# The Association between Polycyclic Aromatic Hydrocarbons Exposure and Health Outcomes in Older United States Adults

by

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## Abstract

***Background:*** The association between air pollutants, such as particulate matters (PM) and ozone (O3), and the risk of cognitive impairment and hypertension among different age groups was deeply investigated. However, limited studies have examined the association between specific components of air pollutants, such as polycyclic aromatic hydrocarbons (PAH) with cognitive performance (CP) risk and hypertension (HTN) among older adults.

***Objectives*** of the current study were to examine the association between urinary PAH biomarkers and both of CP and HTN in older adults, as well as to determine if the associations between PAH and CP scores and HTN differs by individual socioeconomic status and ethnicity.

***Methods:*** Data from 2011-2014 the National Health and Nutrition Examination Survey (NHANES) were used to examine the relationship between urinary PAH metabolites and CP and HTN, after adjusting for different covariates. Data analysis included over 3000 NHANES participants, aged 60 years and older.

***Results****:* A significant negative association was found between PAH exposure and CP ($p<0.001$). For each increase in one unit in log-transformed PAH metabolite levels, all cognitive tests were lower in almost all models. There was a significant association between urinary 1-hydroxynaphthalene relative to race and HTN in older adults. Each increase in one unit in log-transformed urinary 1-hydroxynaphthalene level was associated with greater odds of developing HTN for all race groups.

***Conclusion:*** Higher exposures to PAH were associated with lower CP among males, Blacks, Hispanics, individuals with lower education, lower income, and smokers. The higher urinary concentration of 1-hydroxynaphthalene in HTN relative to race was among Blacks comparing to other ethnic groups. Black individuals with different urinary 1-hydroxynaphthalene biomarker concentrations had the highest probability of developing HTN compared to other racial groups.

***Public Health Impact:*** PAH exposures are a significant public health concern that affects many countries and cause tremendous negative health outcomes. The effects of PAH not only increase the risk of metabolic syndromes and cardiovascular disease, but may also cause mental health problems that may affect ethnic groups differently. Thus, recognizing the impact of PAH exposure will provide evidence for possible new interventions to combat and mitigate air pollution resources.

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# 1.0 Introduction

## 1.1 Overview of Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) are a group of chemical constituents of particulate matters (PM) that are generated by incomplete combustion of organic materials, such as coal, oil, gas, exhaust fumes, garbage, and tobacco (Agency for Toxic Substances and Disease Registry [ATSDR], 2009). PAH are mixtures of hazardous toxic of genotoxic compounds that are highly dispersed in the environment (air, soil and water) (Polanska et al., 2014). PAH are considered as a significant public health concern as exposure to PAH, whether acutely or chronically, may increase the risk of human diseases, including cardiovascular and lung diseases, as well as cancers (Polanska et al., 2014).

According to the International Agency for Research on Cancer (IARC, 2010), the PAH are carcinogenic compounds consisting of carbon and hydrogen that form two to six fused aromatic rings structures. There are approximately 16 compounds that are known as carcinogenic-based diseases for human, such as benzo[a]pyrene (BaP), (IARC, 2010). Because of their physicochemical properties and molecular weights, PAH can persist exist in the environment and continue to have biological impact. For instance, PAH that have up to three rings can dissolve in water, this chemical structure helps PAH to be more readily available for biological degradation (Mackay and Callcott, 1998; Choi et al., 2010). Also, when PAH compounds have more rings (two to four rings), PAH volatilize into the atmosphere in gaseous form (Atkinson and Arey, 1994; Srogi, 2007). However, PAH compounds with more rings (five or more rings) have low solubility in water and low volatility into air, therefore, they remain predominantly in solid form and bound to

particulates in soil or sediment (Choi et al., 2010). More persistent solid PAH are less accessible for biological degradation, but more available for human exposure (Johnsen et al., 2005; Haritash and Kaushik, 2009).

### 1.1.1 Main Sources of PAH

PAH are released from different sources, including natural sources, such as volcanic eruptions or forest fires (Ramesh et al., 2004). However, the major source of PAH is anthropogenic, especially from human and industrial activities that include burning of fossil fuels, transportation, fumes released from manufacturing industries, and smoking (Figure 1) (Ramesh et al., 2004).

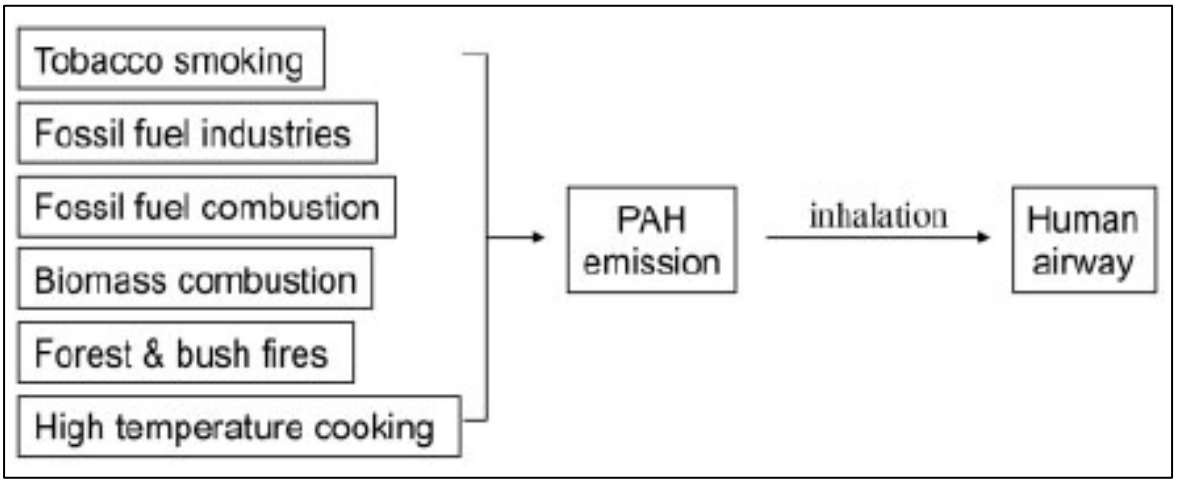



**Figure 1 Examples of PAH sources released to the environment (Moorthy, Chu, & Carlin 2015)**

### 1.1.2 Types, Classifications, and Distribution of PAH

PAH can be classified into three main groups based on its carcinogenicity to humans. First group (Group 1) includes BaP. The second group is subdivided divided into two groups: Group 2A and Group 2B. Group 2A is classified as a probable human carcinogens (e.g. cyclopenta[cd]pyrene,

dibenzo[a,l]pyrene, and dibenz[a,h]anthracene) and group 2B is classified as a possible human carcinogens (e.g. benzo [ j] fluoranthene, benzo[k]fluoranthene, benzo[c]phenanthrene, and dibenzo[a,h]pyrene) (Figure 2). A third group (Group 3) differs from other groups in that they are not classified as carcinogenic to humans (e.g. benzo [a,b,c]fluorene, benzo[a]fluoranthene, fluoranthene, and fluorine) (Jameson, chapter 7, 2019).

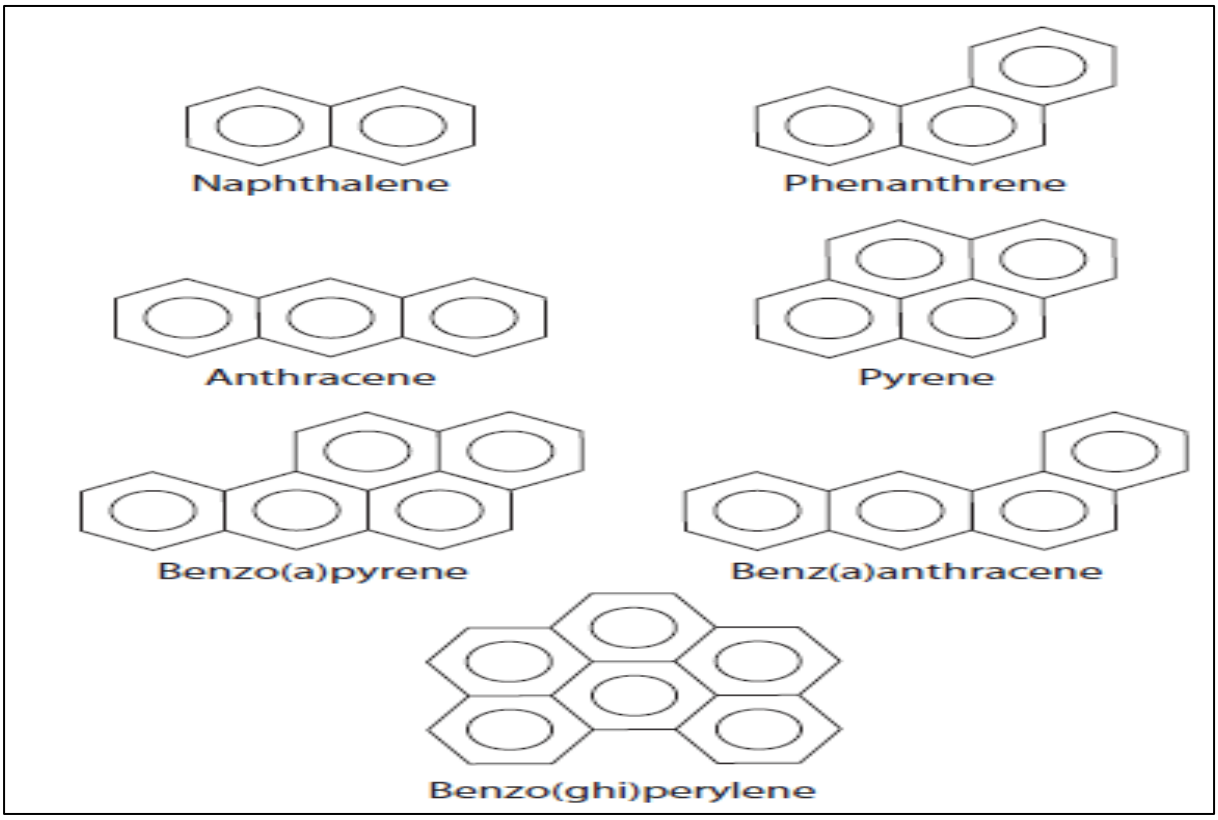



**Figure 2 Examples of selected Polycyclic Aromatic Hydrocarbons (PAH) in the environment (Ramesh et al., 2016)**

PAH are more concentrated in urban areas than in rural areas as population density, industries, and human activities, such as fuel combustion and diesel emissions, are the main anthropogenic sources of the PAH emissions. A study using data from the United States Environmental Protection Agency (EPA)'s Air Quality System examined the health risk of long-term exposure to atmospheric PAH in both urbans and rural areas in the United Stated found that

urban areas had almost twice the PAH concentrations of rural areas (Figure 3) (Liu et al., 2017; EPA, 2015).

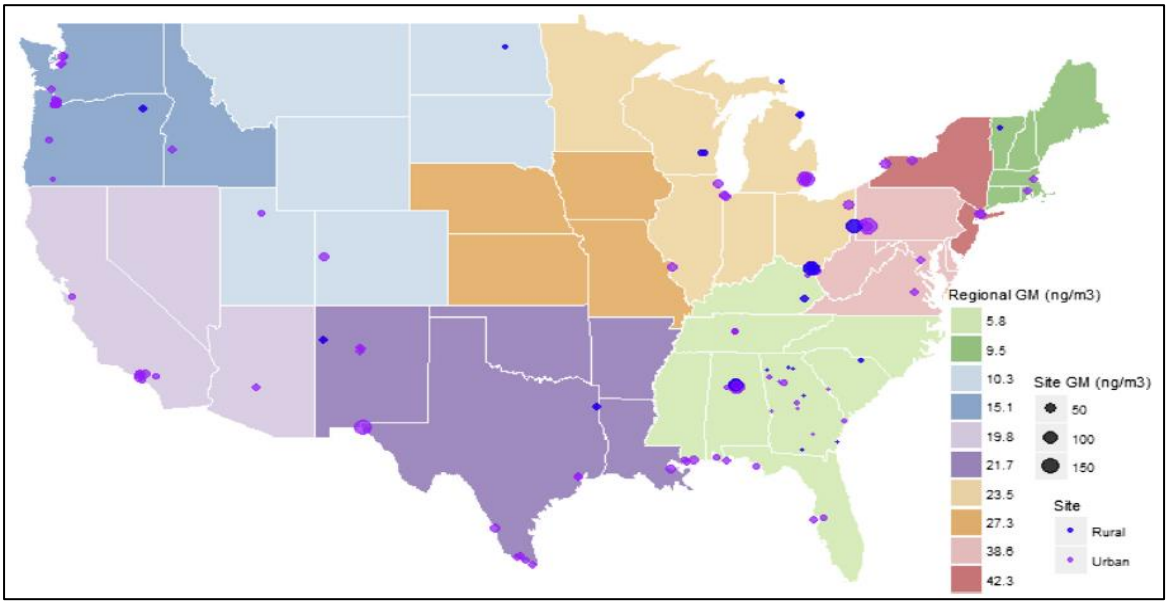



**Figure 3 The spatial distributions of geometric mean of PAH metabolites (ng/m3) between 1990 and 2014 in the United States (Copyrighted to: Liu et al., 2017; EPA, 2015)**

### 1.1.3 Routes of Exposure

Exposure to PAH can occur in both occupational and non-occupational settings through several routs; ingestion, inhalation, and dermal contact. For the general population, inhalation is the main route of PAH exposure, including indoor and outdoor polluted air with PAH (e.g. smoking cigarettes, cooking, from open fireplaces, exhaust fume emissions or from industries) (American Conference of Governmental Industrial Hygienists [ACGIH], 2005). In urban areas, gasoline and diesel vehicle exhausts are considered the major source of PAH that released into atmosphere, since these areas have higher density of population compared to rural areas where PAH emission would be less.

### 1.1.4 Inhalation Route

As PAH are a toxic mixture of chemicals and hazardous genotoxic compounds, their inhalation can increase the risks of different kind of cancerous and non-cancerous diseases. PAH, such as BaP, may affect different organs in human body (Moorthy, Chu, & Carlin 2015). For instance, in tobacco smoke, there is about 100 ng BaP per cigarette (Grimmer et al.,1988). As a result, chronically, smokers may inhale about 0.26 μg of BaP per pack of 20 cigarettes, possibly increasing the risk of lung cancer (Piccardo et al., 2010). Additionally, large bodies of literature have shown that individuals who smoke cigarettes and cigar may be exposed to much large amounts of PAH that can are swallowed and enter the gastrointestinal (Jarup, 2003; Nebert et al., 2013; Rozman and Klaassen, 2007).

### 1.1.5 Toxicokinetics of PAH

Toxicokinetic are processes involving the chemical substances at the moment of exposure and entry into the body through the elimination of the chemical substance or its metabolites from the body (ATSDR, 1995b). These processes are: Absorption, Distribution, Metabolism and metabolites, and Excretion.

#### 1.1.5.1 Absorption of PAH

PAH adsorbed from inhaling soot particles deposit in the airways or bronchial clearance can eliminate those particles. During the transportation process on the ciliated mucosa, PAH can also be absorbed from those particles, and consequently, they penetrate into the bronchial epithelium cells where other metabolic processes begin (World Health Organization [WHO], 2000;

WHO, 2018; ATSDR, 1995b). The absorption level/rate depends on different factors, such as the nature of the PAH metabolites. For instance, when BaP is adsorbed on particles, the rate of the respiratory uptake might be greater, especially if the particles retained for a long period in the respiratory tract (Törnquist, Wiklund, & Toftgård 1985).

In inhalation studies in rats, animals inhaled radiolabeled BaP adsorbed on diesel engine exhaust particles ((Sun et al., 1984)). The inhaled particle-associated radioactivity that occurred from the lung clearance underwent through two main phases. In the first phase, the initial rapid clearance had a half-time of less than one hour. However, in the second, longer phase, the particles had a half-time of 18 days and this represented about 50% of the particle-radioactivity that had initially been deposited in the lungs (Sun et al., 1984). Another study demonstrated that exposed rats to pure BaP and to [$^{14}$C] -BaP adsorbed on carbon black particles found inhalation of [$^{14}$C] -BaP resulted in hundred-fold higher levels of 14C in lungs at the end of a 12-week. Also, rats exposed to [$^{14}$C] -BaP, the half-time for the decline of [$^{14}$C] levels was 34 weeks. In contrast, it was 6 weeks for rats exposed to pure BaP (Wolff et al., 1989).

#### 1.1.5.2 Distribution of PAH

After the absorption phase, PAH enter the lymph, circulate in the blood, and are metabolized primarily in the liver and kidneys (Busbee et al. 1990). Studies have shown that the exposure to BaP can be detected within minutes to hours in internal organs, especially in the liver (IARC 1983; Foth, Kahl, & Kahl 1988). In general, PAH are significantly stored in fatty tissues (Modica et al., 1983), and high levels of PAH metabolites are found in the gastrointestinal tract as the result of hepatobiliary excretion (Schlede, Kuntzman, & Conney 1970; Wiersma & Roth 1983). Other studies found some of PAH metabolites, such as pyrene, was highly distributed in the perirenal fat, in the liver, kidneys and lungs, however, pyrene concentration levels were less

distributed in the heart, testes, spleen and brain (Withey, Law, & Endrenyi 1991; Withey et al., 1992). Also, BaP has the ability to cross the placental barrier of rats and mice (Neubert & Tapken 1988; Withey et al., 1993).

#### 1.1.5.3 Metabolism and Metabolites

PAH are primarily metabolized by the Phase I cytochrome p450 (CYP) enzymes of the liver microsomal mixed fraction is the enzyme system (the CYPs mixed function) in a reaction that converts non-polar PAH into polar hydroxy and epoxy derivatives (Hall et al., 1989). The CYPs are also widely distributed in other cells and tissues, however, the liver is considered to have the highest capacity for PAH metabolism. Compared to the adult tissues, fetal tissues can also metabolize PAH, but at a lower rate (Anderson et al., 1989).

BaP can induce expression of the microsomal monooxygenases and epoxide hydrolases CYPs to stimulate its own metabolism (Nebert, Puga, & Vasiliou 1993). Arene oxides and phenols are produced as a result of the BaP oxidation. The arene oxides are converted to phenols (3-OH-, 6-OH-, 7-OH, and 9-OH-BaP), microsomal epoxide hydrolases (hydration) catalyzed phenols to trans-dihydrodiols (4,5-, 7,8- or 9,10-dihydrodiol), phenols may also be oxidized further to quinones (1,6, 3,6-, or 6,12-quinone). Additionally, secondary epoxides can be formed after further oxidation by the CYPs monooxygenase system (IARC 1983; Gräslund and Jernström 1989). Furthermore, through biotransformation process, PAH start to exert its mutagenic and carcinogenic to chemical reactive intermediates which by then bind to cellular macromolecules (IARC 1983; Gräslund and Jernström 1989).

#### 1.1.5.4 Excretion

After metabolism processed, the hepatobiliary excretion of PAH metabolites is eliminated and removed from the body through feces (the major route) or urine, regardless of route of entry (Foth, Kahl, & Kahl 1988; Wiel et al., 1993). Becher and Bjorseth (1983) reported in their animal studies, that the excretion half-life for PAH through both feces and urine was 22 hours and 28 hours, respectively.

### 1.1.6 Systemic Effect of PAH

As it was mentioned previously, PAH have specific physicochemical properties. These compounds are lipophilic, and therefore, after inhalation, they can easily cross cell membranes through passive diffusion. The parental PAH molecules (before the transformation or being metabolized) could be considered as procarcinogens as they do not directly induce or damage the DNA (Alexandrov et al., 2010). The transformation from procarcinogens into effective carcinogenic through the CYP metabolism to oxides, phenols, epoxides, and quinones (Figure 4) (Moorthy, Chu, & Carlin 2015).

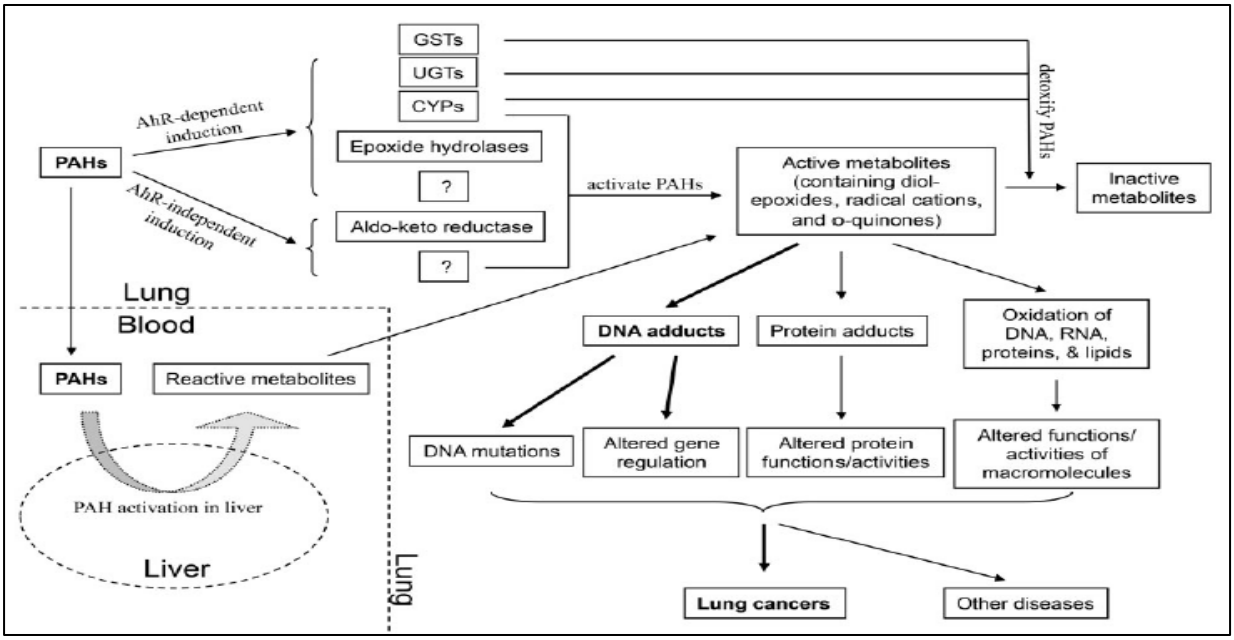



**Figure 4 Example of multiple mechanisms of PAH metabolites that can cause lung cancer (Copyrighted to: Moorthy, Chu, & Carlin 2015)**

The PAH phenol, catechol, and quinone metabolites as well as their diolepoxide precursors are radical cations or reactive and redox-active oquinones, and may all react with DNA to produce DNA adducts. For instance, quinones may react with both of N-3 of adenine and N-7 of guanine in DNA (Liu et al., 2002). The DNA adducts formation can cause mismatch in DNA replication, in addition, it can alter the promoter methylation or the promoter binding (Yang et al., 2012), which may lead to a mutation in the DNA, abnormal gene expression, and tumorigenesis. Moreover, not only DNA adducts can be formed due to the reactive of PAH metabolites, these PAH metabolites may also induce protein adducts formation in cells (Berge et al., 2004; Kafferlein et al., 2010), which may affect protein structure and its activities. Also, PAH metabolites may induce the reactive oxygen species (ROS), which may affect DNA, lipids, or proteins (Kwack and Lee, 2000).

### 1.1.7 PAH Exposure and Dose-Response Relationship

There are different ways to estimate the internal dose of PAH exposure. This includes biomonitoring of PAH concentrations in urine, which is a marker of current exposure as urinary PAH metabolites can be eliminated from the body within one day (Best et al., 2016). Kuang et al (2013) examined the dose−response relationships between PAH exposure and oxidative stress levels of DNA and lipids among 1333 male coke oven workers. The study assessed the correlation between total of urinary PAH biomarkers and oxidative lesions in DNA, including both of urinary 8-hydroxydeoxyguanosine (8-OHdG) (oxidative DNA damage biomarker), and 8-iso-prostaglandin-F2α (8-iso-PGF2α) (lipid peroxidation biomarker) levels. They found significant positive correlations between urinary PAH biomarkers and both of urinary 8-OHdG and 8-iso-PGF2α levels (Figure 5), the correlation was also positive among smokers and non-smokers after adjustment for other confounders (Kuang et al., 2013).

