjusted (pg/g)	Arthritis, Stroke, Cardiovascular, Macular Degeneration, Osteoporosis, Chronic Kidney Disease, Diabetes, Atherosclerosis	8
Cadmium, urine (ng/mL)	Arthritis, Stroke, Cardiovascular, Alzheimer's, Diabetes, Atherosclerosis	6
Molybdenum, urine (ng/mL)	Arthritis, Diabetes	2
Lead (ug/dL)	Arthritis, Stroke, Cardiovascular, Macular Degeneration, Osteoporosis, Chronic Kidney Disease, Alzheimer's, Diabetes, Atherosclerosis	9
Creatinine, urine (mg/dl)	Arthritis, Stroke, Cardiovascular, Macular Degeneration, Osteoporosis, Chronic Kidney Disease, Diabetes, Atherosclerosis	8
Thallium, urine (ng/mL)	Stroke, Osteoporosis, Cardiovascular, Diabetes, Atherosclerosis	5

Figure 1: A number of harmful elements related to aging-associated diseases

DISCUSSION

In this paper, we find that the concentration of cadmium and lead have the most widely effects on the age-related diseases, with 9 kinds of diseases apart from macular degeneration for cadmium and Parkinson's for lead associating with these two harmful elements. Moreover, the concentration of Molybdenum in urine is just associated with 2 diseases. One is the Arthritis, and the other is the diabetes. Corresponding results are noticeable between these results and other researches. For example, in this research, the concentration of molybdenum in urine relates to two aging associated diseases. One is Arthritis and the other is diabetes. This result is also mentioned in other studies. In Kot's research, the researchers showed that the patients who did not have Arthritis had a lower concentration of molybdenum at 0.403 mg/kg dw, than the patients who had

Arthritis at 0.998 mg/kg dw. Noteworthily, in Menke's research, the concentration of molybdenum also relates to diabetes with a consistently positive association [8]. Apropos the concentration of creatine is also mentioned in many times in different research. In the study from Liu, it shows that the group who have osteoporosis has a higher concentration of creatine than the normal group [9]. Also, measuring the concentration of creatine is a traditional way to detect the kidney tubular injury [10]. So based on this, we could deduce that the concentration of creatine also relates to the chronic kidney disease. Not only these two diseases, but also included in many other diseases. According to the other research, the patients who have macular degeneration, stroke or atherosclerosis also exit relationships within creatine [11-13]. These studies' results also correspond to our result. The current research presents a reliable evidence and visualized graph to show the complex relationship between

pollutants and age-related diseases. However, there are still many limitations in our research. First, there is a little data on some harmful elements, such as macular degeneration. There are just 2,136 heavy metal samples, much smaller than other samples, such as 35,346 samples of heavy metals in the blood of patients with stroke [14]. Meanwhile, it is unavailable to link all the 43 harmful elements to Alzheimer's. In this case, we could just link 18 elements to the age-related disease, and the number of samples is also too small. The metals in urine contain only 972 pollutants. However, metals in the blood also just cover 2,148. Hence, based on such conditions, we cannot guarantee that there is no relationship with other harmful elements that are not included in these two, and the P-value in this also might be influenced [15]. The future work would more focus on the datasets used in the research extension, such as adding more harmful elements and including all 43 harmful elements that are not fully included in the original research.

CONCLUSION

In summary, we set the P-value to judge the relationship between 43 harmful elements and 10 age-related diseases. The P-value is an index that indicates cadmium, lead, 2, 3, 7, 8- Tetrachloro-p-dioxn(tcdd), creatine, and mercury have a strong relationship with the age-related diseases, and other harmful elements like 2, 4-dichlorophenol are just associated with one disease. This research has important public health implications because people can try to avoid the age-related diseases by avoiding these harmful elements.

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CONFLICT OF INTEREST

None.

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