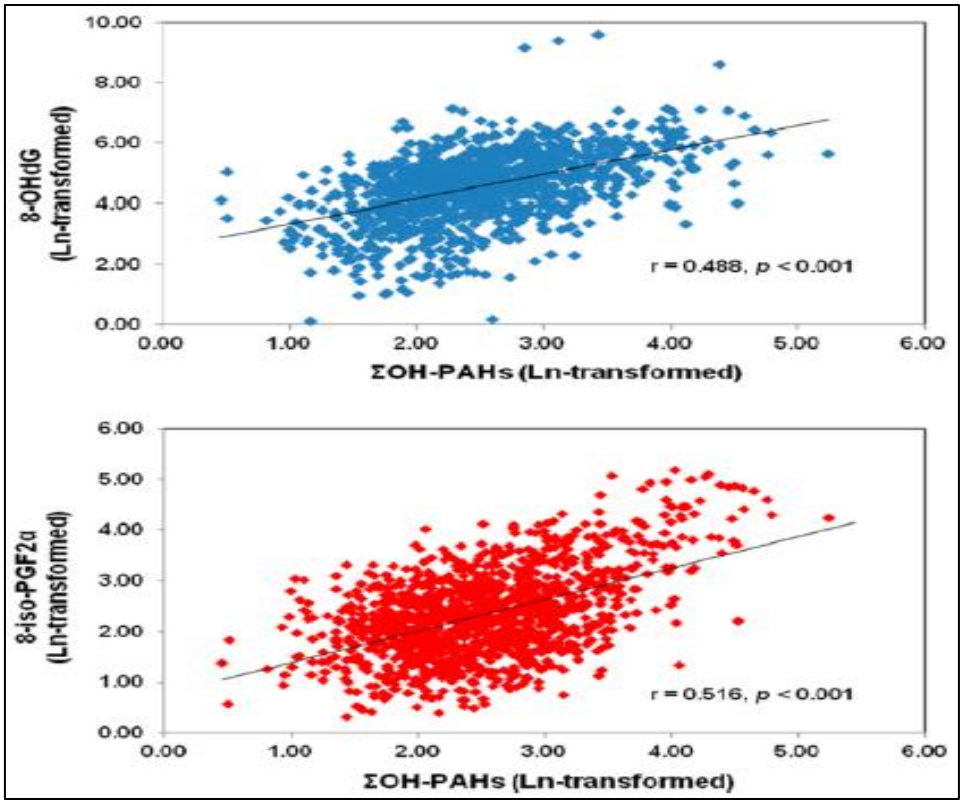



**Figure 5 The correlation between the total of urinary PAH biomarkers and both of urinary 8-OHdG and 8-iso-PGF2α levels in the coke oven workers (Copyrighted to: Kuang et al., 2013)**

### 1.1.8 The Interaction between PAH and other Substances

Humans usually are not exposed to individual PAH, in general, they are exposed to complex mixtures of PAH that can interact with other chemical components. For instance, the exposure to chemical mixtures that includes PAH, such as emissions from roofing tar, coal tar, shale oils, and coke oven have been reported to have negative association with adverse health effect in humans (ATSDR, 1995b). However, the extent of that adverse health effects (whether carcinogenic or non-carcinogenic) depends on the interaction between the PAH mixture with other chemical components. PAH components in cigarette smoke need to interact with other components in the smoke in order to start its tumorigenic effect (ATSDR, 1995b; Akin et al. 1976).

A large body of literature has shown the interaction between noncarcinogenic PAH and carcinogenic PAH in animals. One study concluded that when noncarcinogenic PAH interact with BaP, the interaction exhibits a potential of co-carcinogenic, tumor-initiating, and promoting activity to the skin of mice. Additionally, the compounds of benzo[e]pyrene, fluoranthene, and pyrene increased the BaP-DNA adduct formation (Van, Duuren and Goldschmidt 1976; Van Duuren et al., 1973; Rice et al., 1984; Lau and Baird 1992).

The interactions between PAH components may modify the toxicity level, because PAH mixture requires a metabolic activation by monoxygenases to exhibit its carcinogenic effects. Therefore, any changes or alteration during the metabolic pathways would affect the observed toxicity (Levin et al. 1982). There are different mechanisms by which chemicals may interact with PAH to exhibit toxicity; one compound may interact with the same metabolic activating enzymes, consequently may reduce the toxicity of PAH-carcinogenic, or a compound may induce the metabolizing enzyme levels, consequently may cause more rapid detoxification of PAH-carcinogenic PAH (Levin et al. 1982; ATSDR, 1995b).

### 1.1.9 Industrial Use and Disposal of PAH

There are different PAH compounds produced commercially in the United States, including anthracene, Acenaphthene, fluorene, phenanthrene, and fluoranthene (ATSDR, 1995a). For example, anthracene is used in dye production, in the synthetic fibers, and as a diluent for wood preservatives, as well as in smoke screens, counter crystals, and in organic semiconductor research (ATSDR, 1995a; Hawley 1987). Acenaphthene is used as a dye intermediate, in the manufacture of plastics and pharmaceuticals products, and in insecticides and fungicides (Hazardous Substances Data Bank (HSDB), 1994; Windholz 1983; ATSDR, 1995a). Fluorene can be used in many

chemical processes, such as formation of polyradicals for resins, and in the making of dyestuffs (Hawley, 1993; HSDB, 1994; ATSDR, 1995a). Phenanthrene is used explosives, biological research, and in the manufacture of dyestuffs (Hawley 1987; HSDB 1994). Fluoranthene can be added as lining material to protect the interior of steel drinking water pipes and storage tanks (National Research Council (NRC) 1983; ATSDR, 1995a).

PAH are persistent in industrial solid wastes, therefore, the disposal process of these solid wastes that contain PAH is a very important in avoiding environmental and human contamination (Sisinno et al., 2004). Particle-bound PAH exist in surface waters and needs to be processed and removed by sedimentation, flocculation, and filtration processes. However, residual PAH dissolved in water require oxidation for partial removal or transformation (EPA 1980).

### 1.1.10 PAH and Tobacco Smoke

Cigarettes contain different chemical compositions as well as numerous toxic and carcinogenic PAH components, especially BaP (Vu et al., 2015). It was reported that tobacco smoke contains more than five hundred different PAH (Rodgman and Perfetti, 2009). In addition, the United States Food and Drug Administration (FDA) identified about 93 harmful and potentially harmful compounds in tobacco products and tobacco smoke, sixteen of these compounds are PAH (FDA, 2012).

Since the main route of PAH exposure is inhalation, the dose of PAH exposure can be measured by the level of PAH concentrations in the lung tissues. Goldman et al. (2012) measured eleven PAH compounds in 70 samples of lung tissue (cancer-free), donors were 37 smokers and 33 nonsmokers, as estimated by serum cotinine concentration, the study found that the higher concentration of total PAH was among smokers. There was a dose-response relationship for greater

smoking, and they also stated that tobacco smoke increased concentrations 5 types of PAH in lung tissues including BaP. They also found higher PAH concentrations in lung tissues in males relative to females. In addition, black males had a higher concentration of PAH in lung tissues compared to other ethnic groups (Goldman et al., (2012).

### 1.1.11 PAH Exposure and Public Health Perspective

PAH exposure is considered to be a growing public health issue, many studies indicate that certain PAH can be carcinogenic to humans and animals. PAH exposure in humans comes mostly from occupations that involve PAH mixtures, such as roofing, oil refining, or coal extractions and other work-related PAH exposures (ATSDR, 1995b). As it was mentioned previously, adverse health effects of PAH exposures in animal experiments have shown that several PAH components, including BaP, benzo[b]fluoranthene, chrysene, and other chemical components can cause tumors and different carcinogenic effects, regardless of whether the PAH exposure was by inhalation, ingestion or by long-period of skin contact exposure. Studies also have shown the cancerous effect in humans after long-period of PAH exposure, especially by the inhalation routes (ATSDR, 1995b).

The biggest public health concern is with the mortalities related to the PAH exposure. An old study conducted in animals found that the exposure to BaP for total period of 109 weeks was related to reduced-survival of hamsters after 60 weeks of BaP inhalation. The study concluded that the toxic and carcinogenic effects of BaP might be the cause of the reduced-survival of hamsters (Thyssen et al., 1981). A recent study found that PAH exposure was linked to increasing risk of all-cause mortality and the study concluded that PAH metabolites were associated with increased risks of cancers, cancer mortality, and possibly cardiovascular disease mortality among adults aged 20 years and older (Chen et al., 2021).

The exposure to PAH can be vary within different geographic regions, studies reported that residents of the environmental justice neighborhood can be disproportionally exposed to toxic air pollutants including PAH from both industry and transportation infrastructure, which would increase the negative health consequences among minorities and vulnerable population (Sansom et al., 2018). Communities efforts and research projects attempted to investigate these discriminatory environmental exposures, however, the type of these observational studies did not provide an inadequate evidence by both researchers and affected communities (Bowen, 2002; Sansom et al., 2018).

Multiple large studies showed an evidence of the link between air pollution including PAH exposure and socioeconomic status. A study reported that Non-Hispanic blacks and Hispanics were living in counties that had highest air pollutants concentrations, such as fine particulate matter diameter less than 2.5 micrometers (PM2.5), O3, and PAH (Miranda et al., 2011). Another research study reported that non-Hispanic blacks, unemployed individuals with low income and low education level were living in areas with higher exposures to different air pollutants (Bell and Ebisu, 2012). The variation in the health of disadvantaged populations can be explained by different reasons, for instance, residential segregation is an important factor that plays a big role of determine why communities differ in air pollutants exposures (Massey and Denton 1993). The racial differences may face greater exposure to different air pollutants, especially the carcinogenic PAH group, such as BaP, that could be because of different factors, for instance, racism, class bias, land costs, and housing market dynamics (American Lung Association, 2020).

From a public health perspective, the adverse health effects as a result of PAH exposure, depend on how long the individual has been exposed to PAH (short-term or long-term exposure), the amounts or quantities of PAH toxicants entered the body, and how the body reacted and responded to PAH (Kim et al., 2013). It still not clear whether the exposure to PAH itself for short-

term may cause adverse health effects, however, it was reported that other chemical compounds that exist in PAH may be the cause adverse health effects for short-term, such as nausea, vomiting, diarrhea, eye irritation, and cognitive disorders (Sun et al., 2021). On the other hand, long-term exposure to PAH may cause cataracts, kidney and liver damage, and jaundice, also, inhaling large amounts of naphthalene can cause the breakdown of red blood cells (Sun et al., 2021).

The exposure to PAH may have different negative health consequences. Different epidemiological research studies have found that PAH exposure may cause neurobehavioral disorders, such as cognitive impairment (Wormley, Ramesh, and Hood, 2004). Also, PAH from the environment or tobacco smoking constitute another modifiable exposure that can increase the risk of hypertension, which also increases the risk of cardiovascular diseases (Abboud and Karam, 2021; Sancini et al., 2014; Zhang et al., 2021; Shiue, 2015). The effect of PAH exposure on cognition and increasing the risk of hypertension may also differ with age, gender, and race.

## 1.2 Overview of Cognitive Impairment

## 1.3 Cognitive Impairment Among Older Adults

Cognitive impairment or cognitive decline is defined as confusion or memory loss that generally affects older populations (Centers for Disease Control and Prevention [CDC], 2009). Individuals suffering cognitive impairment may experience difficulty or trouble memorizing, and may have difficulty in learning new things, concentrating, or making decisions. All of which may affect their daily life activities (CDC, 2009). Approximately 20% of the United States population of adults aged 65 years and over have some form of cognitive impairment, such as Alzheimer disease and dementia (Karel, Gatz, & Smyer, 2012; Best et al., 2016).

The geographic distribution of the cognitive impairment among different age groups in the United States varies. For instance, the percentage of adults with cognitive impairment aged 50 years and older ranged from approximately 9% in Iowa to 15% in Michigan (Figure 6) (CDC, 2009).

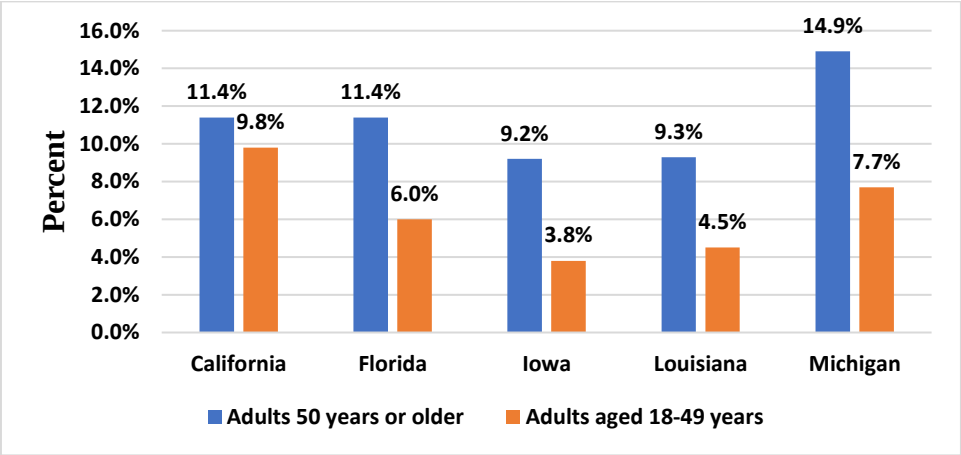



**Figure 6. The percentage of adults with cognitive impairment within different states and age groups (CDC, 2009)**

### 1.3.1 Cognitive Impairment Classifications and Measurements

Cognitive impairment can be classified as mild or severe forms with about 10 to 20 percent having mild cognitive impairment (MCI) among age group of 65 years or older (Best et al., 2016). People with MCI can perform their activities of daily lives normally, however, they may notice some changes in their cognitive functions or behaviors. On the other hand, people with severe cognitive impairment may experience more difficulties, such as losing the ability to understand, talk, or write, which impairs their normal lives and the ability to live independently (CDC, 2009).

Clinically, cognitive function can be measured by different procedures. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) is a comprehensive battery of

neuropsychological tests performed to measure cognitive impairments and assess patients with clinical diagnosis of Alzheimer's disease (Fillenbaum et al., 2008).

### 1.3.2 Cognitive Tests Assessment

CERAD consists of different tests that can be performed to examine the cognitive function among adults. The cognitive tests battery includes: Digit Symbol Substitution Test (DSST), Word list learning (WL), Delayed Word Recall test (DWR), and Animal Fluency (AF) (Brody et al., 2019).

DSST is a subtest performed to assess psychometric cognitive and executive function, including attention, motor and processing speed, and visuoperceptual functions (writing, drawing, or scanning) (Jaeger, 2018). The DSST is performed by giving the individual a single sheet of paper to match symbols to numbers according to a key located on the top of the page, the individual needs to copy the symbol and correctly match it with its number within 90 to 120 seconds. For each correctly matched symbol–number pair, a one point was giving for a total score of 105 (CDC, 2014a).

The DSST is a common test that has been used in most all neuropsychology assessment tests due to its high sensitivity for detecting MCI (Rosano et al., 2016). DSST can also be used to detect the short-term effect of alcohol consumption or drugs after administration on the cognitive changes (Wang et al., 2013; Evans and Levin, 2004). Proust-Lima and colleagues (2007) conducted a cohort study on elderly French adults and found that DSST is highly sensitive to cognitive changes. DSST could detect a one-point change in DSST score in adults who scored 25 or above when performing a cognitive examination (Proust-Lima et al., 2007).

WL and DWR tests can assess cognitive changes by evaluating the verbal learning (to assess new verbal learning, the immediate and delayed memory) among older adults, which may help in early diagnosis of Alzheimer's disease (CDC, 2014a). WL test consists of three consecutive learning trials, each trial list contains 10 un-related words (same words for each of three trials but in different order). Words were read aloud, then, the participants were asked to recall as many words as possible (immediate recall). For the three trials, 1 point was given for each word recalled for a total score of 30 (CDC, 2014a). DWR consists of ten separate words, the individual reads aloud those words from a computer screen, then is asked to recall them after performing another unrelated task or after a delay. The test is scored by giving 1 point for each word recalled for a total score of 10 (Lyness et al., 2014a).

AF test is performed to examine verbal/semantic fluency, which is considered as a component of executive function. The test is performed by asking the participants to name as many animals as possible in one minute. AF test scored by giving 1 point for each named animal for a total score of 40 (CDC, 2014a).

### 1.3.3 Factors that Affect Cognitive Performance

Different studies have examined the factors that may contribute to progressive cognitive decline among older adults. For instance, age and genetic susceptibility are strong risk factors that may increase the risk of cognitive impairment among different age groups (Hendrie et al., 2006, CDC, 2009; Best et al., 2016). It is well documented that genetic factors are the major risk factors for cognitive function decline that leads to developing Alzheimer’s disease (Todd et al., 2017; Rawle et al., 2018; Emrani et al., 2020). Apolipoprotein E (APOE) is the primary genetic risk factor that plays a big role in the onset of dementia and Alzheimer’s disease. APOE is involved in

cholesterol and other lipid metabolism and transport between cellular structures, as well as playing a major role in clearing β-amyloid from the brain (Todd et al., 2017).

APOE consists of ε2, ε3 and ε4 alleles. The ε4 has the highest rate of lipoprotein clearance, therefore, it can affect plasma cholesterol level as well as disrupt brain re-innervation processes that rely on lipids (Rawle et al., 2018). Possession of the ε4 allele (especially homozygosis carriers) is considered as the primary genetic risk factor for developing cognitive function impairment, Alzheimer's disease, and dementia (Emrani et al., 2020). It was reported that APOE ε4 carriers are experiencing more memory declines rapidly than in APOE ε4 noncarriers (Caselli et al., 2004).

Metabolic syndrome, including cardiovascular diseases (heart diseases, hypertension, and stroke), lung disease, diabetes, and tobacco smoke, are also considered possible risk factors that play a strong role in developing cognitive decline among the elderly (Zhang et al., 2015; Hendrie et al., 2006, CDC, 2009; Best et al., 2016). Additionally, different studies have shown that environmental factors, such as pesticides and ambient air pollution could be potential risk factors for cognitive decline overtime with age (Bouchard et al., 2014; Kim et al., 2015; Loop et al., 2013; Weuve et al., 2012; Gatto et al., 2012; Chen and Schwartz, 2009; Best et al., 2016).

### 1.3.4 Cognitive Decline and Public Health

Cognitive impairment is considered a growing public health issue, cognitive decline can interfere with people behaviors, activities, and in their daily lives. Regardless of whether it is subjective cognitive decline (SCD) (a self-reported experience of confusion or memory loss) (Jessen et al., 2014) or actual cognitive decline, both types are considered as subtle markers of early symptoms of Alzheimer's disease, which is also an emerging public health concern (CDC, 2017). Cognitive impairment may affect a person's ability to effectively manage their personal treatment

plans and taking their daily medications, which can result in poor health outcomes of comorbid chronic diseases, such as diabetes and cardiovascular diseases (CDC, 2017).

According to Silvaggi et al. (2020), about 10–20% of people aged under 65 may have early onset dementias or MCI, which may not significantly impact their work performance and allow them to remain active and in the workforce (Silvaggi et al., 2020). However, early onset dementias or MCI may affect and reduced their work ability and their work-related activities (WHO, 2012). Due to a normal decline of cognitive ability and motor functioning, older workers have lower ability to learn, more difficulty in training, and are less flexibility in performing their work tasks during routine work hours (Mutlu et al., 2018).

A recent study found that individuals with MCI or early onset dementias tend to leave their work, considered as a job loss (Sakata and Okumura, 2017). The study involved 220 participants aged 40–59 with early onset dementias against 1100 age and gender-matched controls with non-MCI or any type of dementias. The study stated that after the period of two and half months and after the participants received their diagnosis of early onset dementias, there was an increase in leaving one's job. After six months, approximately 9.1% of participants with early onset dementias and 3% of controls left their job as well (Sakata and Okumura, 2017).

### 1.3.5 Racial Demographic of Cognitive Impairment in the United States

Racial and ethnic disparities in cognitive impairment may differ in prevalence for each racial group. For instance, to identify disparities in prevalence of SCD among different racial groups in the United States population, it was reported that during 2015–2018 of about 180,000 participants aged 45 years or older who participated in a SCD screening, 19,276 had SCD with some other chronic conditions. The prevalence of SCD was; 10.7% in Whites, 12.3% in Blacks,

and 9.9% in Hispanics. Additionally, Blacks and Hispanics with SCD were had less education level, lower income, less access to health care, and more functional limitations (Gupta, 2021).

Another study examined the differences in cognitive function between different race and ethnic groups in the United States population (Díaz-Venegas et al., 2016). This study used in-person or by telephone interview with a modified version of the telephone interview for assessing cognitive status among 19,000 participants. They found that Hispanics and Blacks had lower cognition scores than Whites for all age groups (51–59, 60–69, 70–79, 80 and over) (Figure 7) (Díaz-Venegas et al., 2016).

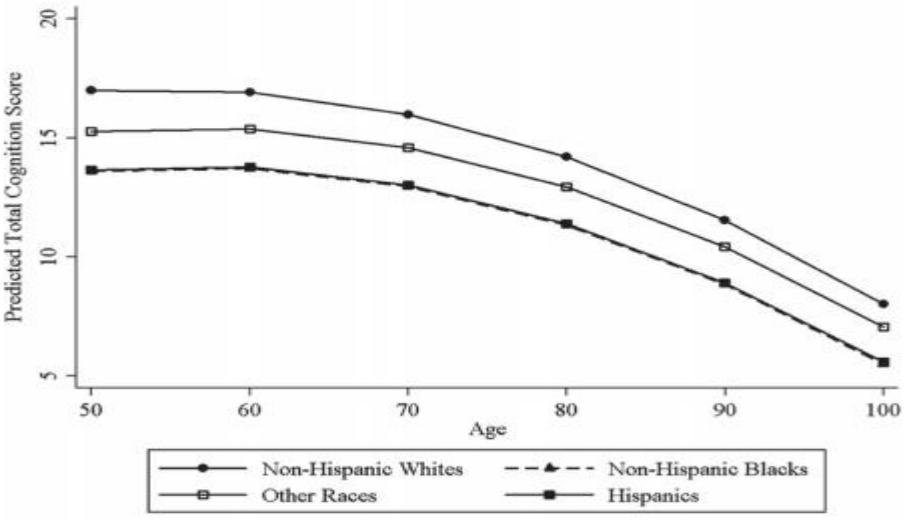



**Figure 7 Predicted cognitive scores of participants aged 52 years and older by race/ethnicity (Díaz-Venegas et al., 2016)**

## 1.4 Overview of Hypertension

Several epidemiological studies provide evidence that elevated blood pressure or hypertension (HTN) (defined as systolic and/or diastolic BP ≥140/90mmHg) is a major risk factor for cardiovascular disease (CVD), the leading cause of death in worldwide (WHO, 2004; Bangia

et al., 2021; Abboud and Karam, 2021; Aryal, Harmon, and Dugas, 2021). HTN is considered a major cause of disability and a leading to risk factor for death worldwide (DeGuire et al., 2019). It was estimated that the prevalence of hypertension is approximately 30 - 40% of the global population (Pereira et al., 2009), and it expected to increase with advanced aging of the population (Myers, 2007).

There are two types of high blood pressure; primary (essential) hypertension that occurs with no identifiable or specific cause, developing over many years and secondary hypertension caused by an underlying condition, such as kidney disease, thyroid problems, adrenal gland tumors, obstructive sleep apnea, and some drugs, including cocaine and amphetamines (Mayo Clinic, 2021). There are different risk factors that can increase the risk of the HTN including age, race (more common among African heritage), family history, obesity, tobacco smoke, alcohol consumption, diet (e.g. consuming too much sodium salt and less amounts of potassium), lack of physical activities, stress, and chronic disease (Mayo Clinic, 2021).

There are different complications for the HTN that can lead to serious health consequences and life-threatening conditions, such as heart attack or stroke, aneurysm, heart failure, weakened and narrowed of blood vessels in the kidneys, metabolic syndrome (including increased of waist size, high triglycerides, decreased high-density lipoprotein (HDL)), memory decline, and Dementia (vascular dementia) (Mayo Clinic, 2021).

Other environmental factors such may also increase the risk of developing HTN. Ambient air pollution is a well know environmental factor associated with developing HTN (Giorgini et al., 2016). For instance, fine particulate matter diameter less than 2.5 micrometers (PM2.5) is an air pollutant that can increase HTN risk whether in short (3 and 4 weeks) or long-term (1 to 3 years) exposures (Wellenius et al., 2012; Dong et al., 2013).

Additionally, various epidemiological studies examined the association between PAH and

HTN, one study found an association between hydroxypyrene (1-OHPr) (one component of PAH) and HTN among outdoor workers (Sancini et al., 2014). Another study assessed the association between different PAH types with HTN, and reported that urinary 4-hydroxyphenanthrene was associated with hypertension (Shiue, 2015). A recent study also found an association between different PAH and HTN (Bangia et al., 2021).

### 1.4.1 Racial Demographic of Hypertension Incidence in the United States

According to the CDC, during the period of 2015-2016 that the percentage of HTN cases occur more in men (51.0%) than woman (39.7%) (CDC, 2020). Among men, the percentage of HTN cases occur more in Black (57.2%) compared to White (50.2%), and Hispanic (50.1%) adults. Among women, the percentage of HTN cases occur more in Black (56.7%) compared to White (36.7%), and Hispanic (36.8%) adults (Figure 8) (CDC, 2020).

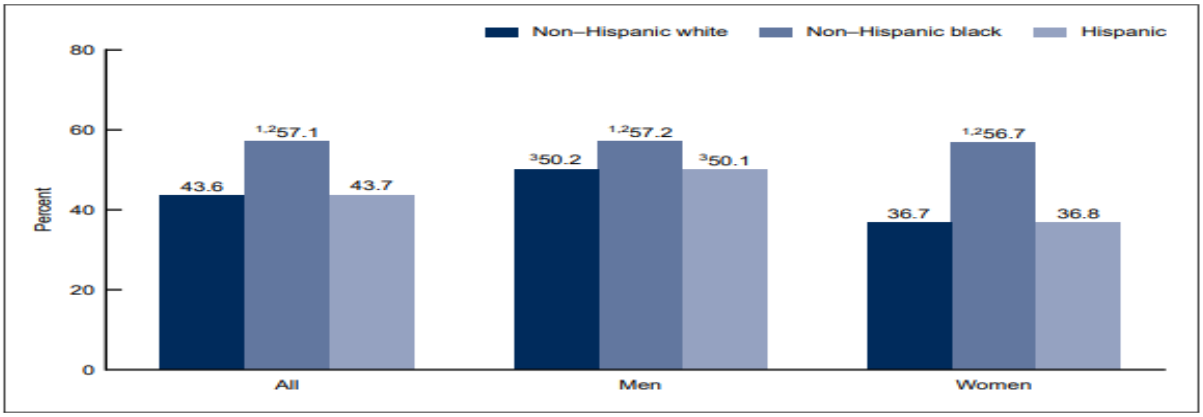



**Figure 8 The prevalence of hypertension among adults aged 18 and over, by sex and race in the United States, between 2017–2018 (CDC, 2020)**

## 1.5 Hypothesis and Aims

As indicated, PAH are a public health concern and the exposure to PAH, whether acutely or chronically, may increase the risk of human diseases among different age, race and ethnic groups worldwide. Multiple reports have shown an association between PAH and cognitive impairment among young age groups and there are some reports assessing the association between PAH exposure and CVD, including the association with developing the risk of hypertension. These studies concluded that the exposure to PAH may affect cognitive performance, and also may affect the developing the risk of hypertension among older adults.

This dissertation research investigated two aims: 1) the hypothesis that exposure to PAH may reduce the cognitive performance in the older population and that effect would differ in race groups; and 2) the hypothesis that the effect of PAH exposure on hypertension may change with race among older adults.

# 2.0 The Association between Polycyclic Aromatic Hydrocarbons Exposure and Cognitive Performance in the United States Older Adults

In review by Plos One, June 2021

## 2.1 Introduction

The World Health Organization (2020) reported that the fast-growing elderly population, especially in developing countries, will increase dementia to a global epidemic in the near future. As life expectancy has doubled recently (Environmental Pollution Centers, 2017), different studies considered aging as a result of lifelong damage to cells and tissues overtime (Kirkwood, 2008), which may harmfully affect the cognitive performance (CP) among this age group (Salthouse, 2009). According to the Alzheimer`s Association (2018), dementia and cognitive decline are major remarkable mental disorders in older people. Statistically, the prevalence of cognitive decline among adults aged 65 years and over is about 30-40% and may increase with increasing age.

Different epidemiological studies and laboratories experiments have found that PAH exposure can cause neurobehavioral deficits (Wormley, Ramesh, and Hood, 2004). Globally, children born in early 1980s in the Czech Republic were experienced learning disorders, these children were presumed to be exposed to PAH in utero due to the increased levels of PAH that in mining and combustion of coal (Otto, Skalik, and Bahboli, 1997). The long-term exposure to B[a]P had developed neurotic syndromes with vegetative dysregulation and a loss of short-term memory among workers in Coke production factories in Poland (Majchrzak, Sroczyński, and Chełmecka,

1990). From the period-time of 1960s until the 1970s, some neurological symptoms were noted and reported from a community in Texas during the chronic exposure to different PAH biomarkers, such as B[a]P, naphthalene, fluorine, and pyrene products that were dumped at nearby national priorities list (NPL) hazardous waste sites. Same in the state of Louisiana, residents who were living close proximity to a combustion superfund site had also neurophysiological problems (Dayal et al., 1995).

### 2.1.1 PAH and Neurodegenerative Diseases

The plausibility of these associations has been demonstrated in animal studies that found that exposure to B[a]P may cause acute neurobehavioral toxicity through oxidative stress (Saunders et al., 2006) poor performance in running after short-term exposure to fluorine and naphthalene (other PAH components) (Peiffer et al., 2013; Kilanowicz et al., 2012).

A recent study was conducted on rats mentioned that B[a]P exposure at early gestation may lead to learning and memory deficit in offspring rats and may affect the neuronal survival in their later-life, the study also demonstrated that B[a]P exposure caused a notable reduction of hippocampal neurons and glial cells at early gestation when compared with the control group (Das, Patel, and Patri, 2019). These results reveal how the PAH exposure affects learning and memory over time-period, these results could be applied as well on human, however, further research projects and experiments are needed to determent the molecular mechanism and the cellular interaction with PAH components to understand the role of PAH and its effect on learning and memory behavior in adults.

The neurotoxic effects of PAH exposure have been reported. Das, Patel & Patri (2011) found that early exposure to Benzo[a]Pyrene (B[a]P) (a high molecular weight PAH constituent of

tobacco smoke) may lead to pathogenic reduction in dopamine neurotransmitter level leading to neurodegenerative diseases and neurobehavioral perturbation in adolescence. Maternal/fetal PAH exposures have been linked to developmental have been associated with cognitive deficits in childhood that can affect behavior, as well academic performance (Perera et al., 2011). Cho et al. (2020) demonstrated that the exposure to PAH was associated with cortical thinning, and decline in verbal learning and memory function in healthy adults.

### 2.1.2 PAH Exposure (Prenatal Development and Genotoxic Effect)

Several studies suggest that PAH exposure during the prenatal and early postnatal stages might affect the developing of fetus and infant (Polanska et al., 2014). It has been reported in different studies that PAH concentrations were found in placental tissues and umbilical cord blood (Polanska et al., 2014; Perera et al., 2005), which may suggest that the transfer of PAH biomarkers and other chemicals can across the placenta and fetal blood brain barrier, consequently, would affect and increase the risk of intrauterine fetal development, growth restrictions, small gestational age, and preterm delivery (Dejmek et al., 2013; Choi et al., 2008).

Importantly, the prenatal exposure to PAH have an impact on fetus parameters at birth, such as birth weight, length, as well as on head and chest circumference (Polanska et al., 2014; Polańska et al., 2010). These parameters were correlated with severe intrauterine growth restriction, poor neurodevelopmental disorders, and subsequent morbidity and mortality (Bassan et al., 2005; Leitner at al., 2007).

Furthermore, it has been reported that prenatal exposure to PAH may affect the infants' neurodevelopment, for instance, it may decrease cognitive and motor functions, reduce child IQ, and increase risk of behavioral problems (Perera et al., 2006; Wang et al., 2010). According to Choi

et al. (2008) a one unit increase in prenatal PAH exposure was associated with a 0.04% increase in cephalization index. A cohort study that was conducted in New York City illustrated that prenatal exposure to PAH was associated with developmental delay at age of 3 years and reduced IQ at age of 5 years (Perera et al., 2009).

Different studies have provided an evidence that prenatal exposure to PAH has been associated with behavior, brain gene expression, impaired neurocognition, and increased anxiety (Chu et al., 2013; Yan et al., 2014). Miller et al. (2016) found that the prenatal exposure to PAH was associated with altered behavior, gene expression reductions, and elevation in brain-derived neurotrophic factor (Bdnf) DNA methylation within the cortex in adulthood mice.

## 2.2 Hypothesis and Aims

The link between air pollutants, such as PM and ozone (O3), and the risk of cognitive impairment among younger individuals has been shown in recent studies (Peters et al., 2019). However, limited studies have examined the association between specific components of air pollutants, such as PAH, and cognitive decline risk among older adults.

We hypothesize that the exposure to PAH may reduce the CP in older population. Most studies have focused on addressing the relationship between PAH and cognitive assessment among newborns and young age groups. However, there are knowledge gaps regarding understanding the impacts of PAH on CP among older adults. Different studies mentioned the risk of environmental factors including air pollution for developing dementia in the elderly (Killin et al., 2016). However, one study conducted over a time-period of two years (2001-2002) and the DSST did find a negative association between PAH and cognitive decline among older adults (Best et al 2016).

To expand on the previous findings, we examined a battery of four cognitive tests (DSST, DWR, WL, and AF) over four years (2011-2014) in a larger cohort of older adults along with an expanded battery of urinary PAH biomarkers (1- and 2-hydroxynaphthalene (1-OHN and 2-OHN), 2- and 3-hydroxyfluorene (2-OHFl, 3-OHFl), 1-, 2-, and 3-hydroxyphenanthrene (1-OHPhe, 2-OHPhe, 3-OHPhe), and 1-hydroxypyrene (1-OHPyr)) to determine associations between CP and PAH exposure. This allowed stratification of exposures and clinical outcomes on the basis of sex, race, ethnicity, and socio-economic status.

## 2.3 Materials and Methods

### 2.3.1 Ethics Statement

The data were exempt from human subjects review as this study used public dataset (NHANES 2011-2014) that were anonymized and de-identified before it was analyzed.

### 2.3.2 Study Population and Data Collection

Data were obtained from National Health and Nutrition Examination Survey (NHANES) for the years 2011-2014. NHANES is a series of cross-sectional surveys conducted by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). NHANES uses complex and multistage design sampling aims to select random samples that contain a specific number of noninstitutionalized civilians across the United States. For each cycle year, the random selected sample data consist of demographic, social, behavioral, dietary, clinical, and laboratory analysis that performed by interviews and physical examinations.

The data survey analysis for this study consists of household interviews and physical examinations performed in a mobile examination center (MEC). Eligible individuals included all adults aged 60 years and over with urinary PAH metabolite measured and with four assessed cognitive tests DSST, DWR, WL, and AF were obtained from NHANES 2011-2014 surveys.

Cognitive function assessment was obtained from NHANES surveys either during household interviews or in the MEC centers for the period of 2011 to 2012 and for 2013 to 2014. CP was assessed, but for limited number of cognitive subdomains, such as working memory, processing speed, and executive functioning evaluation. The CERAD battery module for this study will include DSST, DWR, WL, and AF, and will treated as continuous variables.

#### 2.3.2.1 Urinary Biomarkers of PAH

The urine samples were collected from participants at MEC, the samples were stored under low temperature (–20°C), and sent to National Center for Environmental Health for farther analysis (CDC, 2014b; CDC, 2016). The analysis procedure included enzymatic hydrolysis of glucuronidated/sulfated OH-PAH metabolites in urine to remove PAH conjugates, extraction including mono-hydroxylated PAH metabolites. The urinary metabolites were analyzed using isotope dilution capillary gas chromatography with high-resolution mass spectrometry (GC-MS/MS) (CDC, 2014a; CDC, 2016). Some of PAH metabolites results were below the lower limit of detection (LLOD), for that reason, a value was imputed as a lower limit of detection divided by square root of 2 (CDC, 2014a; CDC, 2016).

For this study, urinary PAH biomarkers were categorized into three groups based on its molecular weights:

1. Total of all urinary PAH metabolites (1-OHN, 2-OHN, 3-OHFl, 2-OHFl, 3-OHPhe, 1-OHPhe, 2-OHPhe, and 1-OHPyr).

2. Total of smaller molecular of PAH (NFP) that include 1-OHN, 2-OHN, 2-OHFl, 3-OHFl, OHPhe, and 2-OHPhe.

3. 1-OHPyr.

Measure of urinary creatinine was added as a potential confounder in linear regression models to account for PAH biomarker variation due to differences in urine dilution. Each urinary PAH biomarker group was used as predictor for each cognitive test in separate linear regression model. To satisfying normality assumptions, we took the natural logarithmic transformation of all PAH metabolite measures for all statistical analyses.

#### 2.3.2.2 Socio-Demographic Variables, Risk Factors, and Confounders

The study cohort consisted of 3,181 adult survey participants who had one or more cognitive test scores (Figure 9). Data were used to examine the association between the urinary PAH biomarkers and cognitive tests after adjusting for risk factors, such as age, socio-economic status, medical conditions, cardiovascular diseases, diabetes, tobacco smoking, alcohol consumption, kidneys problems, lack of physical activity, and self-reported assessment physical function limitations. The risk factors, were categorized into different groups similarly to earlier studies (Best et al., 2016)

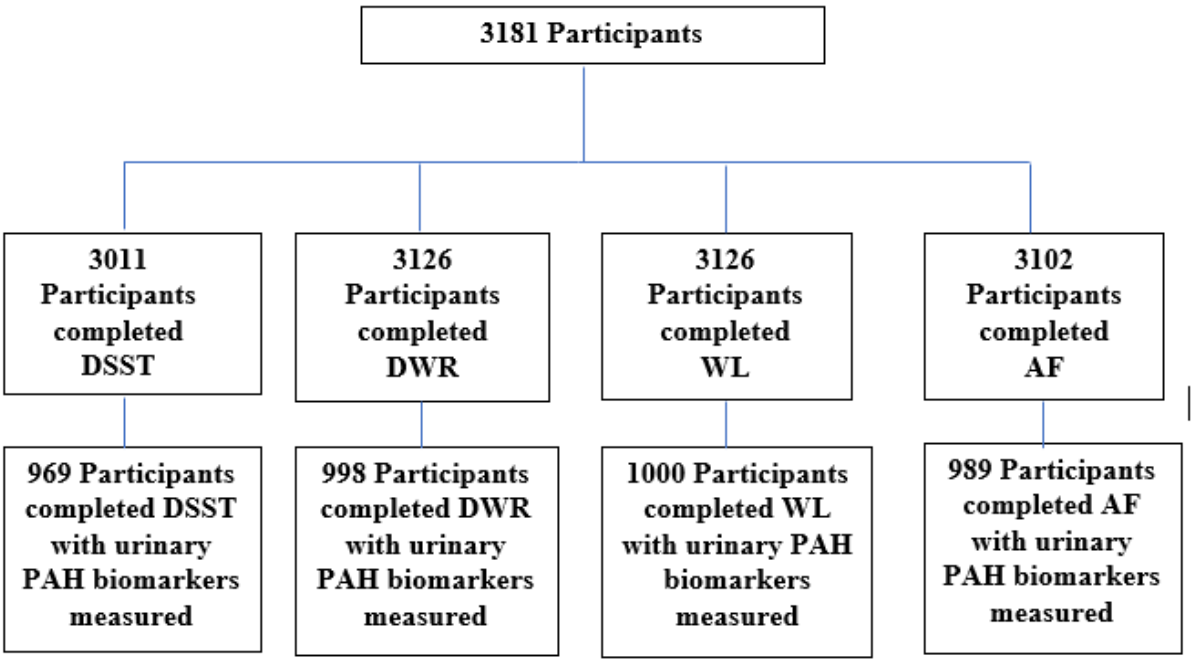



**Figure 9 The total number of NHANES participants completed cognitive tests and with urinary PAH biomarkers measured**

Age at the time of screening is categorized into three groups: 60–69, 70–79, and 80 and over. Race and ethnicity groups are classified as Whites, Blacks, Asians, and Hispanic. Sex was categorized as male or female. Annual family income was collected as a range value in US dollars and categorized as low income (<25,000), middle income (25,000-54,999), and high income (>=55,000). Education level was classified into four groups: having less than high school education, having completed high school or a GED (high school equivalency diploma), having some college, or being a college graduate or higher. Smoking - cigarette use was classified as smoker (individuals who smoked at least 100 cigarettes in entire their lives or non-smoker (smoking less than 100 cigarettes in life) (yes/no). Alcohol consumption was categorized into Alcohol drinker (drinking more than 12 alcoholic drinks a year) or non-drinker (drinking less than 12 alcoholic drinks a year) (yes/no).

Medical condition variables were constructed on self-reported answers (yes/no) for different health aspects, such as heart diseases (congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack), stroke, emphysema, memory and thinking. Diabetes was categorized into diabetic as self-reported answers (yes/no) (individuals who have been told by doctors that they are diabatic) or not diabetic. Kidney problems were categorized as self-reported answers (yes/no) for individuals who had kidney problems (who have been told that they have weak or failing kidneys), or individuals who were not aware of kidney problems. Physical activity variable included participants who reported (yes/no) that they practice and engage in daily activities, such as vigorous work activity, walking or using bicycle, or practicing some vigorous recreational activities. Physical functioning limitation variable measured self-reported functional limitation conditions that was caused by long-term physical, mental, and emotional problems, for instance, limitations that keep individual from working, limited work amount that individual can does, or if individual experiences any confusion or memory problems.

Body mass index (BMI) is defined as weight in kilograms divided by height in meters squared, this variable was categorized into three groups normal (<25), obese (25-29.9), and over weight (=>30). Blood pressure and cholesterol variable was categorized into individuals who have hypertension (participants take prescribed medicine for hypertension) or non-hypertension, as self-reported answers (yes/no), for cholesterolemia, it was categorized into individuals who have high cholesterol in blood (taking prescribed medicine for cholesterol) or individuals who do not take medicine for cholesterol as self-reported answers (yes/no).

## 2.4 Statistical Analysis

### 2.4.1 Descriptive Statistics

Descriptive statistics used to characterize the study participants included counts, means, and standard error (SE) for continuous variables for both cognitive scores and urinary PAH biomarkers. Counts, percentages (weighted), SE for categorical variables. Missing data (N) was not included, since NHANES collected the sample data randomly.

Univariate linear regression analyses were used to measure the association of CP scores and urinary PAH biomarkers for each individual risk factor in separate models (Models 1-4) (S1 Appendix). This tested for statistically significant associations between each covariate and cognitive tests and only significant co-factors were included in the multivariate model. The linear regression model is:

$y= \beta o + \beta 1 \log(X1),$

where y is DSST, DWR, WL, or AF score for each individual, βo is the intercept of the regression line, β1 is the slope of the regression line, X1 is the logarithm of the PAH biomarker concentration. Furthermore, categorical variables were dummy-coded to create reference groups. Dummy variables allowed for multiple comparisons in a single multivariate model while controlling experiment wise error.

Multivariate linear regression analysis was used to measure the independent association of CP scores with urinary PAH biomarker groups for the significant covariates identified in the univariate models. A single multivariate model was constructed for each cognitive test. These models (models 5-8) (S1 Appendix) utilized the dummy coded variables used in the univariate models. The multivariate linear regression models are:

$y = \beta o + \beta 1 \log(X1) + \beta 2 \log(X2) + \beta 3 \log(X3) \ldots + e,$

where y is the DSST, DWR, WL, or AF score for each individual, βo is the intercept of the regression line, β1 is coefficient of the regression model that represents the change in the mean of the DSST, DWR, WL, or AF score for each unit change in the log of a specific PAH biomarker, X1 is the logarithm of a specific PAH biomarker, X2 is another covariate to adjust for in the model, e is the error term.

All data were analyzed using SAS Version 9.4

## 2.5 Results

### 2.5.1 Descriptive Statistics

Descriptive statistics were generated for demographic variables (Table 1) (S1 Appendix). The majority of participants were between 60 and 69 years old (~55%), also, the percentage of female participants was higher than males 55% to 45%. Additionally, the percentage of white participants was the highest 78%. Table 2 (S1 Appendix) represents mean and SE for DSST, DWR, WL, and AF test scores. Overall, the mean score for DSST, DWR, WL, and AF were 52, 6, 19, and 18 respectively. Table 3 (S1 Appendix) shows descriptive statistics for mean and SE for urinary biomarkers of PAH. Overall, the mean urinary biomarkers concentration for each of PAH-total and PAH smaller molecular metabolites was approximately the same (55000 ng/L), and for 1-OHPyr metabolites was 137 ng/L.

Table 4 (S1 Appendix) shows the descriptive statistics for categorical variables by urinary PAH metabolite groups, and for DSST, DWR, WL, and AF scores. Males had higher urinary PAH metabolite concentrations than females, as well as lower scores in all cognitive tests. Participants with low income (<$25000) had relatively the highest urinary PAH metabolites and lowest test scores comparing to middle and high income. Blacks had the highest urinary PAH biomarkers concentrations (Figure 10). Also, Hispanics and Blacks had the lowest DSST scores (Figure 11). Smokers had the highest urinary PAH metabolite concentrations and lowest test scores comparing to non-smokers. Overall, whites had the highest smoking rates (~48%) compared to other ethnic groups (Figure 12).

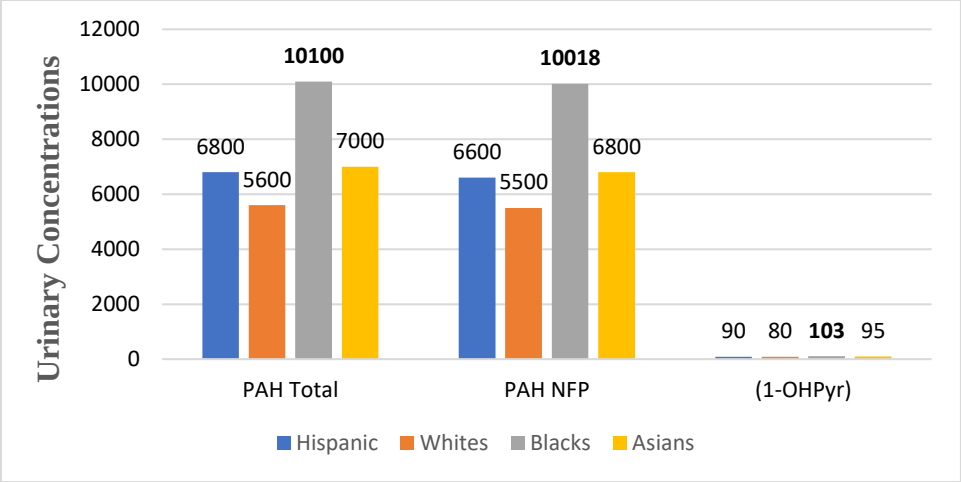



**Figure 10 Urinary PAH biomarkers by race and ethnicity (p<0.001)**

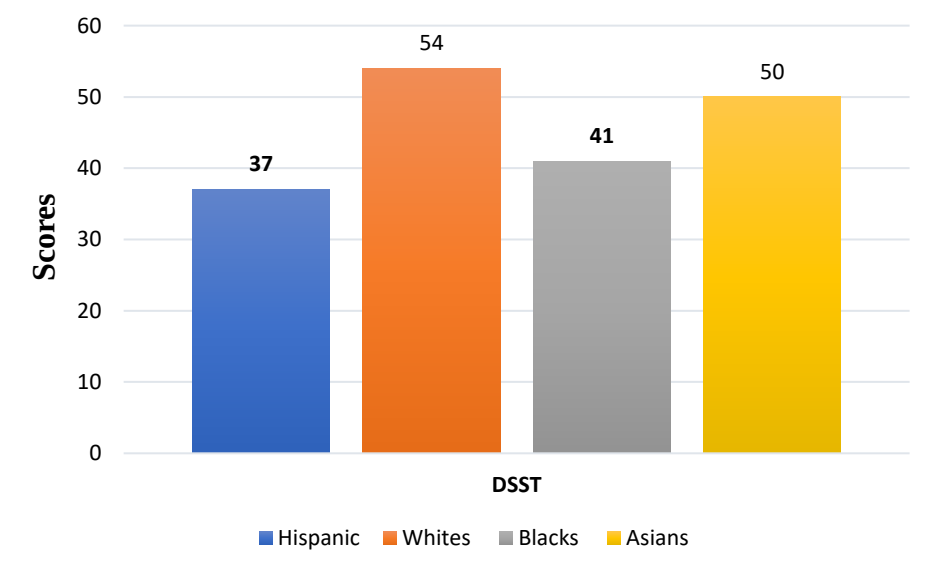



**Figure 11 Cognitive DSST scores by race and ethnicity (p<0.001)**

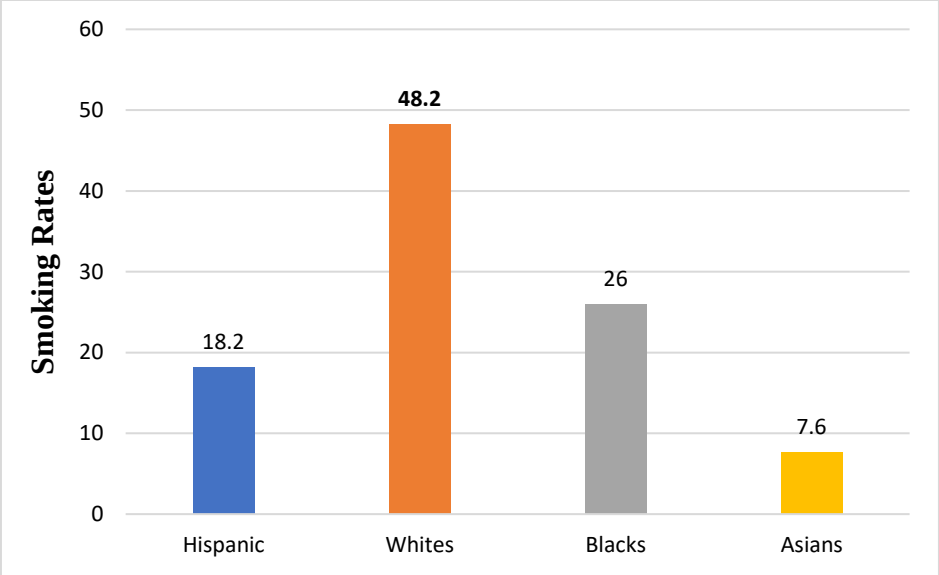



**Figure 12. Smoking rates by race and ethnicity (p<0.001)**

### 2.5.2 Univariate Linear Regression

The univariate linear regression analysis evaluated the relationship between DSST score, and urinary PAH metabolites groups and each covariate of interest using separate models (Table 5) (S1 Appendix). A negative significant association was found between all urinary PAH metabolites and DSST score ($p<0.001$). In addition, all other variables, including age (categorical), education level, annual family income, smoking status, and physical activity were also significantly associated with DSST score. Individuals aged 80 years and over were associated with poorer performance on the DSST, conversely, younger age participants were associated with better performance on the DSST. Blacks participants had poorer performance on the DSST comparing to another ethnic group performance on the DSST.

Table 6 (S1 Appendix) represents univariate linear regression analysis that examined the DWR score and each covariate of interest using separate models. All explanatory variables were

significantly associated with the DWR score (P<0.001), including age, gender, ethnicity, and annual family income. Individuals aged 80 years and older, Blacks, and participants who had a lower educational level were associated with poorer performance on the DWR.

Table 7 (S1 Appendix) shows univariate linear regression analysis that assess the WL score and each covariate of interest using separate models. Age, gender, ethnicity, education, annual income, smoking, alcohol consumption, and other variables were significantly associated with the WL score (P<0.001). Individuals aged 80 years and older, Hispanic group, and participants who have less educational level were associated with poorer performance on the WL cognitive test.

In Table 8 (S1 Appendix), a significant negative association was found between urinary PAH (only for each Log transformed of PAH total and PAH NFP metabolites) and AF score (p=0.03). In addition, all other variables, including age, race and ethnicity, education level, annual income, alcohol consumption, and other covariates were also significantly associated with AF score. Individuals aged 80 years and over were associated with poorer performance on the AF, conversely, younger age participants were associated with better performance on the AF. All ethnic groups were negatively associated with poorer performance on the AF. Individuals with low level education were negatively associated with poorer performance on the AF as well.

### 2.5.3 Multiple Linear Regression

Tables 9-11 (S1 Appendix) represent a multiple linear regression analysis to evaluate the relationship between each of urinary PAH metabolites group and DSST test score adjusted for all covariates (age, gender, race and ethnicity, annual family income, smoking and alcohol status, and other covariates).

There is a significant negative association between each of the total urinary PAH metabolites, as well as with NFP urinary metabolites, and DSST score (p-value 0.04 for each model). For every 1 percent increase in logarithm of PAH-total and PAH (NFP), there was a significant decrease of 0.88% in DSST score after adjusting for age, gender, race and ethnicity, annual family income, smoking and alcohol status, and other covariates. The same was true for 1-OHPyr in urine (Table 11), where there was a significant negative association between 1-OHPyr and DSST score (p-value 0.04).) For every 1 percent increase in logarithm of 1-OHPyr, there was a significant decrease of 1.64% in DSST score after adjusting for age, gender, race and ethnicity, annual family income, smoking and alcohol status, and other covariates.

Urinary creatinine was examined as a potential confounder in linear regression models to adjust for urinary dilution of PAH and metabolites. However, urinary creatinine was not a significant predictor and was not significant in final models. Thus, it was not added to the modeling since its addition did not change the root mean squared error for the biomarkers of total PAH, NFPs, and 1-OHPyr models, respectively.

Tables 12-14 (S1 Appendix) represent a multiple linear regression analysis to evaluate the relationship between each urinary PAH metabolites group and DWR test score adjusted for all covariates (age, gen-der, race and ethnicity, annual family income, smoking and alcohol status, and other co-variates).

There was a significant negative association between each of total urinary PAH metabolites, NFP urinary metabolites, and DWR score (p-value 0.04 for both models). For every 1 percent increase in logarithm of PAH-total and PAH (NFP), there was a significant decrease of 0.12% in DWR score after adjusting for age and the medical condition of coronary heart disease. Conversely for 1-OHPyr in urine (Table 14), there was a significant positive association between urinary 1-OHPyr metabolite and DWR score ($p<0.05$). For every 1 percent increase in logarithm of 1-OHPyr,

there was a significant increase of 0.23% in DWR score after adjusting for age, gender, race and ethnicity, education level, smoking status, and other covariates.

Tables 15-16 (S1 Appendix) represent a multiple linear regression analysis to evaluate the relationship between urinary PAH metabolites group and WL test score adjusted for only (age, diabetes, and coronary heart disease covariates).

As shown in Tables 15 and 16, there is a significant negative association between each of total urinary PAH metabolites, NFP urinary metabolites, and WL score (p-value 0.03 for both models. For every 1 percent increase in logarithm of PAH-total and PAH (NFP), there is a significant decrease of 0.27% in WL score after adjusting for age, diabetes, and coronary heart disease covariates.

Tables 17-18 (S1 Appendix) represent a multiple linear regression analysis to evaluate the relationship between urinary PAH metabolites group and AF test score adjusted for age, annual income, alcohol consumptions, kidneys problems, and physical activities.

As shown in Tables 17 and 18, there is a significant negative association between each of total urinary PAH metabolites, NFP urinary metabolites, and AF score (p-value 0.04 for both models. For every 1 percent increase in logarithm of PAH-total and PAH (NFP), there is a significant decrease of 0.39% in AF score after adjusting for age, annual income, alcohol consumptions, kidneys problems, and physical activities.

## 2.6 Discussion

Our study used NHANES data collected from 2011-2014 to examine the association between urinary PAH metabolites and each of DSST, DWR, WL, and AF scores for cognitive function among adult US residents. Our main findings were that overall males, Blacks, people with lower education level (less than high school), people with low income, and people who are considered smokers were more exposed to PAH. Also, males, the oldest age group (80 years and over), Hispanics and Blacks, people with lower education level (less than high school), individuals with low income, and smokers had lower scores for all cognitive tests.

Our socio-economic status results were similar to previous reports that found an association between socio-economic status and poor performance in cognitive test scores among adults (Millán-Calenti et al., 2009; Wee et al., 2012; Wu et al., 2016). A study conducted in Portugal among individuals aged 50 years and over found a positive association between age and cognitive decline, the study stated that with increasing age, the number of people with cognitive impairment was increased as well (Paúl, Ribeiro, and Santos 2010). Xu et al. (2015) found that low income or poor financial status had an association with cognitive decline among adults aged 65 years and older. Another study that was conducted in Taiwan among individuals aged 65 years and over found that low education, history of medical condition, such as stroke, poor physical activity and physical function had an association with a higher risk of cognitive impairment (Wu et al., 2011). Having a lower education level may affect cognitive function among adults, and that could be explained by the fact that individuals who are well educated may have a larger brain reserve capacity than people with less education (Schmand et al., 1997). It has been suggested that highly educated people are more used to searching more during their school life, which may enhance their

mental stimulation, and consequently affects the brain function and its structure (Beydoun et al., 2014).

### 2.6.1 DSST

Our findings showed a negative association between all urinary PAH metabolites groups and measures of DSST scores. Our results showed that DSST scores were lower by 1.93–2.81 points per one unit increase in log-transformed PAH metabolite levels, and lower by 0.88-1.64 points per one unit increase in log-transformed PAH metabolite levels when adjusted for other covariates. These results confirm the trend presented by previous studies. Best et al. (2016) found a negative association between each of log-transformed urinary PAH metabolites (total PAH, PAH (NFP), 1-hydroxypyrene) and DSST scores. They also found that DSST scores were lower by 1.93–2.03 points per one unit increase in log-transformed PAH metabolite levels. However, they only found a negative association between urinary log-transformed for 1-hydroxypyrene metabolite adjusted with other co-variates and DSST score, which was lower by 1.81 points per one unit increase in log-transformed PAH metabolite levels.

Regarding ethnicity and race, our study shows that the highest prevalence of PAH exposure, as well as the lowest test scores, was among individuals Blacks and Hispanic groups for both unadjusted and adjusted models. These results could be explained by the role of the interaction between the exposure to PAH and DNA Adducts during pregnancy. According to Wang et al. (2008), their study mentioned that there is an interaction effects between PAH exposure and genetic markers in Blacks and Dominicans (Hispanic) population, they illustrated that maternal adducts were higher in mothers with homozygous wild-type GG within the high PAH exposure group in Black. They also found that maternal adducts were higher in mothers with homozygous wild-type

CC within the high PAH exposure group among Dominican people. This PAH-DNA interaction may affect the CP among these ethnic groups particularly with increasing age (Wang et al., 2008).

Moreover, individuals who smoke have the highest prevalence of urinary PAH biomarkers concentration, as well as have lower DSST scores comparing to non-smokers. In fact, smoking status was also significantly associated with DSST score (P=0.01). We found that smokers have lower DSST scores than non-smokers by 3.57 points. We also found in adjusted models that per one unit increase in each of log-transformed for total PAH, PAH (NFP), and 1-hydroxypyrene metabolites levels, smokers had lower DSST scores than non-smokers by 3,83, 3,83, 3.05, respectively.

Our results for the exposure to PAH metabolites and DSST scores among smokers was similar to Akhtar`s et al (2013) results, they found that among former smokers, the DSST scores were lower by 0.91–0.93 points per one unit increase in log-transformed PAH metabolite levels. Akhtar et al used blood cotinine (a metabolite of nicotine) concentrations as a predictor variable. Since we found that self-reported smoking status was a significant predictor in our analysis and thus did not incorporate cotinine, the more specific marker of smoking into our models. In addition to being a marker of smoking status, cotinine levels reflect the internal dose of nicotine from tobacco smoke. In our analysis, we found overall the highest smoking rate was among white participants although blacks and Hispanics had worse PAH and test scores, which would suggest additional PAH exposure that is beyond the PAH in tobacco smoke. Our results for smoking and racial disparities are similar to Nguyen et al (2020) results, in their comprehensive cohort study that sought to examine the racial disparities and the exposure to different chemical biomarker concentrations, including cotinine among United States women, they found that Non-Hispanic white women had the highest cotinine levels compared to Mexican-American and other Hispanic women (Nguyen et al 2020).

Moreover, an overview study that sought to understanding nicotine effects on cognitive function using preclinical models and human studies reported that the worse performance on some cognitive functions, such as working memory task, impaired response inhibition, and motor impulsivity were found among smokers (Valentine and Sofuoglu, 2018).

### 2.6.2 DWR

To the best of our knowledge, this is the first report that examined the association between PAH exposure and neuropsychological tests measurement using other cognitive function tests other than the DSST.

There was no association between any of urinary PAH metabolites groups and measures of DWR scores. We found a negative association between each of log-transformed of total urinary PAH and log-transformed of PAH (NFP) metabolites and measures of DWR scores only after adjusting for age and the medical condition of coronary heart disease variables (P=0.04). DWR scores were lower by 0.12 points per one unit increase in each of log-transformed of total PAH and log-transformed of PAH (NFP) metabolites.

This relationship between age and DWR test performance was most pronounced in the elder age group of 80 years and over. The elder group had lower DWR scores that were 1.53 points lower than the 70-79 age group and 2.23 points lower than the 60-69 age group per one unit increase in each of log-transformed of total PAH and log-transformed of PAH (NFP) metabolites. Our results suggest that the exposure to PAH can worsen the memory function among older adults. A recent study conducted on rats stated that the exposure to B[a]P at early gestation causes learning and memory deficit in offspring rats affecting the neuronal survival in their later-life (Das, Patel, and Patri, 2019). The study found a significant reduction of hippocampal neurons and glial cells after

exposure to B[a]P at early gestation when compared with control group and possibly show how PAH exposure might affect learning and memory over life-time. However, further research is needed to determine how these results translate to human exposures and to determine the molecular mechanisms and the cellular interactions underlying PAH altered learning and memory in adults.

There was a positive association between coronary heart disease and DWR test performance. Individuals with coronary heart disease had lower DWR scores than individuals who do not by a 1.18 per one unit increase in each of log-transformed of total PAH and log-transformed of PAH (NFP) metabolites. There are many studies that found a decline in cognition, especially in executive function domain, among patients with heart diseases (Burkauskas et al. 2018; Eggermont et al., 2012; Burstyn et al., 2005). Our results suggest that adding the factor of the exposure to PAH would further increase the risk of cognitive decline among patients with heart diseases.

### 2.6.3 WL

There was no association between any of urinary PAH metabolites groups and measures of WL scores. We only found a negative association between each of log-transformed of total urinary PAH and log-transformed of PAH (NFP) metabolites and measures of WL scores after adjusting for age, diabetes, and coronary heart disease variables (P=0.03). WL scores were lower by 0.27 points per one unit increase in each of log-transformed of total PAH and log-transformed of PAH (NFP) metabolites.

There was a positive association between diabetes and WL test performance (p<.0001), individuals with diabetes had lower WL scores compared to individuals with no diabetes by 1.03 per one unit increase in each of log-transformed of total PAH and log-transformed of PAH (NFP) metabolites. Different studies concluded that diabetes mellitus type 1 and type 2 have been

associated with reduced performance on different domains of cognitive function, insulin resistance, vascular disease hyperglycemia, and hypoglycemia may play roles of the pathophysiology of cognitive dysfunction in diabetic patients (Kodl and Seaquist, 2008).

Type 2 diabetes may affect and decrease each of psychomotor speed, executive function, and verbal memory (Gregg et al., 2000; Reaven et al., 1999). In fact, type 2 diabetes may increase the incidence of Alzheimer's disease and vascular dementia (Cukierman, Gerstein, and Williamson, 2005; Luchsinger et al., 2001). According to Bruce et al. (2003), about 11 % of elderly patients with type 2 diabetes had cognitive impairment, and 14 % had depression which have a negative effect on both of cognitive function and daily activities (Bruse et al., 2003).

### 2.6.4 AF

There is a negative association between urinary PAH metabolites groups (PAH total and PAH [NFP]) and measures of AF scores for both unadjusted and adjusted models. Our results exhibit that AF scores were lower by almost 0.43 points per one unit increase in log-transformed PAH metabolite levels, and lower by 0.39 points per one unit increase in log-transformed PAH metabolite levels when adjusted for other covariates.

There was association between kidney problems and AF test performance, individuals with kidney problems had lower AF scores than individuals who do not have kidney problems by 1.77 per one unit increase in each of log-transformed of total PAH and log-transformed of PAH (NFP) metabolites. Chronic kidney disease (CKD) almost affects 45% of adults aged 70 years and older in the United States (Coresh et al., 2007). In general, patients with CKD may have large and small blood vessel disease, which may cause white matter disease, reduction and impairment in white

matter lead to poor physical function, vascular dysfunction, cognitive decline and other neurodegenerative diseases (Lau, Huisa, and Fisher, 2017; Bronas, Puzantian, and Hannan, 2017).

There was a negative association between physical activities and AF test performance, individuals who do not practice any physical activities had lower AF scores than individuals who practice any physical activities by 3.55 per one unit increase in each of log-transformed of total PAH and log-transformed of PAH (NFP) metabolites. A study stated that practicing physical activities may improve and enhance the cognitive function in older adults with mild cognitive impairment, the study involved 170 elderly persons asked to begin a 24-week physical exercise program (home-based), when the physical exercise program finished (after 6 months), the study found an improvement in the intervention among the group, especially for episodic memory, attention and working memory (Lautenschlager et al., 2008).

# 3.0 The Effect of Polycyclic Aromatic Hydrocarbons Exposure on Hypertension by Race in the United States Older Adults (National Health and Nutrition Examination Survey: 2011-2014)

In preparation for submission

## 3.1 Introduction

There is substantial epidemiological evidence that elevated blood pressure, hypertension (HTN), is a major risk factor for cardiovascular disease (CVD), the leading cause of death in worldwide (WHO, 2004; Bangia et al., 2021; Abboud and Karam, 2021; Aryal, Harmon, and Dugas, 2021). The general consensus indicates that elevations of 5 mmHg systolic blood pressure (BP) and 10 mmHg diastolic BP are associated with increase the risk of CVD (Brook and Rajagopalan, 2009). For most individuals, HTN presents as asymptomatic, yet consequences of sustained HTN increase CVD morbidity and mortality if not diagnosed early and treated with proper HTN medications (Aranda, Calderon, and Aranda, 2008).

HTN is a multifaceted disease or syndrome that is often of unknown etiology. Multiple factors, including the environmental airborne pollutants particulate matter (PM) and ozone (Aryal, Harmon, and Dugas, 2021; Kreutz et al., 2021; Giorgini et al., 2010) are known to affect development of HTN disease. PAH from the environment or tobacco smoking constitute another modifiable exposure that can increase the risk of HTN (Abboud and Karam, 2021; Sancini et al., 2014; Zhang et al., 2021; Shiue, 2015).

PAH are chemical constituents of PM that are generated by incomplete combustion of organic materials, such as coal, oil, gas, exhaust fumes, garbage, and tobacco (National Toxicology Program, 2014). They are mixtures of hazardous toxic and genotoxic compounds that are highly dispersed in the environment (air, soil and water) (Polanska et al., 2014). PAH are considered as a significant public health concern as exposure to PAH, whether acutely or chronically may increase the risk of human diseases, including cardiovascular and lung diseases, as well as cancers (Polanska et al., 2014). According to International Agency for Research on Cancer (IARC) 2010, the PAH are carcinogenic compounds consisting of carbon and hydrogen that form two to six fused aromatic rings structures.

PAH are released from different sources, including natural resources, such as volcanic eruptions or forest fires (Ramesh et al., 2004). However, the major source of PAH is anthropogenic, especially from human and industrial activities that include burning of fossil fuels, transportation, fumes released from manufacturing industries, and smoking (Ramesh et al., 2004) There are different ways to estimate the internal dose of PAH exposure. This includes biomonitoring of PAH concentrations in urine, which is a marker of current exposure as urinary PAH metabolites can be eliminated from the body within one day (half-life of <35hours) (Li et al., 2010).

The link between air pollutants and the risk of cardiovascular diseases, including HTN has been well investigated in recent studies (Lee, Kim, and Lee, 2014; Tibuakuu et al., 2018; Burroughs and Rollins, 2017; Baccarelli and Ghosh, 2012). However, limited studies have examined the effect of PAH on HTN risk by race among older adults.

## 3.2 Hypothesis and Aims

We hypothesize that the effect of PAH exposure on HTN may change by race among older adults. Most studies have focused on addressing the relationship between PAH and HTN. However, there are knowledge gaps regarding understanding the impacts of PAH on HTN by race and ethnicity among older adults. One study conducted over a period of two years (2011-2012) found an association between PAH exposure and HTN among older adults (Shiue, 2015), however, the study did not examine whether that association would differ by race and ethnicity. To expand on the previous findings, we examined HTN incidence over four years (2011-2014) in a cohort of older adults combined with a battery of urinary PAH biomarkers (1- and 2-hydroxynaphthalene (1-OHN and 2-OHN), 2- and 3-hydroxyfluorene (2-OHFl, 3-OHFl), 1-, 2-, and 3-hydroxyphenanthrene (1-OHPhe, 2-OHPhe, 3-OHPhe), and 1-hydroxypyrene (1-OHPyr)) to determine associations between HTN and PAH exposure. This allowed stratification of exposures and clinical outcomes on the basis of race and ethnicity.

## 3.3 Materials and Methods

### 3.3.1 Study population and data collection

The study cohort consisted of 3,181 adult survey participants. Surprisingly, 3059 of the participants had HTN, but only 988 of these participants had both HTN and urinary PAH measures. Only 122 participants did not have HTN (non-HTN), and only 50 of these participants had both non-HTN and urinary PAH measures (Figure 13).

Data were obtained from National Health and Nutrition Examination Survey (NHANES) for the years 2011-2014. NHANES is a series of cross-sectional surveys conducted by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). The data survey analysis for this study consists of household interviews and physical examinations performed in a mobile examination center (MEC). Eligible individuals included all adults aged 60 years and over with urinary PAH metabolite measurements.

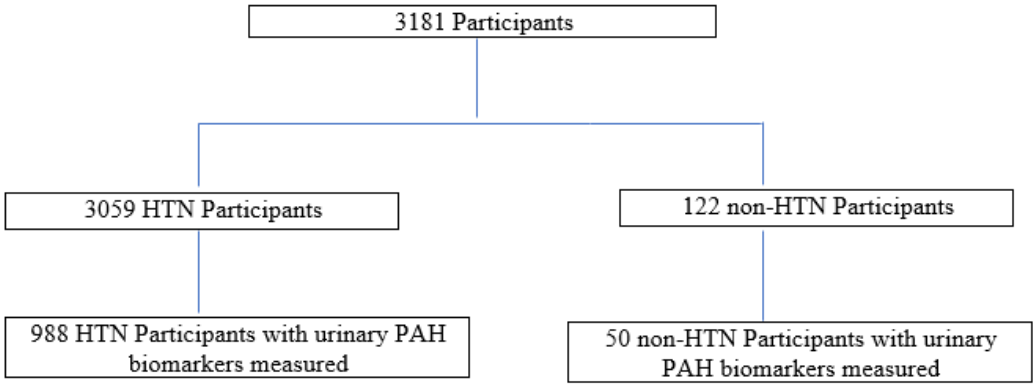



**Figure 13 The total number of NHANES HTN and non-HTN participants, with urinary PAH biomarkers measured**

Blood pressure assessment was obtained from NHANES surveys during household interviews for the period of 2011 to 2012 and for 2013 to 2014.

### 3.3.1.1 Urinary biomarkers of PAH

Urine samples were collected from participants at MEC, the samples were stored under low temperature (–20°C), and sent to National Center for Environmental Health for farther analysis (CDC, 2014b; CDC, 2016). The analysis procedure included enzymatic hydrolysis of glucuronidated/sulfated OH-PAH metabolites in urine to remove PAH conjugates, extraction

including mono-hydroxylated PAH metabolites. The urinary metabolites were analyzed using isotope dilution capillary gas chromatography with high-resolution mass spectrometry (GC-MS/MS) (CDC, 2014b; CDC, 2016). Some of PAH metabolites results were below the lower limit of detection (LLOD), for that reason, a value was imputed as a lower limit of detection divided by square root of 2 (CDC, 2014b; CDC, 2016).

For this study, urinary PAH biomarkers were:

1-OHN and 2-OHN,

2-OHFl and 3-OHFl

1-OHPhe, 2-OHPhe, and 3-OHPhe

1-OHPyr

Measure of urinary creatinine was added as a potential confounder in regression models to account for PAH biomarker variation due to differences in urine dilution. Each urinary PAH biomarker group was used as predictor for HTN in logistic regression model. To satisfying normality assumptions, we took the natural logarithmic transformation of each PAH metabolite measures for all statistical analyses.

#### 3.3.1.2 Socio-demographic variables, risk factors, and confounders

Data were used to examine the hypothesis that the PAH biomarkers associated with HTN change by race after adjusting for risk factors, such as age, gender, tobacco smoking, alcohol consumption, body mass index (BMI), and lack of physical activity. The risk factors, were categorized into different groups similarly to earlier studies (Shiue, 2015).

Racial groups were classified as Hispanic, Asians, Blacks, and Whites. Age at the time of screening is categorized into three groups: 60–69, 70–79, and 80 and over. Gender was categorized as male or female. Smoking - cigarette use was classified as smoker (individuals who smoked at

least 100 cigarettes in entire their lives or non-smoker (smoking less than 100 cigarettes in life) (yes/no). Alcohol consumption was categorized into alcohol drinker (drinking more than 12 alcoholic drinks a year) or non-drinker (drinking less than 12 alcoholic drinks a year) (yes/no). BMI is defined as weight in kilograms divided by height in meters squared, this variable was categorized into three groups normal (<25), obese (25-29.9), and over weight (=>30). Physical activity variable included participants who reported (yes/no) that they practice and engage in daily activities, such as walking or using bicycle. Blood pressure was categorized into individuals who had HTN (participants take prescribed medicine for hypertension) or Non-HTN, as self-reported answers (yes/no).

The data were exempt from human subjects review as this study used public dataset (NHANES 2011-2014) that were anonymized and de-identified before it was analyzed.

### 3.4 Statistical Analysis

Descriptive statistics used to characterize the study participants included counts, means, and standard error (SE) for continuous variables, and for counts, percentages (weighted), SE for categorical variables. Missing data (N) were not included, since NHANES collected the sample data randomly.

Survey-weight logistic regression analyses were used to measure the association of urinary PAH biomarkers with race and HTN presenting with odds ratios (OR) and 95%confidence intervals (CI). The regression model is:

$y = \beta o + \beta 1 \log(X1) + \beta 2\ (X2) + \beta 3\ (X3) + \beta 4\ (X4)$…….

where y is the hypertension status (yes/no), βo is the intercept of the regression line, β1 is

coefficient of the regression model that represents the change in the mean of the hypertension status for each unit change in the log of a specific PAH biomarker, X1 is the logarithm of a specific PAH biomarker, X2 is another covariate to adjust for in the model.

All data were analyzed using SAS Version 9.4

## 3.5 Results

### 3.5.1 Descriptive Statistics

The majority of participants were between 60 and 69 years old (~55%), and there were more female participants than male (55% versus 45%) (Table 19) (S1 Appendix). Additionally, the percentage of White participants was the highest 78%. Race was significantly associated with the total of urinary PAH biomarkers (1-OHN, 2-OHN, 3-OHFl, 2-OHFl, 3-OHPhe, 1-OHPhe, 2-OHPhe, and 1-OHPyr) (Table 20) (S1 Appendix). The difference in natural log mean of the total of urinary PAH biomarkers between blacks and whites was 0.58 ng/L. Also Race and smoking were significantly associated with the total of urinary PAH biomarkers after adjusting for the other variables (age, gender, alcohol consumption, physical activities, and hypertension (Table 21) (S1 Appendix), he difference in natural log mean of the total of urinary PAH biomarkers between black and white was 0.61 ng/L after adjusting for other variables.

Table 22 (S1 Appendix) shows the descriptive statistics for HTN participants with urinary PAH biomarkers measured by race (categorical) variable. Black individuals had the highest urinary PAH biomarkers concentrations (Figure 14).

Only one urinary PAH biomarker (1-hydroxynaphthalene relative to racial categories was

significantly associated with HTN (p<0.0001) adjusting for age, gender, smoking, alcohol consumption, BMI, and physical activity status.

Tables 23-25 (S1 Appendix) demonstrate the probability of developing HTN for individuals with different urinary 1-hydroxynaphthalene concentrations by race groups. Overall, Blacks with different urinary concentrations (2.5, 5, 7.5 ng/L) of log-1-hydroxynaphthalene biomarker had the highest probability (~99%) of developing HTN compared to other race groups.

Table 26 (S1 Appendix) shows the Odds ratio of developing HTN. Each increase in one unit of urinary Log-1-hydroxynaphthalene biomarker is associated with 1.1 greater odds of developing HTN among Hispanic, 2.0 among Asians, 0.5 among Blacks, and 1.0 among Whites. Figure 15 represents an example of a plot predicted probabilities of developing HTN among participants males with urinary 1-hydroxynaphthalene measured, aged 80 years and over, smokers, non-consuming alcohol, BMI=>30, and practice physical activities.

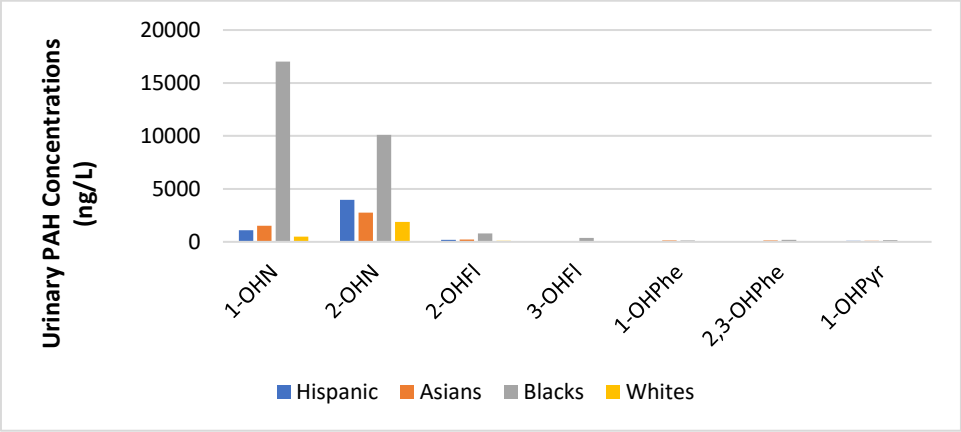



**Figure 14 The geometric means of Log urinary PAH biomarkers concentrations for HTN participants by different racial groups**

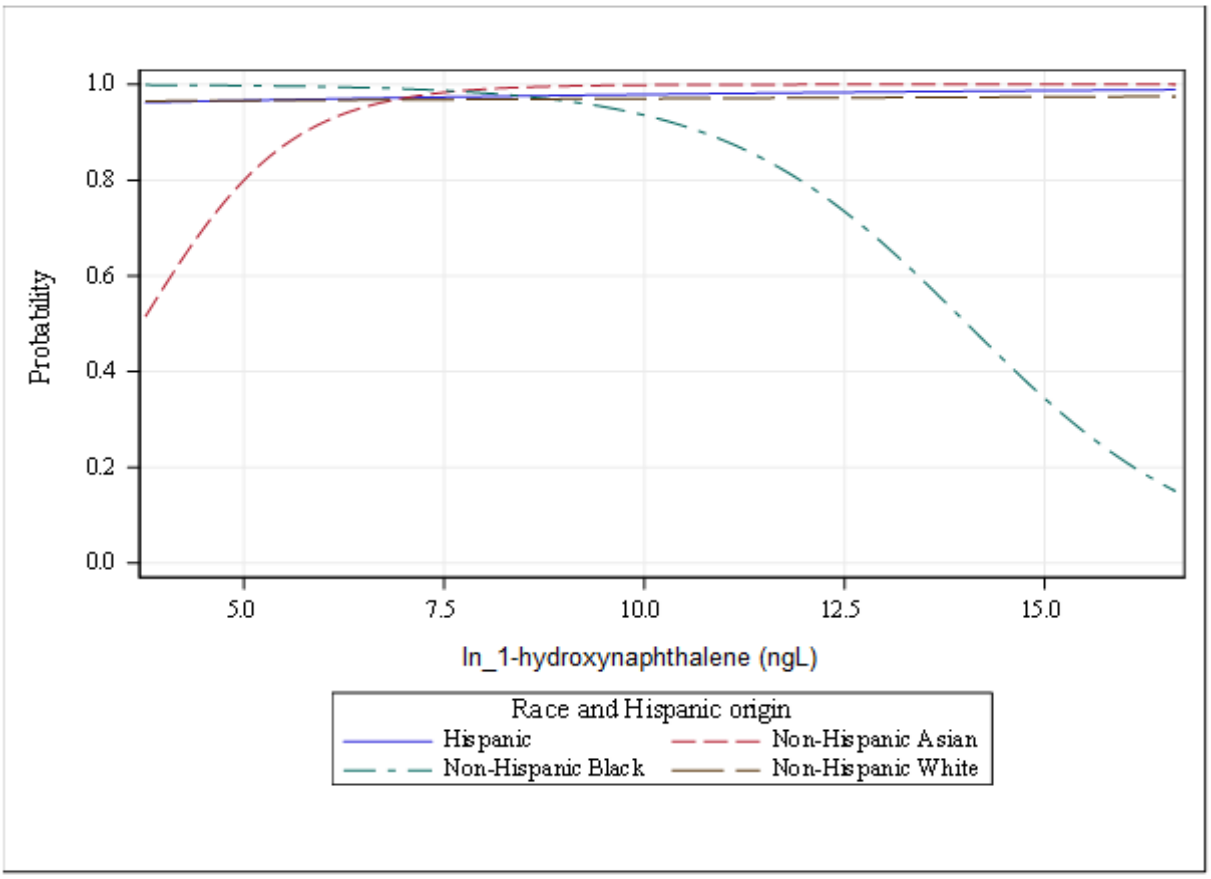



**Figure 15 A plot of predicted probabilities of developing HTN by different racial groups with urinary of 1-hydroxynaphthalene measured**

## 3.6 Discussion

Our study used NHANES data collected from 2011-2014 to examine whether urinary PAH biomarkers associated with HTN differ by race in older adults. We found that there was an association between only one urinary PAH metabolite (urinary 1-hydroxynaphthalene biomarker) relative to race and HTN ($p<0.001$). Overall, blacks had the highest concentrations of urinary PAH metabolites compared to other ethnic groups. Also, overall, Blacks with different urinary 1-hydroxynaphthalene biomarkers had the highest probability of developing HTN compared to other

race groups. Additionally, for each increase in one unit in log-transformed 1-hydroxynaphthalene level is associated with greater odds of developing HTN relatively for all races.

Our results were similar to previous studies that found an association between PAH metabolites and HTN. Ranjbar et al. (2015) found an association between different urinary PAH biomarkers, such as 2-naphthalene and 2-phenanthrene and HTN, however, there study did not include a race as an interaction factor/effect modifier with HTN, instead, they included obesity as an effect modifier in HTN among individuals with high concentrations of urinary PAH metabolites. Another study found an association between urinary PAH biomarkers and different cardiovascular diseases, including HTN (Shiue, 2015). However, the study also did not examine race as an effect modifier in HTN.

Our findings show that black individuals with different urinary 1-hydroxynaphthalene biomarker concentrations had the highest probability of developing HTN compared to other race groups. Also, the odds of developing HTN for relatively all racial groups was greater for each increase in one unit in log-transformed of urinary 1-hydroxynaphthalene biomarker level. This effect modification in the association between PAH and blood pressure by race may also reflect differences in factors not examined in this study, such as gene-environment interactions or nutrition-environment interactions (Song et al., 2010).

## 4.0 Conclusions and Future Directions

We conclude that there was a significant negative association between PAH metabolites and CP in older adults. The highest associations between PAH and lowest CP were among males, Blacks and Hispanics, individuals with lower education level, individuals with low income, and individuals who are considered smokers. In addition, the oldest age group of 80 years and over had the lowest CP. DSST was the most sensitive test of detections the CP among older adults. Lastly, Urinary 1-OHPyr metabolite had a strong negative association with CP in older adults.

We also conclude that there was a significant association between urinary 1-hydroxynaphthalene biomarker relative to race and HTN in older adults. For each increase in one unit in log-transformed of 1-hydroxynaphthalene level was associated with greater odds of developing HTN relatively for all race groups. Additionally, higher urinary concentrations of 1-hydroxynaphthalene biomarker were among Blacks comparing to other ethnic groups. Black individuals with different urinary 1-hydroxynaphthalene biomarker concentrations also had the highest probability of developing HTN compared to other race groups.

The findings of our study may be used to increase the awareness of exposure impacts among the highest risk groups. Also, the translation of our results would be a great step to residents, stakeholder, and policy makers to prevent and mitigate air pollution resources

Our findings among minorities and vulnerable populations confirm the trend presented by previous studies. Different research studies and reports attempted to observe the linkages between PAH exposure and different diseases in environmental justice neighborhoods. For instance, a recent study showed that in eastern Houston (the Houston Ship Channel) in Manchester, Texas, where the most population are Hispanic neighborhoods had medical conditions related to environmental

justice communities including chronic exposure to air pollution, the study reported that these communities are at high risk of hazardous substances exposure, for instance, within 1 mile of these neighborhoods, there are 21 facilities that report to the EPA's Toxic Release Inventory, such as 4 facilities that dispose hazardous wastes and about 9 major air pollution dischargers. (Chakraborty et al., 2014; Sansom et al., 2018).

public health efforts should work to create new plans, policies, and regulations that help to mitigate the release of PAH into the atmosphere. In addition, the efforts should seek an effective treatment for cognitive impairment.

## 4.1 Limitations and Strengths

The limitations of our study include the sample selection, which omitted people with missing data. The survey for the cognitive tests does not include all components/domains of cognition. Individuals who perform well in one domain may not perform well in another domain. Most of cognitive measurements, cognitive assessments, and cardiovascular diseases assessments, including blood pressure were performed as self-reported binary questions. This kind of survey cannot replace a clinical diagnose for cognitive disorders or for hypertension. The genotypic data of the study group that may link to cognitive decline were not available. In addition, PAH metabolites are eliminated from the body with a half-life of <35 hours, and thus the urinary PAH measurements may not represent chronic or long-term exposures. There was a small number of non-HTN participants with PAH measures (the control group), therefore, if the number was larger, the outcomes might be different.

The strengths of our study are that cognitive assessments and cardiovascular diseases assessments were administered in private examination centers, which were more similar clinical than household settings. In addition, we used urinary PAH concentrations in our analysis rather than using the PAH-air pollution exposures as an aggregated measurement from environmental monitoring. The large sample size of older adults, the use of generalizable NHANES data, and use of biomarkers of specific chemical groups added to the significance of our results.

### 4.2 Future Directions, Guidelines and Regulations of PAH Exposure

Our findings would enhance public health efforts to combat against PAH emission, especially among minorities. Public health has taken different approaches to reduce PAH exposure, for instance, cigarette smoke is an important source of PAH emission and exposure at the same time, therefore, different efforts, such as awareness campaigns were conducted to stop this negative behavior for reducing PAH exposure among smokers and second-hand smokers (ATSDR, 2009a). Also, different efforts were taken to recommend individuals to avoid the exposure to PAH, for instance, wearing gloves when working with cutting oils or any other substances that include PAH, and avoiding burning practices that increase the PAH release to the atmosphere (ATSDR, 2009a).

Our finding may also increase the awareness among minorities, the need for new polices and regulation should be implemented to reduce the emission of PAH, and the exposure among vulnerable ethnic groups, consequently, different United Stated agencies established standards concentration limits for PAH in the environment and in the workplace. For instance, Occupational Safety and Health Administration (OSHA) air contaminants standard established specific standard limits for PAH substances, such as coal tar pitch volatiles (CTPVs) and coke oven emissions which

is covered by the coke oven emissions standard (ATSDR, 2009a). OSHA requires from employers to control employee exposure to coke oven emissions by using different engineering controls and work practices, employers should use engineering controls and work practices to reduce employee exposures to the lowest level achievable, as well as using supplemental engineering controls like respiratory protection procedures (ATSDR, 2009a). The OSHA permissible exposure limit (PEL) for PAH exposure in the workplace is 0.2 milligram/cubic meter (mg/m3) (Table 27) (S1 Appendix).

### 4.2.1 Future Directions, Policies and Regulations of Cognitive Impairment

According to the CDC report (2011), about more than 16 million people in the United States have cognitive impairment disorders. Because of the increasing number of people living with cognitive impairment, and the cost of cognitive impairment treatment, different efforts and steps should be taken to maintain effective policies and programs to address the needs of people living with cognitive impairment (CDC, 2011).

To understand the needs of individuals with cognitive impairment, states, local agencies, and different health departments can gather more clinical data related to patients with cognitive impairment to understand the impact, burden, and their special needs, which may help to determine which age group that should be focus on for treatment more than others (CDC, 2011).

State agencies, private and public organizations can also develop comprehensive plans that can respond to the needs of individuals with cognitive impairment. Also, medical, public health, and comprehensive systems should be developed by supporting individuals with cognitive impairment, their families, and caregivers (CDC, 2011).

Finally, it is recommended to have extra training for health professionals, such as doctors, nurses and other health providers to find and detect cognitive impairment especially in early stages, and help patients with different health conditions to manage their care (CDC, 2011).

Further studies should be conducted on this topic, to better define the influence of the confounding variables, such as the genetic variability of the enzymes involved in the biotransformation of PAH.

### 4.3 Cognitive Impairment and Methods of Treatment

There are extensive efforts to find a treatment for cognitive impairment as well as for both Alzheimer`s disease and dementia. However, there are still limitations and challenges involved in the treatment process, such as the efficacy for treatment plans. This is especially true for long-term, the side effect of medications, the cost of the treatment, and other challenges (Mehlman, 2004). Cognitive impairment treatment may include pharmacological or non-pharmacological options, or maybe both combined for special treatment plan (University Health System, 2012).

Lifestyle modifications are an important factor that play a significant role in enhancing cogitation performance. For instance, engaging and practicing in daily physical activities, walking running, cycling, swimming, and hiking are all examples of practicing physical activities that may promote and activate memory functions. A caveat is that increased physical activity in contaminated environments can increase exposures and consequently disease risk. In addition, activities like socialization may also improve mood and increase quality of life among older adults with cognitive disorders (University Health System, 2012).

Regarding pharmacological options, the FDA has approved different drugs for treating dementia and these drugs improve and enhance the CP among patients with different cognitive deficits types (Mehlman, 2004). (Table 28) (S1 Appendix) summarizes an example of some medications and the appropriate dose intake per mg daily for patients with dementia (University Health System, 2012).

## **Appendix A Supporting** Data

Appendix A.1 includes outcome of statistical analysis for urinary PAH metabolites and each of DSST, DWR, WL, and AF tests and other covariates.

## Appendix A.1 Tables

**Table 1 Characteristics of 2011-2014 NHANES participants**

| **Characteristic** | **N** | **Percent (weighted)** | **SE** |
|---|---|---|---|
| Total | 3,181 | | |
| **Age** | | | |
| 60-69 | 1671 | 54.67 | 1.19 |
| 70-79 | 950 | 29.53 | 1.04 |
| 80+ | 560 | 15.79 | 0.73 |
| **Gender** | | | |
| Male | 1547 | 45.32 | 1.23 |
| Female | 1634 | 54.67 | 1.23 |
| **Race** | | | |
| Hispanic | 615 | 7.50 | 0.34 |
| Whites | 1470 | 78.23 | 0.71 |
| Blacks | 779 | 8.98 | 0.38 |
| Asians | 317 | 5.27 | 0.42 |
| **Education level** | | | |
| Less than high school | 875 | 17.30 | 0.77 |
| High school graduate or GED | 732 | 22.18 | 1.01 |
| Some college | 868 | 30.82 | 1.14 |

| | | | |
|---|---|---|---|
| College graduate or higher | 702 | 29.64 | 1.18 |
| **Annual family income** | | | |
| <$25000 | 1077 | 25.31 | 0.96 |
| $25000 to <$55000 | 882 | 30.71 | 1.16 |
| $55000+ | 957 | 43.96 | 1.30 |
| **Smoking Status (Self-reported)** | | | |
| Smoker | 1601 | 50.26 | 1.23 |
| Non-Smoker | 1577 | 49.73 | 1.23 |
| **Alcohol consumption (Self-reported)** | | | |
| Yes | 171 | 5.81 | 0.57 |
| No | 2997 | 94.18 | 0.57 |
| **Diabetes (Self-reported)** | | | |
| Yes | 766 | 19.79 | 0.92 |
| No | 2268 | 75.93 | 1.00 |
| **Medical conditions (Self-reported)** | | | |
| Congestive heart failure | | | |
| Yes | 232 | 7.08 | 0.58 |
| No | 2934 | 92.91 | 0.58 |
| Coronary heart disease | | | |
| Yes | 290 | 9.44 | 0.68 |
| No | 2891 | 90.55 | 0.68 |
| Angina/angina pectoris | | | |
| Yes | 171 | 5.81 | 0.57 |
| No | 2997 | 94.18 | 0.57 |
| Heart attack | | | |
| Yes | 278 | 8.69 | 0.66 |
| No | 2899 | 91.30 | 0.66 |
| Stroke | | | |

| | | | |
|---|---|---|---|
| Yes | 246 | 6.95 | 0.57 |
| No | 2929 | 93.04 | 0.57 |
| Emphysema | | | |
| Yes | 116 | 4.60 | 0.52 |
| No | 3060 | 95.39 | 0.52 |
| Memory and thinking problems | | | |
| Yes | 493 | 13.53 | 0.76 |
| No | 2686 | 86.46 | 0.76 |
| **Kidneys problems (Self-reported)** | | | |
| Yes | 197 | 4.89 | 0.45 |
| No | 2980 | 95.10 | 0.45 |
| **Physical Activity (Self-reported)** | | | |
| Vigorous work activity | | | |
| Yes | 320 | 12.40 | 0.88 |
| no | 2860 | 87.56 | 0.88 |
| Walk or bicycle | | | |
| Yes | 666 | 18.98 | 0.98 |
| No | 2515 | 81.01 | 0.98 |
| Vigorous recreational activities | | | |
| Yes | 278 | 10.90 | 0.84 |
| No | 2903 | 89.09 | 0.84 |
| **Physical functioning limitation (Self-reported)** | | | |
| Limitations that keeps individual from working | | | |
| Yes | 674 | 16.49 | 0.82 |

| | | | |
|---|---|---|---|
| No | 2506 | 83.49 | 0.82 |
| Limitation in amounts work that individual can do | | | |
| Yes | 1044 | 28.81 | 1.06 |
| No | 2134 | 71.12 | 1.06 |
| Experience confusion/memory problems | | | |
| Yes | 425 | 10.02 | 0.62 |
| No | 2754 | 89.92 | 0.62 |
| **Body Mass Index (BMI)** | | | |
| <25 | 844 | 26.17 | 1.08 |
| 25-29.9 | 1091 | 36.03 | 1.19 |
| =>30 | 1184 | 37.78 | 1.20 |
| **Hypertension (Self-reported)** | | | |
| HTN | 3059 | 96.54 | 0.42 |
| Non-HTN | 122 | 3.45 | 0.42 |
| **Cholesterolemia (Self-reported)** | | | |
| Yes | 1589 | 53.69 | 1.27 |
| No | 1344 | 46.30 | 1.27 |

N- number
SE—standard error
mg/dL—milligrams per deciliter

**Table 2 Means and standard errors for continuous variables**

| Characteristic | N | Mean (SE) | 95% CI |
|---|---|---|---|
| Total | 3181 | | |
| DSST total scores | 3011 | 51.86 (0.40) | (51.06, 52.66) |
| WDR total scores | 3126 | 6.13 (0.05) | (6.02, 6.24) |
| WL total scores | 3126 | 19.49 (0.10) | (19.28, 19.71) |
| AF total scores | 3102 | 17.89 (0.14) | (17.61, 18.17) |

DSST- Digit symbol substitution test
DWR- Delayed Word Recall test
WL- Word list learning
AF- Animal Fluency
SE—standard error
CI-confidence intervals

**Table 3 Means and standard errors for urinary PAH biomarkers**

| Characteristic | N | Mean | SE | 95% CI |
|---|---|---|---|---|
| PAH-total metabolites[1] (ng/L) | 1013 | 55387 | 18936 | (18000, 92000) |
| PAH-smaller molecular metabolites[1] (ng/L) | 1013 | 55250 | 18936 | (18000, 92000) |
| 1-OHPyr[1] (ng/L) | 1013 | 137.26 | 10.61 | (116, 158) |
| Urinary creatinine[1] (ng/L) | 1031 | 96.24 | 2.53 | (91, 101) |

1 Geometric means
ng/L—nanograms per liter

**Table 4 Characteristics of 2011-2014 NHANES participants for categorical variables by urinary PAH metabolite groupings, and all of DSST, DWR, WL, AF scores**

| Variable | PAH_Total[1] ng/LGM (GSE) | PAH_NFP[1] ng/LGM (GSE) | (1-OHPyr)[1] ng/LGM (GSE) | U. Creatinine[2] ng/LGM (GSE) | DSST Mean (SE) | DWR Mean (SE) | WL Mean (SE) | AF Mean (SE) |
|---|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | | |
| 60-69 | 6247.5 (1.1) | 6120.2 (1.1) | 90.1 (1.1) | 75.8 (1.0) | 56.4 (1.0) | 6.7 (0.1) | 20.8 (0.2) | 19.6 (0.4) |
| 70-79 | 6020.9 (1.1) | 5885.8 (1.1) | 81.1 (1.1) | 80.4 (1.0) | 48.5 (1.0) | 6.0 (0.2) | 18.8 (0.3) | 16.9 (0.4) |
| 80+ | 5781.6 (1.1) | 5659.9 (1.1) | 63.9 (1.1) | 77.6 (1.1) | 38.9 (1.2) | 4.4 (0.2) | 16.5 (0.5) | 13.7 (0.4) |
| **Gender** | | | | | | | | |
| Male | 6877.1 (1.1) | 6729.4 (1.1) | 95.0 (1.1) | 98.6 (1.0) | 49.0 (1.0) | 5.7 (0.2) | 18.6 (0.3) | 18.4 (0.4) |
| Female | 5522.0 (1.1) | 5406.7 (1.1) | 74.0 (1.0) | 63.9 (1.0) | 53.4 (1.0) | 6.5 (0.1) | 20.3 (0.2) | 17.4 (0.4) |
| **Race** | | | | | | | | |
| Hispanic | 6796.8 (1.1) | 6645.1 (1.1) | 90.4 (1.1) | 77.6 (1.1) | 36.9 (1.3) | 5.2 (0.2) | 17.3 (0.3) | 15.2 (0.4) |
| Whites | 5653.6 (1.1) | 5531.5 (1.1) | 79.6 (1.0) | 75.5 (1.0) | 54.0 (0.9) | 6.3 (0.1) | 19.8 (0.2) | 18.6 (0.3) |
| Blacks | 10178.7 (1.1) | 10018.0 (1.1) | 102.7 (1.1) | 104.9 (1.0) | 40.7 (1.1) | 5.8 (0.2) | 19.4 (0.3) | 15.0 (0.4) |
| Asian | 7003.2 (1.3) | 6849.8 (1.3) | 94.9 (1.3) | 69.8 (1.1) | 49.8 (2.3) | 6.3 (0.3) | 18.3 (0.6) | 15.0 (0.4) |
| **Education Level** | | | | | | | | |
| Less than high school | 7797.4 (1.1) | 7650.8 (1.1) | 95.2 (1.1) | 85.9 (1.1) | 36.4 (1.1) | 5.1 (0.2) | 16.8 (0.3) | 14.4 (0.4) |
| High school graduate or GED | 6040.6 (1.1) | 5907.6 (1.1) | 77.2 (1.1) | 74.2 (1.1) | 48.0 (1.4) | 5.8 (0.2) | 19.2 (0.4) | 15.8 (0.4) |
| Some college | 6001.9 (1.1) | 5870.6 (1.1) | 86.1 (1.1) | 76.7 (1.1) | 54.6 (1.3) | 6.4 (0.2) | 20.1 (0.3) | 18.0 (0.4) |
| College graduate or higher | 5385.0 (1.1) | 5270.3 (1.1) | 77.3 (1.1) | 76.2 (1.1) | 59.0 (1.3) | 6.8 (0.2) | 20.8 (0.3) | 21.2 (0.6) |
| **Annual family income** | | | | | | | | |
| <$25000 | 6585.9 (1.1) | 6449.3 (1.1) | 82.4 (1.1) | 79.1 (1.1) | 42.3 (1.3) | 5.7 (0.2) | 18.5 (0.3) | 16.1 (0.4) |

| Variable | PAH_Total[1] ng/LGM (GSE) | PAH_NFP[1] ng/LGM (GSE) | (1-OHPyr)[1] ng/LGM (GSE) | U. Creatinine[2] ng/LGM (GSE) | DSST Mean (SE) | DWR Mean (SE) | WL Mean (SE) | AF Mean (SE) |
|---|---|---|---|---|---|---|---|---|
| $25000 to <$55000 | 6107.1 (1.1) | 5985.1 (1.1) | 81.4 (1.1) | 79.9 (1.1) | 49.1 (1.3) | 6.0 (0.2) | 19.0 (0.3) | 17.1 (0.5) |
| $55000+ | 5451.4 (1.1) | 5328.7 (1.1) | 84.4 (1.1) | 74.3 (1.1) | 59.0 (1.1) | 6.6 (0.2) | 20.7 (0.3) | 19.9 (0.5) |
| **Smoking Status (Self-reported)** | | | | | | | | |
| Smoker | 6850.0 (1.1) | 6706.3 (1.1) | 93.3 (1.1) | 80.7 (1.0) | 49.8 (1.0) | 5.9 (0.1) | 19.1 (0.2) | 18.0 (0.4) |
| Non-Smoker | 5360.9 (1.1) | 5246.5 (1.1) | 72.5 (1.0) | 74.1 (1.0) | 53.3 (1.1) | 6.5 (0.1) | 20.0 (0.3) | 17.7 (0.4) |
| **Alcohol consumption (Self-reported)** | | | | | | | | |
| Drinker | 6121.6 (1.1) | 5984.4 (1.1) | 88.4 (1.0) | 78.3 (1.0) | 53.1 (0.9) | 6.3 (0.1) | 19.8 (0.2) | 18.6 (0.3) |
| Non-Drinker | 6062.5 (1.1) | 5954.3 (1.1) | 70.0 (1.1) | 75.7 (1.1) | 46.9 (1.4) | 5.9 (0.2) | 18.8 (0.4) | 16.0 (0.4) |
| **Diabetes (Self-reported)** | | | | | | | | |
| Yes | 6134.7 (1.1) | 6020.0 (1.1) | 72.5 (1.1) | 80.6 (1.1) | 43.5 (1.1) | 6.0 (0.2) | 18.7 (0.4) | 16.5 (0.6) |
| No | 6079.1 (1.1) | 5946.7 (1.1) | 85.5 (1.0) | 76.3 (1.0) | 53.5 (0.9) | 6.2 (0.1) | 19.7 (0.2) | 18.2 (0.3) |
| **Medical conditions (Self-reported)** | | | | | | | | |
| Congestive heart failure | | | | | | | | |
| Yes | 7703.6 (1.3) | 7571.3 (1.3) | 81.1 (1.2) | 83.8 (1.1) | 40.6 (2.5) | 5.0 (0.4) | 17.3 (0.8) | 16.1 (0.9) |
| No | 6005.9 (1.1) | 5877.0 (1.1) | 83.1 (1.0) | 77.2 (1.0) | 52.2 (0.8) | 6.3 (0.1) | 19.7 (0.2) | 18.0 (0.3) |
| Coronary heart disease | | | | | | | | |
| Yes | 6118.1 (1.2) | 5985.7 (1.2) | 78.3 (1.1) | 83.0 (1.1) | 43.4 (1.6) | 5.0 (0.3) | 17.4 (0.6) | 16.1 (0.8) |
| No | 6104.1 (1.1) | 5975.2 (1.1) | 83.3 (1.0) | 77.1 (1.0) | 52.2 (0.8) | 6.3 (0.1) | 19.7 (0.2) | 18.1 (0.3) |
| Angina/angina pectoris | | | | | | | | |

| Variable | PAH_Total[1] ng/LGM (GSE) | PAH_NFP[1] ng/LGM (GSE) | (1-OHPyr)[1] ng/LGM (GSE) | U. Creatinine[2] ng/LGM (GSE) | DSST Mean (SE) | DWR Mean (SE) | WL Mean (SE) | AF Mean (SE) |
|---|---|---|---|---|---|---|---|---|
| Yes | 7010.6 (1.3) | 6876.8 (1.3) | 88.5 (1.2) | 80.0 (1.1) | 44.8 (4.0) | 5.3 (0.4) | 18.7 (0.7) | 16.5 (1.0) |
| No | 6056.1 (1.1) | 5927.2 (1.1) | 82.6 (1.0) | 77.5 (1.0) | 51.8 (0.7) | 6.2 (0.1) | 19.6 (0.2) | 18.0 (0.3) |
| Heart attack | | | | | | | | |
| Yes | 8349.1 (1.2) | 8171.1 (1.2) | 106.2 (1.2) | 87.5 (1.1) | 42.9 (1.8) | 5.1 (0.4) | 17.6 (0.6) | 16.0 (0.7) |
| No | 5905.5 (1.1) | 5780.7 (1.1) | 80.8 (1.0) | 76.6 (1.0) | 52.4 (0.8) | 6.3 (0.1) | 19.7 (0.2) | 18.1 (0.3) |
| Stroke | | | | | | | | |
| Yes | 6998.8 (1.2) | 6861.4 (1.2) | 75.5 (1.1) | 78.9 (1.1) | 43.7 (3.0) | 5.0 (0.4) | 18.0 (0.8) | 15.0 (1.0) |
| No | 6042.7 (1.1) | 5914.5 (1.1) | 83.0 (1.0) | 77.4 (1.0) | 51.8 (0.8) | 6.2 (0.1) | 19.6 (0.2) | 18.1 (0.3) |
| Emphysema | | | | | | | | |
| Yes | 10230.4 (1.3) | 10049.1 (1.4) | 115.3 (1.2) | 92.3 (1.1) | 45.5 (2.0) | 5.2 (0.4) | 18.2 (0.7) | 16.9 (1.0) |
| No | 5948.5 (1.1) | 5821.6 (1.1) | 81.5 (1.0) | 76.9 (1.0) | 51.8 (0.8) | 6.2 (0.1) | 19.6 (0.2) | 17.9 (0.3) |
| Memory and thinking problems | | | | | | | | |
| Yes | 7414.9 (1.2) | 7284.9 (1.2) | 74.0 (1.1) | 86.1 (1.1) | 41.4 (1.7) | 4.3 (0.3) | 16.3 (0.5) | 15.0 (0.6) |
| No | 5882.8 (1.1) | 5754.5 (1.1) | 84.3 (1.0) | 76.1 (1.0) | 53.1 (0.8) | 6.5 (0.1) | 20.1 (0.2) | 18.4 (0.3) |
| **Kidneys problems (Self-reported)** | | | | | | | | |
| Yes | 6989.9 (1.2) | 6893.2 (1.2) | 62.9 (1.1) | 79.9 (1.1) | 39.9 (1.9) | 5.3 (0.3) | 17.5 (0.8) | 15.9 (0.9) |
| No | 6079.2 (1.1) | 5948.6 (1.1) | 84.3 (1.0) | 77.7 (1.0) | 52.1 (0.8) | 6.2 (0.1) | 19.6 (0.2) | 18.0 (0.3) |
| **Physical Activity (Self-reported)** | | | | | | | | |
| Vigorous work activity | | | | | | | | |
| Yes | 5519.8 (1.2) | 5397.0 (1.2) | 86.7 (1.1) | 86.2 (1.1) | 56.3 (2.0) | 6.9 (0.3) | 20.7 (0.5) | 19.7 (0.7) |
| No | 6201.8 (1.1) | 6071.7 (1.1) | 82.3 (1.0) | 76.4 (1.0) | 50.7 (0.8) | 6.1 (0.1) | 19.4 (0.2) | 17.6 (0.3) |

| Variable | PAH_Total[1] ng/LGM (GSE) | PAH_NFP[1] ng/LGM (GSE) | (1-OHPyr)[1] ng/LGM (GSE) | U. Creatinine[2] ng/LGM (GSE) | DSST Mean (SE) | DWR Mean (SE) | WL Mean (SE) | AF Mean (SE) |
|---|---|---|---|---|---|---|---|---|
| Walk or bicycle | | | | | | | | |
| Yes | 7128.1 (1.1) | 6975.7 (1.1) | 101.8 (1.1) | 90.0 (1.1) | 53.1 (1.7) | 6.4 (0.2) | 19.7 (0.4) | 19.0 (0.6) |
| No | 5891.2 (1.1) | 5766.9 (1.1) | 79.1 (1.0) | 75.0 (1.0) | 51.1 (0.8) | 6.1 (0.1) | 19.5 (0.2) | 17.6 (0.3) |
| Vigorous recreational activities | | | | | | | | |
| Yes | 4152.2 (1.1) | 4069.2 (1.1) | 62.3 (1.2) | 73.6 (1.1) | 63.2 (2.0) | 7.2 (0.3) | 21.6 (0.5) | 22.5 (1.1) |
| No | 6363.6 (1.1) | 6228.2 (1.1) | 85.5 (1.0) | 78.0 (1.0) | 50.2 (0.8) | 6.1 (0.1) | 19.3 (0.2) | 17.4 (0.3) |
| **Physical functioning limitation (Self-reported)** | | | | | | | | |
| Limitations that keeps individual from working | | | | | | | | |
| Yes | 8596.0 (1.1) | 8449.8 (1.1) | 87.5 (1.1) | 88.6 (1.1) | 40.9 (1.6) | 5.2 (0.2) | 18.0 (0.5) | 15.5 (0.5) |
| No | 5748.5 (1.1) | 5622.7 (1.1) | 82.1 (1.0) | 75.7 (1.0) | 53.3 (0.8) | 6.4 (0.1) | 19.8 (0.2) | 18.3 (0.3) |
| Limitation in amounts work that individual can do | | | | | | | | |
| Yes | 8550.1 (1.1) | 8394.0 (1.1) | 87.2 (1.1) | 82.5 (1.1) | 45.0 (1.4) | 5.4 (0.2) | 18.5 (0.3) | 16.6 (0.4) |
| No | 5421.2 (1.1) | 5301.0 (1.1) | 81.4 (1.0) | 75.9 (1.0) | 53.7 (0.8) | 6.4 (0.1) | 19.9 (0.2) | 18.4 (0.3) |
| Experience confusion/memory problems | | | | | | | | |
| Yes | 9204.1 (1.2) | 9057.9 (1.2) | 74.1 (1.1) | 85.5 (1.1) | 35.3 (1.4) | 3.8 (0.3) | 15.0 (0.6) | 13.0 (0.5) |
| No | 5844.3 (1.1) | 5717.5 (1.1) | 83.9 (1.0) | 76.7 (1.0) | 53.1 (0.8) | 6.4 (0.1) | 20.0 (0.2) | 18.4 (0.3) |
| **Body Mass Index (BMI)** | | | | | | | | |

| Variable | PAH_Total[1] ng/LGM (GSE) | PAH_NFP[1] ng/LGM (GSE) | (1-OHPyr)[1] ng/LGM (GSE) | U. Creatinine[2] ng/LGM (GSE) | DSST Mean (SE) | DWR Mean (SE) | WL Mean (SE) | AF Mean (SE) |
|---|---|---|---|---|---|---|---|---|
| <25 | 5776.8 (1.1) | 5657.3 (1.1) | 73.4 (1.1) | 68.6 (1.1) | 52.3 (1.4) | 5.9 (0.2) | 19.1 (0.4) | 17.5 (0.5) |
| 25-29.9 | 5737.5 (1.1) | 5608.8 (1.1) | 85.4 (1.1) | 78.7 (1.1) | 53.3 (1.2) | 6.2 (0.2) | 19.6 (0.3) | 18.3 (0.5) |
| =>30 | 6669.5 (1.1) | 6533.4 (1.1) | 89.6 (1.1) | 85.6 (1.1) | 49.6 (1.2) | 6.4 (0.2) | 19.8 (0.3) | 18.0 (0.5) |
| **Blood Pressure (Self-reported)** | | | | | | | | |
| HTN | 6098.3 (1.1) | 5969.5 (1.1) | 82.6 (1.0) | 77.3 (1.0) | 51.4 (0.8) | 6.2 (0.1) | 19.6 (0.2) | 17.9 (0.3) |
| Non- HTN | 6306.3 (1.2) | 6168.5 (1.2) | 91.5 (1.2) | 87.9 (1.1) | 51.4 (3.4) | 5.8 (0.5) | 18.8 (0.9) | 17.6 (1.3) |
| **Cholesterolemia (Self-reported)** | | | | | | | | |
| Yes | 6911.0 (1.1) | 6771.3 (1.1) | 86.2 (1.1) | 76.5 (1.0) | 50.7 (1.0) | 5.9 (0.1) | 19.1 (0.3) | 17.4 (0.4) |
| No | 5210.7 (1.1) | 5093.7 (1.1) | 79.7 (1.1) | 78.5 (1.0) | 53.4 (1.2) | 6.5 (0.1) | 20.1 (0.3) | 18.7 (0.4) |

[1]geometric means
SE- standard error
GM- geometric mean
GSE- geometric standard error
ng/L—nanograms per liter
mg/dL—milligrams per deciliter

**Table 5 Univariate model showing association between digit symbol substitution test scores, urinary PAH metabolites, and other covariates among 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_Total[1] (ng/L)** | -1.93 (0.56) | - | <0.0006* | 0.02 |
| **ln_PAH_NFP[1] (ng/L)** | -1.91 (0.55) | - | <0.0006* | 0.02 |
| **ln_1-OHPyr[1] (ng/L)** | -2.81 (0.97) | - | <0.0038* | 0.01 |
| | | | | |
| **Age** | | | <0.0001* | 0.12 |
| 60-69 | 17.51 (1.62) | (14.31, 20.70) | | |
| 70-79 | 9.58 (1.57) | (6.50, 12.66) | | |
| 80+ | - | - | | |
| **Gender** | | | <0.002* | 0.01 |
| Female | 4.41 (1.45) | (1.55, 7.27) | | |
| Male | - | | | |
| **Race** | | | <0.0001* | 0.10 |
| Hispanic | -17.02 (1.54) | -(20.05, 13.99) | | |
| Asians | -4.17 (2.42) | (-8.93, 0.58) | | |
| Blacks | -13.21 (1.43) | -(16.02, 10.40) | | |
| Whites | - | - | | |
| **Education Level** | | | <0.0001* | 0.21 |
| Less than high school | -18.12 (1.74) | (-21.54, 14.70) | | |
| High school graduate or GED | -6.59 (1.95) | (-10.42, -2.75) | | |
| College graduate or higher | 4.45 (1.83) | (0.85, 8.0424) | | |
| Some college | - | - | | |
| **Annual family income** | | | <0.0001* | 0.16 |
| $55000+ | 16.65 (1.70) | (13.29, 20.0) | | |
| $25000 to <$55000 | 6.75 (1.82) | (3.18, 10.33) | | |
| <$25000 | - | - | | |
| **Smoking Status (self-reported)** | | | 0.01 | 0.01 |
| Non-Smoker | 3.57 (1.47) | (0.68, 6.46) | | |
| Smoker | - | - | | |
| **Alcohol consumption Self-reported)** | | | <0.0001* | 0.02 |
| Drinker | 6.23 (1.62) | (3.04, 9.42) | | |
| Non-Drinker | - | - | | |
| **Diabetes (Self-reported)** | | | <0.0001* | 0.05 |
| No | 9.97 (1.41) | (7.20, 12.74) | | |

| | | | | |
|---|---|---|---|---|
| Yes | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Congestive heart failure | | | <0.0001***** | 0.02 |
| No | 11.64 (2.55) | (6.62, 16.66) | | |
| Yes | - | - | | |
| Coronary heart disease | | | <0.0001* | 0.02 |
| No | 8.76 (1.74) | (5.34, 12.18) | | |
| Yes | - | - | | |
| Heart attack | | | <0.0001* | 0.02 |
| No | 9.49 (1.92) | (5.71, 13.27) | | |
| Yes | - | - | | |
| Stroke | | | <0.0001* | 0.01 |
| No | 8.10 (3.06) | (2.09, 14.12) | | |
| Yes | - | - | | |
| Emphysema | | | <0.002 | 0.006 |
| No | 6.23 (2.07) | (2.15, 10.30) | | |
| Yes | - | - | | |
| Memory and thinking problems | | | <0.0001* | 0.05 |
| No | 11.68 (1.89) | (7.96, 15.40) | | |
| Yes | - | | | |
| **Kidneys Problems** | | | <0.0001* | 0.02 |
| No | 12.24 (2.06) | (8.18, 16.30) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Vigorous work activity | | | <0.0088 | 0.01 |
| No | -5.61 (2.13) | (-9.80, -1.41) | | |
| Yes | - | - | | |
| Vigorous recreational activities | | | <0.0001* | 0.05 |
| No | -13.01 (2.12) | (-17.18, -8.83) | | |
| Yes | - | - | | |
| **Physical function limitations (Self-reported)** | | | | |
| Limitations that keeps individual from working | | | <0.0001* | 0.06 |
| No | 12.48 (1.78) | (8.98, 15.97) | | |
| Yes | - | - | | |
| Limitation in amounts work that individual can do | | | <0.0001* | 0.05 |
| No | 8.77 (1.62) | (5.59, 11.95) | | |
| Yes | - | - | | |

| | | | | |
|---|---|---|---|---|
| Experience confusion/memory problems | | | <0.0001* | 0.09 |
| No | 17.81 (1.58) | (14.69, 20.92) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 6 Univariate model showing association between word delayed recall test scores and other covariates among 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **Age** | | | <0.0001* | 0.10 |
| 60-69 | 2.34 (0.25) | (1.84, 2.85) | | |
| 70-79 | 1.60 (0.27) | (1.07, 2.14) | | |
| 80+ | - | - | | |
| **Gender** | | | <0.0001* | 0.02 |
| Female | 0.80 (0.20) | (0.40, 1.20) | | |
| Male | - | - | | |
| **Race** | | | <0.0001* | 0.01 |
| Hispanic | -1.05 (0.21) | (-1.47, -0.62) | | |
| Asian | -0.02 (0.28) | (--0.58, 0.53) | | |
| Blacks | -0.52 (0.20) | (-0.92, -0.12) | | |
| Whites | - | - | | |
| **Education Level** | | | <0.0001* | 0.06 |
| Less than high school | -1.33 (0.26) | (-1.85, -0.81) | | |
| High school graduate or GED | -0.62 (0.28) | (-1.18, -0.06) | | |
| College graduate or higher | 0.34 (0.27) | (-0.18, 0.87) | | |
| Some college | - | - | | |
| **Annual family income** | | | <0.0001* | 0.02 |
| $55000+ | 0.88 (0.24) | (0.41, 1.36) | | |
| $25000 to <$55000 | 0.27 (0.25) | (-0.21, 0.77) | | |
| <$25000 | - | - | | |
| **Smoking Status (Self-reported)** | | | <0.002* | 0.01 |
| Non-Smoker | 0.59 (0.19) | (0.20, 0.98) | | |
| Smoker | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Congestive heart failure | | | <0.0007* | 0.001 |
| No | 1.30 (0.38) | (0.55, 2.06) | | |
| Yes | - | - | | |
| Coronary heart disease | | | <0.0001* | 0.02 |
| No | 1.31 (0.33) | (0.65, 1.97) | | |
| Yes | - | - | | |
| Heart attack | | | <0.0001* | 0.02 |
| No | 1.18 (0.36) | (0.46, 1.89) | | |

| | | | | |
|---|---|---|---|---|
| Yes | - | - | | |
| Stroke | | | <0.0001* | 0.01 |
| No | 1.20 (0.44) | (0.32, 2.08) | | |
| Yes | - | - | | |
| Angina/angina pectoris | | | 0.03 | 0.006 |
| No | 0.90 (0.43) | (0.05, 1.75) | | |
| Yes | - | - | | |
| Emphysema | | | 0.01 | 0.008 |
| No | 1.04 (0.43) | (0.19, 1.89) | | |
| Yes | - | - | | |
| Memory and thinking problems | | | <0.0001* | 0.10 |
| No | 2.20 (0.28) | (1.64, 2.76) | | |
| Yes | - | - | | |
| **Kidneys Problems** | | | <0.003* | 0.008 |
| No | 0.96 (0.33) | (0.31, 1.61) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Vigorous work activity | | | <0.003* | 0.01 |
| No | -0.80 (0.27) | -1.34, -0.25) | | |
| Yes | - | - | | |
| Vigorous recreational activities | | | <0.0006* | 0.01 |
| No | -1.09 (0.31) | (-1.71, -0.46) | | |
| Yes | - | - | | |
| **Physical function limitations (Self-reported)** | | | | |
| Limitations that keeps individual from working | | | <0.0001* | 0.02 |
| No | 1.12 (0.26) | (0.59, 1.64) | | |
| Yes | - | - | | |
| Limitation in amounts work that individual can do | | | <0.0001* | 0.03 |
| No | 0.99 (0.21) | (0.57, 1.42) | | |
| Yes | - | - | | |
| Experience confusion/memory problems | | | <0.0001* | 0.11 |
| No | 2.67 (0.31) | (2.05, 3.28) | | |
| Yes | - | - | | |

* p value was significant at 0.05 level

**Table 7 Univariate model showing association between word list learning test scores and other covariates among 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **Age** | | | <0.0001* | 0.10 |
| 60-69 | 4.28 (0.50) | (3.29, 5.26) | | |
| 70-79 | 2.29 (0.55) | (1.20, 3.39) | | |
| 80+ | - | - | | |
| **Gender** | | | <0.0001* | 0.03 |
| Female | 1.76 (0.36) | (1.04, 2.49) | | |
| Male | - | - | | |
| **Race** | | | <0.0001* | 0.02 |
| Hispanic | -2.58 (0.40) | (-3.38, -1.77) | | |
| Asians | -1.48 (0.62) | (-2.70, -0.26) | | |
| Blacks | -0.47 (0.38) | (-1.23, 0.28) | | |
| Whites | - | - | | |
| **Education Level** | | | <0.0001* | 0.08 |
| Less than high school | -3.26 (0.47) | (-4.20, -2.32) | | |
| High school graduate or GED | -0.90 (0.50) | (-1.89, 0.09) | | |
| College graduate or higher | 0.72 (0.47) | (-0.20, 1.65) | | |
| Some college | - | - | | |
| **Annual family income** | | | <0.0001* | 0.04 |
| $55000+ | 2.18 (0.44) | (1.31, 3.06) | | |
| $25000 to <$55000 | 0.52 (0.47) | (-0.40, 1.45) | | |
| <$25000 | - | - | | |
| **Smoking Status (Self-reported)** | | | 0.01 | 0.008 |
| Non-Smoker | 0.87 (0.36) | (0.14, 1.59) | | |
| Smoker | - | - | | |
| **Alcohol consumption (Self-reported)** | | | 0.01 | 0.01 |
| Drinker | 1.06 (0.41) | (0.24, 1.87) | | |
| Non-Drinker | - | - | | |
| **Diabetes (Self-reported)** | | | 0.04 | 0.007 |
| No | 1.03 (0.42) | (0.19, 1.88) | | |
| Yes | - | - | | |

| | | | | |
|---|---|---|---|---|
| **Medical Conditions Self-reported** | | | | |
| Congestive heart failure | | | <0.0004* | 0.01 |
| No | 2.42 (0.85) | (0.75, 4.09) | | |
| Yes | - | - | | |
| Coronary heart disease | | | <0.0001* | 0.01 |
| No | 2.29 (0.59) | (1.11, 3.46) | | |
| Yes | - | - | | |
| Heart attack | | | <0.0001* | 0.01 |
| No | 2.09 (0.63) | (0.84, 3.33) | | |
| Yes | - | - | | |
| Memory and thinking problems | | | <0.0001* | 0.08 |
| No | 3.74 (0.56) | (2.62, 4.85) | | |
| Yes | - | - | | |
| **Kidneys Problems** | | | <0.008* | 0.01 |
| No | 2.11 (0.79) | (0.55, 3.67) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Vigorous work activity | | | 0.02 | 0.008 |
| No | -1.28 (0.55) | (-2.38, -0.19) | | |
| Yes | - | - | | |
| Vigorous recreational activities | | | <0.0001* | 0.02 |
| No | -2.29 (0.54) | (-3.36, -1.23) | | |
| Yes | - | - | | |
| **Physical function limitations (Self-reported)** | | | | |
| Limitations that keeps individual from working | | | <0.0003* | 0.02 |
| No | 1.87 (0.51) | (0.86, 2.87) | | |
| Yes | - | - | | |
| Limitation in amounts work that individual can do | | | <0.0001* | 0.01 |
| No | 1.42 (0.40) | (0.63, 2.22) | | |
| Yes | - | - | | |
| Experience confusion/memory problems | | | <0.0001* | 0.10 |
| No | 5.03 (0.64) | (3.76, 6.29) | | |
| Yes | - | - | | |

* p value was significant at 0.05 level

**Table 8 Univariate model showing Association between animal fluency test scores and other covariates among 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_Total[1] (ng/L)** | -0.43 (0.20) | - | 0.03 | 0.008 |
| **ln_PAH_NFP[1] (ng/L)** | -0.42 (0.20) | - | 0.03 | 0.007 |
| | | | | |
| **Age** | | | <0.0001* | 0.12 |
| 60-69 | 5.96 (0.54) | (4.90, 7.03) | | |
| 70-79 | 3.26 (0.54) | (2.18, 4.33) | | |
| 80+ | - | - | | |
| **Race** | | | <0.0001* | 0.054 |
| Hispanic | -3.42 (0.48) | (-4.37, -2.46) | | |
| Asians | -3.59 (0.55) | (-4.67, -2.51) | | |
| Blacks | -3.56 (0.48) | (-4.52, -2.61) | | |
| Whites | - | - | | |
| **Education Level** | | | <0.0001* | 0.17 |
| Less than high school | -3.58 (0.54) | (-4.65, -2.50) | | |
| High school graduate or GED | -2.14 (0.58) | (-3.30, -0.99) | | |
| College graduate or higher | 3.20 (0.71) | (1.79, 4.60) | | |
| Some college | - | - | | |
| **Annual family income** | | | <0.0001* | 0.07 |
| $55000+ | 3.78 (0.62) | (2.56, 5.01) | | |
| $25000 to <$55000 | 0.95 (0.69) | (-0.40, 2.30) | | |
| <$25000 | - | - | | |
| **Alcohol consumption Self-reported)** | | | <0.0001* | 0.03 |
| Drinker | 2.56 (0.54) | (1.49, 3.63) | | |
| Non-Drinker | - | - | | |
| **Diabetes (Self-reported)** | | | 0.04 | 0.01 |
| No | 1.69 (0.67) | (0.37, 3.02) | | |
| Yes | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Congestive heart failure | | | 0.04 | 0.006 |
| No | 1.89 (0.95) | (0.02, 3.76) | | |
| Yes | - | - | | |
| Coronary heart disease | | | 0.01 | 0.008 |
| No | 1.95 (0.80) | (0.38, 3.53) | | |
| Yes | - | - | | |
| Heart attack | | | <0.004* | 0.01 |
| No | 2.11 (0.75) | (0.64, 3.58) | | |

| | | | | |
|---|---|---|---|---|
| Yes | - | - | | |
| Stroke | | | <0.002* | 0.01 |
| No | 3.09 (1.02) | (1.09, 5.09) | | |
| Yes | - | - | | |
| Memory and thinking problems | | | <0.0001* | 0.03 |
| No | 3.37 (0.68) | (2.03, 4.71) | | |
| Yes | - | - | | |
| **Kidneys Problems** | | | 0.03 | 0.006 |
| No | 2.09 (0.96) | (0.19, 3.99) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Walk or bicycle | | | 0.04 | 0.007 |
| No | -1.38 (0.69) | (-2.76, -0.01) | | |
| Yes | - | - | | |
| Vigorous work activity | | | <0.006* | 0.01 |
| No | -2.11 (0.76) | (-3.62, -0.60) | | |
| Yes | - | - | | |
| Vigorous recreational activities | | | <0.0001* | 0.06 |
| No | -5.12 (1.14) | (-7.37, -2.87) | | |
| Yes | - | - | | |
| **Physical function limitations (Self-reported)** | | | | |
| Limitations that keeps individual from working | | | <0.0001* | 0.02 |
| No | 2.81 (0.60) | (1.63, 3.99) | | |
| Yes | - | - | | |
| Limitation in amounts work that individual can do | | | <0.0005* | 0.01 |
| No | 1.77 (0.54) | (0.70, 2.85) | | |
| Yes | - | - | | |
| Experience confusion/memory problems | | | <0.0001* | 0.07 |
| No | 5.46 (0.60) | (4.27, 6.65) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 9 Multivariate model showing association between digit symbol substitution test scores, total PAH in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_Total[1] (ng/L)** | -0.88 (0.43) | (-1.74, -0.03) | 0.04 | 0.48 |
| | | | | |
| **Age** | | | <0.0001* | |
| 60-69 | 17.87 (1.55) | (14.81, 20.92) | | |
| 70-79 | 9.40 (1.44) | (6.57, 12.22) | | |
| 80+ | - | - | | |
| **Gender** | | | <0.0001* | |
| Female | 5.94 (1.19) | (3.58, 8.29) | | |
| Male | - | | | |
| **Race** | | | <0.0001* | |
| Hispanic | -15.97 (1.62) | (-19.15, -12.79) | | |
| Asians | -3.37 (2.11) | (-7.52, 0.78) | | |
| Blacks | -12.46 (1.29) | (-15.00, -9.91) | | |
| Whites | - | - | | |
| **Annual family income** | | | <0.0001* | |
| $55000+ | 8.65 (1.47) | (5.76, 11.55) | | |
| $25000 to <$55000 | 4.11 (1.39) | (1.38, 6.85) | | |
| <$25000 | - | - | | |
| **Smoking Status (self-reported)** | | | <0.0019* | |
| Non-Smoker | 3.83 (1.22) | (1.42, 6.24) | | |
| Smoker | - | - | | |
| **Alcohol consumption Self-reported)** | | | <0.0001* | |
| Drinker | 4.44 (1.27) | (1.93, 6.94) | | |
| Non-Drinker | - | - | | |
| **Diabetes (Self-reported)** | | | <0.0001* | |
| No | 6.10 (1.36) | (3.42, 8.78) | | |
| Yes | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Congestive heart failure | | | <0.0013* | |
| No | 5.34 (1.66) | (2.09, 8.60) | | |
| Yes | - | - | | |

| | | | | |
|---|---|---|---|---|
| Memory and thinking problems | | | <0.0010* | |
| No | 5.53 (1.68) | (2.23, 8.84) | | |
| Yes | - | | | |
| **Kidneys Problems** | | | 0.02 | |
| No | 4.42 (1.89) | (0.69, 8.15) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Vigorous recreational activities | | | <0.0012* | |
| No | -6.88 (2.11) | -(11.03, -2.72) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 10 Multivariate model showing association between digit symbol substitution test scores, PAH (NFP) in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_NFP[1] (ng/L)** | -0.88 (0.43 | (-1.73, -0.02) | 0.04 | 0.48 |
| | | | | |
| **Age** | | | <0.0001* | |
| 60-69 | 17.87 (1.55) | (14.81, 20.92) | | |
| 70-79 | 9.39 (1.44) | (6.57, 12.22) | | |
| 80+ | - | - | | |
| **Gender** | | | <0.0001* | |
| Female | 5.94 (1.19) | (3.58, 8.29) | | |
| Male | - | | | |
| **Race** | | | <0.0001* | |
| Hispanic | -15.97 (1.62) | (-19.15, -12.79) | | |
| Asians | -3.37 (2.11) | (-7.52, 0.78) | | |
| Blacks | -12.46 (1.29) | (-15.00, -9.91) | | |
| Whites | - | - | | |
| **Annual family income** | | | <0.0001* | |
| $55000+ | 8.65 (1.47) | (5.76, 11.55) | | |
| $25000 to <$55000 | 4.11 (1.39) | (1.38, 6.85) | | |
| <$25000 | - | - | | |
| **Smoking Status (self-reported)** | | | <0.0019* | |
| Non-Smoker | 3.83 (1.22) | (1.42, 6.24) | | |
| Smoker | - | - | | |
| **Alcohol consumption Self-reported)** | | | <0.0005* | |
| Drinker | 4.44 (1.27) | (1.93, 6.94) | | |
| Non-Drinker | - | - | | |
| **Diabetes (Self-reported)** | | | <0.0001* | |
| No | 6.10 (1.36) | (3.42, 8.78) | | |
| Yes | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Congestive heart failure | | | <0.0013* | |
| No | 5.34 (1.66) | (2.09, 8.60) | | |
| Yes | - | - | | |

| | | | | |
|---|---|---|---|---|
| Memory and thinking problems | | | <0.0010* | |
| No | 5.53 (1.68) | (2.23, 8.84) | | |
| Yes | - | | | |
| **Kidneys Problems** | | | 0.02 | |
| No | 4.42 (1.90) | (0.69, 8.15) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Vigorous recreational activities | | | <0.0012* | |
| No | -6.88 (2.11) | -(11.03, -2.72) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 11 Multivariate model showing association between digit symbol substitution test scores, 1-Hydroxypyrene in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_1-OHPyr (ng/L)[1]** | -1.64 (0.80) | (-3.21, -0.07) | 0.04 | 0.42 |
| **Age** | | | <0.0001* | |
| 60-69 | 15.28 (1.72) | (11.90, 18.66) | | |
| 70-79 | 9.38 (1.60) | (6.22, 12.53) | | |
| 80+ | - | - | | |
| **Gender** | | | <0.0001* | |
| Female | 7.50 (1.34) | (4.87, 10.13) | | |
| Male | - | | | |
| **Annual family income** | | | <0.0001* | |
| $55000+ | 10.89 (1.83) | (7.29, 14.50) | | |
| $25000 to <$55000 | 4.87 (1.70) | (1.52, 8.22) | | |
| <$25000 | - | - | | |
| **Smoking Status (self-reported)** | | | 0.03 | |
| Non-Smoker | 3.05 (1.43) | (0.23, 5.86) | | |
| Smoker | - | - | | |
| **Alcohol consumption Self-reported)** | | | <0.0003* | |
| Drinker | 5.44 (1.49) | (2.51, 8.38) | | |
| Non-Drinker | - | - | | |
| **Diabetes (Self-reported)** | | | <0.0018* | |
| No | 5.64 (1.63) | (2.44, 8.84) | | |
| Yes | - | - | | |
| **Kidneys Problems** | | | 0.01 | |
| No | 5.57 (2.16) | (1.32, 9.82) | | |
| Yes | - | - | | |
| **Physical function limitations (Self-reported)** | | | | |
| Limitations that keeps individual from working | | | <0.0001* | |
| No | 7.03 (1.79) | (3.51, 10.55) | | |
| Yes | - | - | | |
| Experience confusion/memory problems | | | <0.0001* | |
| No | 10.02 (2.09) | (5.92, 14.12) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 12 Multivariate model showing association between delay word recall test scores, total PAH in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_Total[1] (ng/L)** | -0.12 (0.06) | (-0.25, -0.004) | 0.04 | 0.13 |
| | | | | |
| **Age** | | | <.0001* | |
| 60-69 | 2.23 (0.26) | (1.71, 2.76) | | |
| 70-79 | 1.53 (0.27) | (0.98, 2.08) | | |
| 80+ | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Coronary heart disease | | | <0.0008* | |
| No | 1.18 (0.35) | (0.49, 1.87) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 13 Multivariate model showing association between delay word recall test scores, PAH (NFP) in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_NFP[1] (ng/L)** | -0.12 (0.06) | (-0.25, -0.004) | 0.04 | 0.13 |
| | | | | |
| **Age** | | | <.0001* | |
| 60-69 | 2.23 (0.26) | (1.71, 2.76) | | |
| 70-79 | 1.53 (0.27) | (0.98, 2.08) | | |
| 80+ | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Coronary heart disease | | | <0.0008* | |
| No | 1.18 (0.35) | (0.49, 1.87) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 14 Multivariate model showing association between delay word recall test scores, 1-Hydroxypyrene in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_1-OHPyr [1] (ng/L)** | 0.23 (0.09) | (0.06, 0.42) | <0.0091* | 0.31 |
| | | | | |
| **Age** | | | <0.0001* | |
| 60-69 | 1.84 (0.24) | (1.36, 2.32) | | |
| 70-79 | 1.30 (0.24) | (0.81, 1.79) | | |
| 80+ | - | - | | |
| **Gender** | | | <0.0001* | |
| Female | 0.84 (0.18) | (0.47, 1.21) | | |
| Male | - | | | |
| **Race** | | | <0.0006* | |
| Hispanic | -0.71 (0.24) | (-1.20, -0.23) | | |
| Asians | 0.10 (0.25) | (-0.38, 0.60) | | |
| Blacks | -0.64 (0.19) | (-1.03, -0.26) | | |
| Whites | - | - | | |
| **Education Level** | | | <0.0005* | |
| Less than high school | -0.81 (0.25) | -1.31, -0.31) | | |
| High school graduate or GED | -0.40 (0.24) | (-0.88, 0.07) | | |
| College graduate or higher | 0.24 (0.25) | (-0.25, 0.74) | | |
| Some college | - | - | | |
| **Smoking Status (self-reported)** | | | <0.0046* | |
| Non-Smoker | 0.51 (0.18) | (0.15, 0.86) | | |
| Smoker | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Memory and thinking problems | | | <0.0001* | |
| No | 0.92 (0.26) | (0.40, 1.43) | | |
| Yes | - | - | | |
| **Physical function limitations (Self-reported)** | | | | |
| Experience confusion/memory problems | | | <0.0001* | |
| No | 1.73 (0.32) | (1.09, 2.38) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 15 Multivariate model showing association between world list learning test scores, total PAH in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_Total[1] (ng/L)** | -0.27 (0.13) | (-0.53, -0.02) | 0.03 | 0.13 |
| | | | | |
| **Age** | | | <.0001* | |
| 60-69 | 4.18 (0.51) | (3.16, 5.20) | | |
| 70-79 | 2.24 (0.57) | (1.11, 3.38) | | |
| 80+ | - | - | | |
| **Diabetes (Self-reported)** | | | <0.0081* | |
| No | 1.30 (0.42) | (0.46, 2.14) | | |
| Yes | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Coronary heart disease | | | <0.0063* | |
| No | 1.78 (0.65) | (0.50, 3.05) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 16 Multivariate model showing association between world list learning test scores, PAH (NFP) in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_NFP[1] (ng/L)** | -0.27 (0.12) | (-0.53, -0.02) | 0.03 | 0.13 |
| | | | | |
| **Age** | | | <.0001* | |
| 60-69 | 4.18 (0.51) | (3.16, 5.20) | | |
| 70-79 | 2.24 (0.57) | (1.11, 3.38) | | |
| 80+ | - | - | | |
| **Diabetes (Self-reported)** | | | <0.0081* | |
| No | 1.30 (0.42) | (0.46, 2.14) | | |
| Yes | - | - | | |
| **Medical Conditions Self-reported** | | | | |
| Coronary heart disease | | | <0.0063* | |
| No | 1.78 (0.65) | (0.50, 3.05) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 17 Multivariate model showing association between animal fluency test scores, total PAH in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_Total[1] (ng/L)** | -0.39 (0.20) | (-0.79, -0.0006) | 0.04 | 0.21 |
| | | | | |
| **Age** | | | <0.0001 | |
| 60-69 | 4.91 (0.55) | (3.82, 6.01) | | |
| 70-79 | 2.69 (0.60) | (1.51, 3.88) | | |
| 80+ | - | - | | |
| **Annual family income** | | | <0.0017 | |
| $55000+ | 2.11 (0.59) | (0.95, 3.27) | | |
| $25000 to <$55000 | 0.62 (0.58) | (-0.52, 1.77) | | |
| <$25000 | - | - | | |
| **Alcohol consumption Self-reported)** | | | <0.0023 | |
| Drinker | 1.53 (0.50) | (0.54, 2.52) | | |
| Non-Drinker | - | - | | |
| **Kidneys Problems** | | | 0.02 | |
| No | 1.77 (0.79) | (0.20, 3.34) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Vigorous recreational activities | | | <0.0026* | |
| No | -3.55 (1.17) | (-5.87, -1.24) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 18 Multivariate model showing association between animal fluency test scores, PAH (NFP) in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **ln_PAH_NFP[1] (ng/L)** | -0.39 (0.20) | (-0.78, -0.002) | **0.051** | 0.21 |
| | | | | |
| **Age** | | | <0.0001* | |
| 60-69 | 4.91 (0.55) | (3.82, 6.01) | | |
| 70-79 | 2.69 (0.60) | (1.51, 3.88) | | |
| 80+ | - | - | | |
| **Annual family income** | | | <0.0017* | |
| $55000+ | 2.11 (0.59) | (0.95, 3.27) | | |
| $25000 to <$55000 | 0.62 (0.58) | (-0.52, 1.77) | | |
| <$25000 | - | - | | |
| **Alcohol consumption Self-reported)** | | | <0.0024* | |
| Drinker | 1.53 (0.50) | (0.54, 2.52) | | |
| Non-Drinker | - | - | | |
| **Kidneys Problems** | | | 0.02 | |
| No | 1.77 (0.79) | (0.20, 3.34) | | |
| Yes | - | - | | |
| **Physical Activity (Self-reported)** | | | | |
| Vigorous recreational activities | | | <0.0026* | |
| No | -3.55 (1.17) | (-5.87, -1.24) | | |
| Yes | - | - | | |

[1] Log transformed

* p value was significant at 0.05 level

**Table 19 Characteristics of NHANES participants for 2011-2014**

| Characteristic | N | Percent (weighted) | SE |
|---|---|---|---|
| **Age** | | | |
| 60-69 | 1671 | 54.67 | 1.19 |
| 70-79 | 950 | 29.53 | 1.04 |
| 80+ | 560 | 15.79 | 0.73 |
| **Gender** | | | |
| Male | 1547 | 45.32 | 1.23 |
| Female | 1634 | 54.67 | 1.23 |
| **Race** | | | |
| Hispanic | 615 | 7.50 | 0.34 |
| Asians | 317 | 5.27 | 0.42 |
| Blacks | 779 | 8.98 | 0.38 |
| Whites | 1470 | 78.23 | 0.71 |
| **Smoking Status** | | | |
| Smoker | 1601 | 50.26 | 1.23 |
| Non-Smoker | 1577 | 49.73 | 1.23 |
| **Alcohol consumption** | | | |
| Yes | 171 | 5.81 | 0.57 |
| No | 2997 | 94.18 | 0.57 |
| **Physical Activity** | | | |
| Walk or bicycle | | | |
| Yes | 666 | 18.98 | 0.98 |
| No | 2515 | 81.01 | 0.98 |
| **Body Mass Index (BMI)** | | | |
| <25 | 844 | 26.17 | 1.08 |
| 25-29.9 | 1091 | 36.03 | 1.19 |
| =>30 | 1184 | 37.78 | 1.20 |
| **Hypertension** | | | |
| HTN | 3059 | 96.54 | 0.42 |
| Non-HTN | 122 | 3.45 | 0.42 |

N- number
SE—standard error

**Table 20 Univariate model showing the association between race and total PAH biomarkers in urine, and other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **Race** | | | <0.0001* | 0.01 |
| Hispanic | 0.18 (0.10) | (-0.02, 0.39) | | |
| Asians | 0.21 (0.25) | (-0.29, 0.72) | | |
| Blacks | 0.58 (0.10) | (0.38, 0.78) | | |
| Whites | - | - | | |
| **Smoking Status (Self-reported)** | | | 0.01 | 0.009 |
| Non-Smoker | -0.24 (0.10) | (-0.44, -0.04) | | |
| Smoker | - | - | | |

* p value was significant at 0.05 level

**Table 21 Multivariate model showing the association between race and total PAH biomarkers in urine adjusted with other covariates, 2011-2014 NHANES participants**

| Variable | Estimate (SE) | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|
| **Race** | | | <0.0001* | 0.03 |
| Hispanic | 0.18 (0.10) | (-0.02, 0.39) | | |
| Asian | 0.22 (0.25) | (-0.28, 0.71) | | |
| Blacks | 0.61 (0.10) | (-0.41, 0,81) | | |
| Whites | - | - | | |
| **Smoking Status (Self-reported)** | | | <0.03 | |
| Non-Smoker | 0.59 (0.19) | (0.20, 0.98) | | |
| Smoker | - | - | | |

* p value was significant at 0.05 level

**Table 22 Characteristics of 2011-2014 NHANES for hypertensive participants with urinary PAH metabolites measured by different racial groups**

| Variable | 1-OHN[1] (ng/L) GM (GSE) | 2-OHN[1] (ng/L) GM (GSE) | 2-OHFl[1] (ng/L) GM (GSE) | 3-OHFl[1] (ng/L) GM (GSE) | 1-OHPhe[1] (ng/L) GM (GSE) | 2,3-OHPhe[1] (ng/L) GM (GSE) | 1OHPyr[1] (ng/L) GM (GSE) |
|---|---|---|---|---|---|---|---|
| **Race** | | | | | | | |
| **Hispanic** | 1109.1 (1.8) | 3960.0 (1.4) | 181.0 (1.6) | 67.6 (1.5) | 59.0 (1.7) | 85.8 (1.6) | 97.0 (1.3) |
| **Asians** | 1523.2 (1.3) | 2767.1 (1.2) | 210.0 (1.3) | 82.6 (1.3) | 132.5 (1.3 | 133.2 (1.3) | 90.9 (1.3) |
| **Blacks** | **17031.0 (1.4)** | **10109.6 (2.0)** | **807.2 (1.8)** | **384.5 (2.1)** | **117.9 (1.4)** | **200.6 (1.4)** | **147.1 (1.5)** |
| **Whites** | 506.3 (1.3) | 1887.6 (1.3) | 93.3 (1.3) | 36.1 (1.3) | 41.9 (1.2) | 58.5 (1.3) | 55.5 (1.2) |

[1]geometric means
GM- geometric mean
GSE- geometric standard error
ng/L—nanograms per liter

**Table 23 The probability of developing HTN with 2.5 ng/L of urinary 1-hydroxynaphthalene biomarker by different racial groups**

| Race | ln_1-hydroxynaphthalene (ng/L) | Estimate | SE | DF | t - value | Pr > \|t\| | Alpha | Lower | Upper | Mean | Standard Error of Mean | Lower Mean | Upper Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hispanic** | 2.50 | 3.2943 | 1.5455 | 987 | 2.13 | 0.03 | 0.05 | 0.261 | 6.32 | 0.9642 | 0.0533 | 0.56 | 0.998 |
| **Asians** | 2.50 | -1.1396 | 1.6228 | 987 | -0.70 | 0.48 | 0.05 | - | 2.04 | 0.2424 | 0.2980 | 0.01 | 0.885 |
| **Blacks** | 2.50 | 7.8441 | 1.1806 | 987 | 6.64 | <.00 | 0.05 | 5.527 | 10.1 | 0.9996 | 0.0004 | 0.99 | 1.000 |
| **Whites** | 2.50 | 3.4633 | 0.7905 | 987 | 4.38 | <.00 | 0.05 | 1.912 | 5.01 | 0.9696 | 0.0232 | 0.87 | 0.993 |

ng/L—nanograms per liter

**Table 24 The probability of developing HTN with 5 ng/L of urinary 1-hydroxynaphthalene biomarker increased by different racial groups**

| Race | ln_1-hydroxynaphthalene (ng/L) | Estimate | SE | DF | t-value | Pr > \|t\| | Alpha | Lower | Upper | Mean | Standard Error of Mean | Lower Mean | Upper Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hispanic** | 5.00 | 3.5367 | 0.8605 | 987 | 4.11 | <.0001 | 0.05 | 1.8480 | 5.2254 | 0.9717 | 0.02365 | 0.8639 | 0.9947 |
| **Asians** | 5.00 | 1.5539 | 0.8617 | 987 | 1.80 | 0.0717 | 0.05 | 0.1372 | 3.2449 | 0.8255 | 0.1241 | 0.4658 | 0.9625 |
| **Blacks** | 5.00 | 6.1801 | 0.8454 | 987 | 7.31 | <.0001 | 0.05 | 4.5210 | 7.8391 | **0.9979** | 0.001743 | 0.9892 | 0.9996 |
| **Whites** | 5.00 | 3.5295 | .4994 | 87 | .07 | .0001 | .05 | .5495 | .5095 | .9715 | .01382 | .9275 | .9891 |

ng/L—nanograms per liter

**Table 25 The probability of developing HTN with 7.5 ng/L of urinary 1-hydroxynaphthalene biomarker increased by different race groups**

| Race | 1-hydroxynaphthalene (ng/L) | Estimate | SE | DF | t-value | Pr > \|t\| | Alpha | Lower | Upper | Mean | Standard Error of Mean | Lower Mean | Upper Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hispanic** | 7.50 | 3.7791 | 0.5225 | 987 | 7.23 | <.0001 | 0.05 | 2.7539 | 4.8044 | 0.9777 | 0.01141 | 0.9401 | 0.9919 |
| **Asians** | 7.50 | 4.2474 | 0.6740 | 987 | 6.30 | <.0001 | 0.05 | 2.9248 | 5.5699 | 0.9859 | 0.009369 | 0.9491 | 0.9962 |
| **Blacks** | 7.50 | 4.5160 | 0.6640 | 987 | 6.80 | <.0001 | 0.05 | 3.2131 | 5.8190 | 0.9892 | 0.007103 | 0.9613 | 0.9970 |
| **Whites** | 7.50 | 3.5958 | 0.3170 | 987 | 11.34 | <.0001 | 0.05 | 2.9737 | 4.2178 | 0.9733 | 0.008240 | 0.9514 | 0.9855 |

ng/L—nanograms per liter

**Table 26 The Odds ratio of developing HTN with urinary 1-hydroxynaphthalene biomarker measured by different racial groups**

| Estimates | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Label** | **Estimate** | **SE** | **DF** | **t-value** | **Pr > \|t\|** | **Alpha** | **Lower** | **Upper** | **Exponentiated** | **Exponentiated Lower** | **Exponentiated Upper** |
| **Biomarker OR, Hispanic** | 0.09696 | 0.307 | 98 | 0.32 | 0.752 | 0.05 | -0.5126 | 0.7065 | 1.1018 | 0.6029 | 2.0138 |
| **Biomarker OR, Asians** | 1.0774 | 0.358 | 98 | 3.01 | 0.002 | 0.05 | 0.3748 | 1.7801 | 2.9370 | 1.4547 | 5.9301 |
| **Biomarker OR, Blacks** | -0.6656 | 0.180 | 98 | -3.70 | 0.000 | 0.05 | -1.0225 | -0.3087 | 0.5140 | 0.3610 | 0.7317 |
| **Biomarker OR, Whites** | 0.02649 | 0.134 | 98 | 0.20 | 0.844 | 0.05 | -0.2397 | 0.2926 | 1.0268 | 0.7884 | 1.3374 |

**Table 27 Standard limits and regulations for PAH exposure (ATSDR, 2009b)**

| Agency | Focus | Level | Comments |
|---|---|---|---|
| American Conference of Governmental Industrial Hygienists | Air: workplace | 0.2 (mg/m3) for benzene-soluble coal tar pitch fraction | Advisory: TLV (8-hour TWA) |
| National Institute for Occupational Safety and Health | Air: workplace | 0.1 mg/m3 for coal tar pitch volatile agents | Advisory: REL (8-hour TWA) |
| Occupational Safety and Health Administration | Air: workplace | 0.2 mg/m3 for benzene-soluble coal tar pitch fraction | Regulation: (benzene soluble fraction of coal tar volatiles) PEL (8-hour workday) |

TLV: threshold limit value
TWA: (time-weighted average): defined as a concentration for a normal 8-hour workday and a 40-hour workweek that nearly all workers may be repeatedly exposed.
REL (recommended exposure limit): recommended airborne exposure limit for CTPVs averaged over a 10-hour work shift.
PEL (permissible exposure limit): the legal airborne permissible exposure limit for CTPVs averaged over an 8-hour work shift.
(mg/L): milligrams per liter
($mg/m^3$): milligrams per cubic meter

**Table 28 Medications for patients with dementia (University Health System, 2012)**

| Eligible population | Line | Medication | Initial dose | Maximum dose |
|---|---|---|---|---|
| Mild cognitive impairment | Medications are not recommended | | | |
| Early-to midstage dementia | 1st | Donepezil | 5 mg daily for 4 weeks, then increase to 10 mg daily if tolerated | 10 mg daily1 |
| | 2nd | Galantamine Immediate release (NF) | 4 mg twice daily for 4 weeks, then 8 mg twice daily for 4 weeks, then increase to 12 mg twice daily if tolerated. | 12 mg twice daily |
| | | Galantamine extended release (NF) | 8 mg daily x 4 weeks, 16 mg daily x 4 weeks, then increase to 24 mg daily if tolerated | 24 mg daily |
| | 2nd | Rivastigmine immediate release (NF) | 1.5 mg twice daily for 2 weeks, 3 mg twice daily for 2 weeks, 4.5 mg twice daily for 2 weeks, then increase to 6 mg twice daily if tolerated | 6 mg twice daily |
| | | Rivastigmine transdermal patch (NF) | 4.6 mg daily for 4 weeks, then increase to 9.5 mg daily if tolerated | 9.5 mg daily |
| Mid-stage dementia no longer or too slowly responding to an acetylcholinesterase inhibitor | | Memantine (PA) | 5 mg daily for 1 week, then 5 mg twice daily for 1 week, then 5 mg in the morning and 10 mg in the evening for 1 week, then 10 mg twice daily if tolerated. | 10 mg twice daily |
| Late-stage dementia | For this level of dementia, medications may be more harmful than benefit for patients. | | | |

**Table 29 Studies of measured PAH exposure and cognitive disorders among older adults (Humphreys and Hernández, 2021)**

| Citation | Sample Size | Sample Characteristics | Male: Female | ean age (SD) | Age Range | Comorbidities | ir Pollution Data Acquisition Method |
|---|---|---|---|---|---|---|---|
| Du *et al.* 2020 | 697 | Employed at a coking plant in Shanxi province, China for minimum of 1 year | 470:227 | 39.73 (9.74) | years 12 months | N/A | The sum of the concentrations of eleven urinary PAH bolites Σ-OHPAH |
| Cho *et al.* 2020 | 949 | ≥50 year-old individuals, no known neurological diseases, resident in Seoul, Incheon, Wonju and Pyeongchang, Republic of Korea. | 421:528 | 67.24 (6.39) | ≥50 years | Hypertension Diabetes ipidaemia Angina Myocardial infarction | Concentrations of urinary PAH bolites including: 1hydroxypyrene |
| Ha *et al.* 2012 | 565 | Volunteers in the Hebei Spirit oil spill, 2007, near the shore of Taean, Korea. | 275:288 | N/A | N/A | Asthma | ydroxypyrene and 2naphthol metabolites in urine |
| Niu *et al.* 2009 | 176 | Male 23–48-year-old coke oven workers Taiyuan, China, employed for a minimum of 1-year, middle school educated. | 176:00 | 37.86 (6.61) | ars to 48 years 12 months | N/A | Concentration of urinary PAH metabolite 1hydroxypyrene (1-OHP) |
| Best *et al.* 2016 | 454 | ≥60-year-old individuals without known neurological diseases, resident in 15 randomly selected states in the US | 221:233 | 70.1 (0.02) | 60 years | Hypertension Thyroid Disease Stroke Kidney Disease Liver Disease | The sum of the concentrations of eight urinary PAH olites (ΣOHPAH) |

**Table 30 Studies of measured PAH exposure and neurobehavioral development among childhood**

**(Humphreys and Hernández, 2021)**

| Citation | Sample Size | Sample Characteristics | Male: Female | Mean age (SD) | Age Range | Co-morbidities | Air Pollution Data Acquisition Method |
|---|---|---|---|---|---|---|---|
| Suter *et al.* 2018 | 31 | Children aged 5-12 resident in Nairobi, Kenya, Infected with HIV and previously enrolled in the Optimizing HIV-1 Therapy Study | N/A | 6.6 (0.8) | 5 years 12 years 12 months | HIV | Concentration of urinary PAH metabolite 1hydroxypyrene (1OHP) |
| Mortamai s *et al.* 2017 | 242 | Children 7- 10 years, resident and enrolled in one of 40 schools in Barcelona, Spain, no dental braces | 123:119 | 8.4 (0.8) | 7 years - 10 years 12 months | N/A | Environmental air sampling |
| Abid *et al.* 2014 | 83 | Children 6-15 years of age, Part of a civilian population resident in the US | 58:25 | 11.2 (0.5) | 6 years - 15 years 12 months | N/A | Urinary metabolite concentrations of 2napthol |
| Alemany *et al.* 2018 | 1589 | Children aged 7-11, attending 1 of 38 schools in Barcelona, Spain, and 1 school in the adjacent municipality, Sant Cugat del Vallés | 831: 758 | 8.52 (0.87) | 7 years- 11 years 12 months | APOE e4 allele | Environmental samples analysed for 7 PAH |

**Table 31 Studies of measured prenatal PAH exposure and neurobehavioral development (Humphreys and Hernández, 2021)**

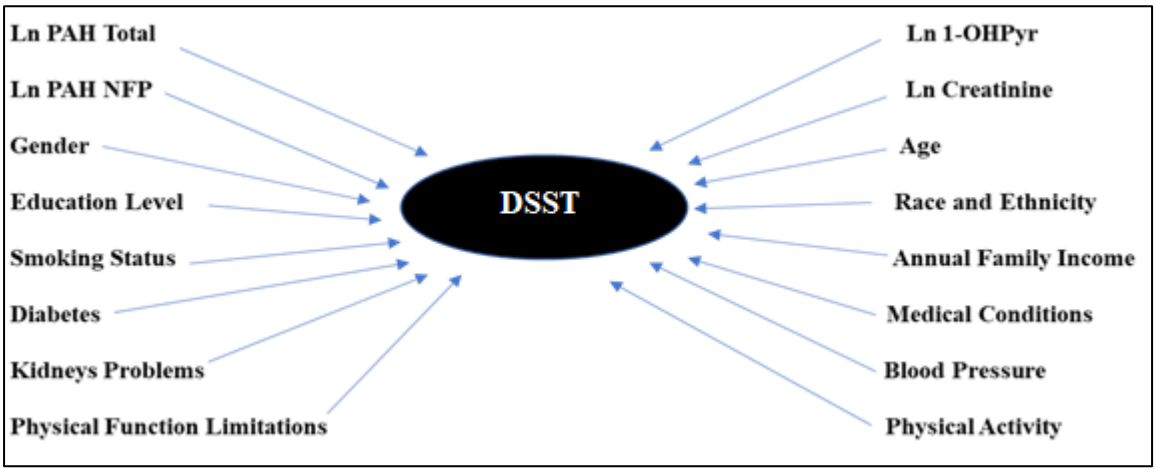
| Citation | Sample Size | Sample Characteristics | Male: Female | Mean age (SD) | Age Range | Air Pollution Data Acquisition Method |
|---|---|---|---|---|---|---|
| Perera *et al.* 2018 | 351 | Children 9 years of age, mothers 18-35 years, nonsmoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City. | 163: 188 | 9.01 (0.19) | 9 years- 9 years 12 months | Cord blood Benzo[a]pyreneDNA adducts (ng/mL) |
| Perera *et al.* 2012 | 253 | Children 6-7 years of age, mothers 18-35 years, nonsmoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City. | 131:122 | 6.5 (0.5) | 6 years - 7 years 12 months | Environmental samples analyzed for 8 PAH |
| Perera *et al.* 2011 | 215 | Children 3 years 9 months- 5 years 11 months of age, mothers 18-35 years, non- | 87: 128 | 4.8 (not reported) | 3 years 9 months - 5 years 11 months | Cord blood Benzo[a]pyreneDNA adducts (ng/mL) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City. | | | | |
| Pagliaccio *et al.* 2020 | 319 | Children 11 years old, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City. | 177: 142 | 11.5 (0.5) | 11 years - 11 years 12 months | Environmental samples analysed for 8 PAH |
| Nie *et al.* 2019 | 247 | Infants 3 days of age, mothers ≥ 18 years, non-smoking, no chronic disease or family history of neurological disease, single gestational viable fetus, who delivered in the Sixth Hospital of Shanxi Medical University and the Eighth People's Hospital of | 132: 115 | 3 days (not reported) | 3 days | Urinary metabolite concentrations of 2-hydroxyfluorene |

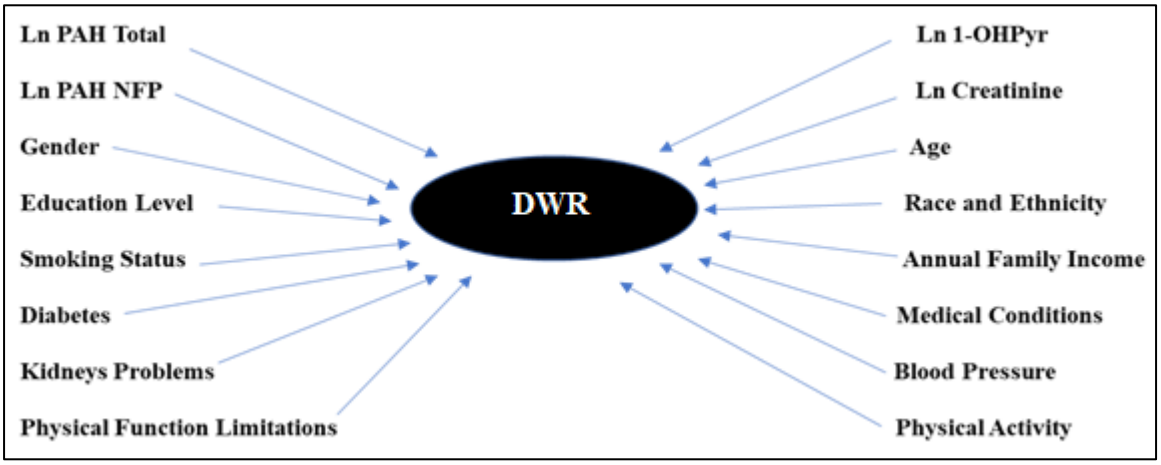
| | | | | | | |
|---|---|---|---|---|---|---|
| | | Taiyua, resident in Taiyuan for at least a year | | | | |

# Appendix A.2 Models

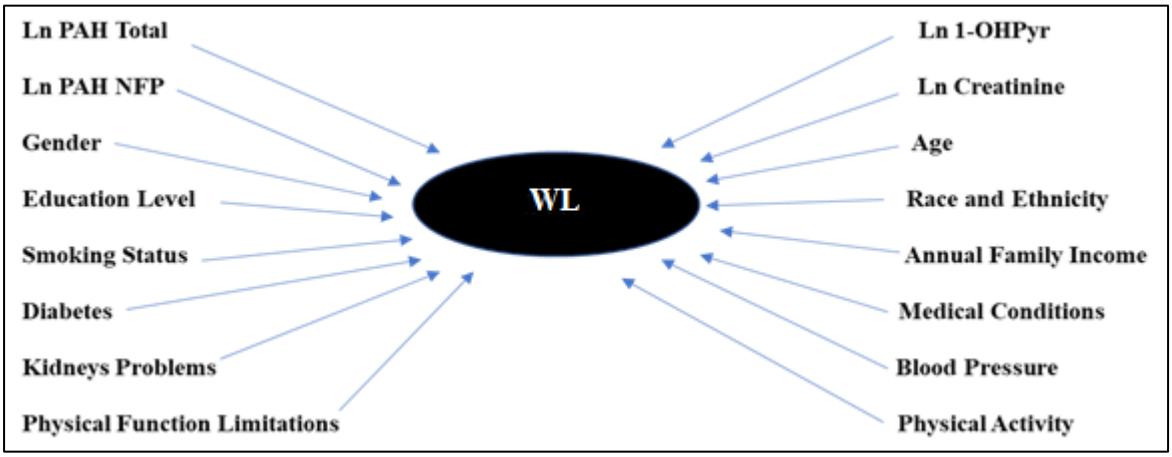
**Model 1. Individual univariate models of the association between digit symbol substitution test (DSST), urinary PAH biomarkers, and other covariates among 2011-2014 NHANES participants**



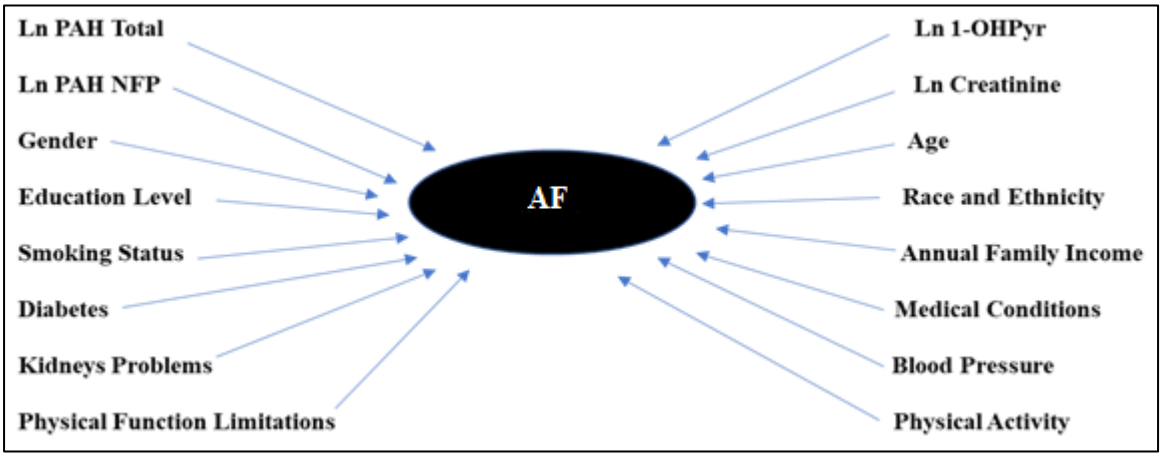

**Model 2. Individual univariate models of the association between delayed word recall test (DWR), urinary PAH biomarkers, and other covariates among 2011-2014 NHANES participants**



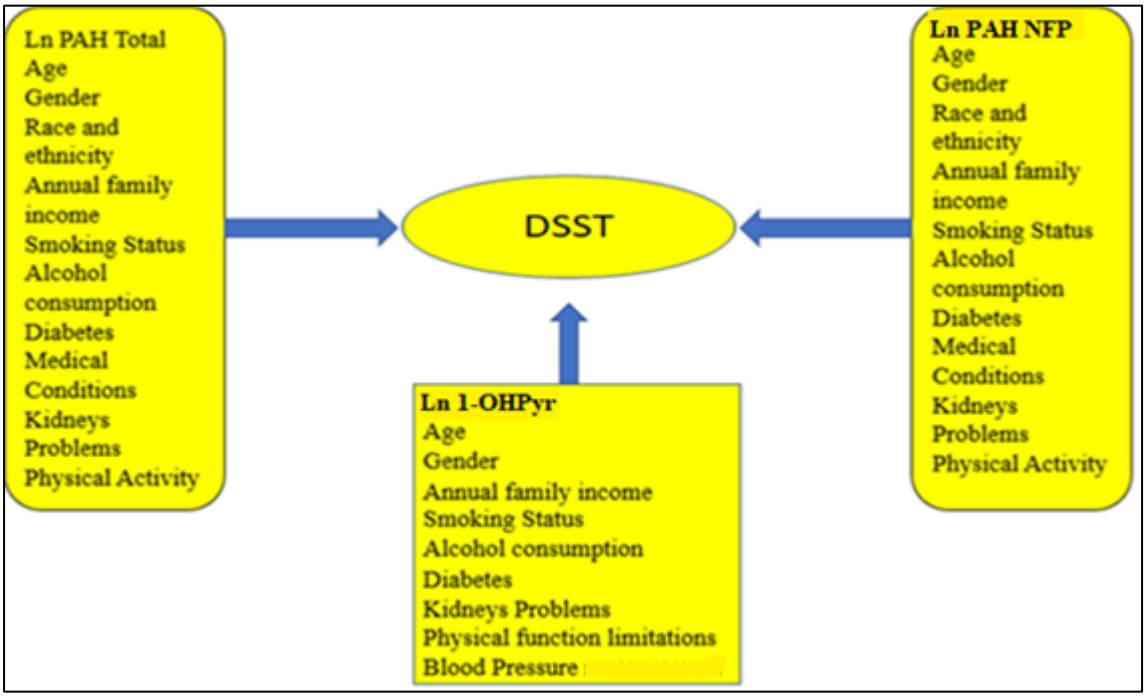
**Model 3. Individual univariate models of the association between world list learning test (WL), urinary PAH biomarkers, and other covariates among 2011-2014 NHANES participants**



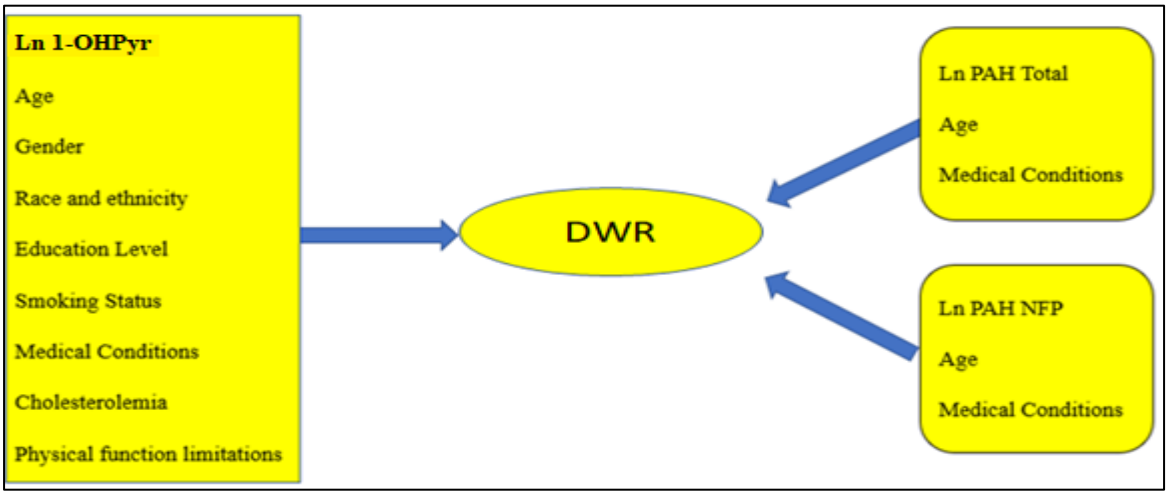

**Model 4. Individual univariate models of the association between animal fluency test (AF), urinary PAH biomarkers, and other covariates among 2011-2014 NHANES participants**



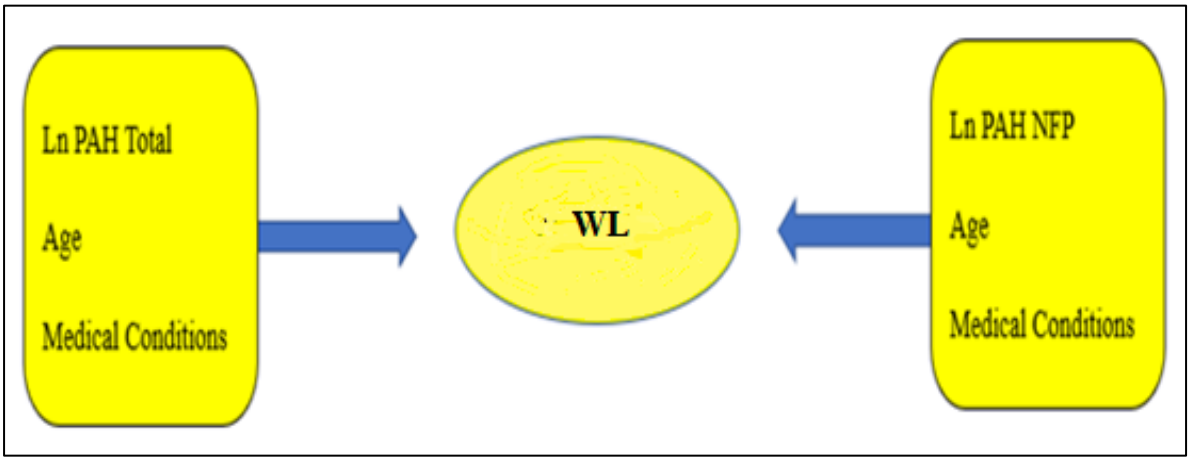
**Model 5. Multivariate model of the association between digit symbol substitution test (DSST), urinary PAH biomarkers, and other covariates among 2011-2014 NHANES participants**



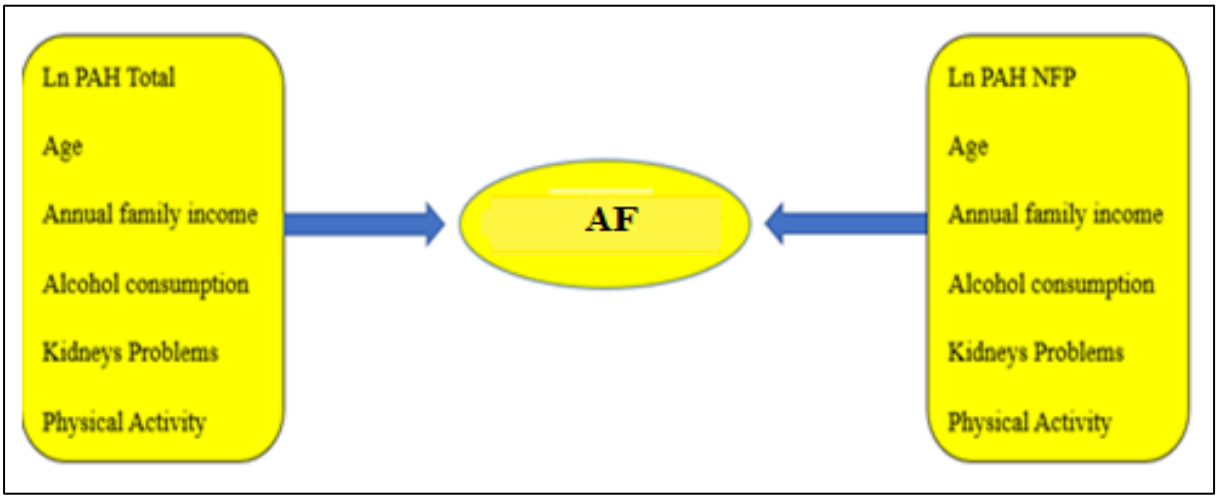

**Model 6. Multivariate model of the association between delayed word recall test (DWR), urinary PAH biomarker, and other covariates among 2011-2014 NHANES participants**



**Model 7. Multivariate model of the association between world list learning test (WL), urinary PAH biomarker, and other covariates among 2011-2014 NHANES participants**

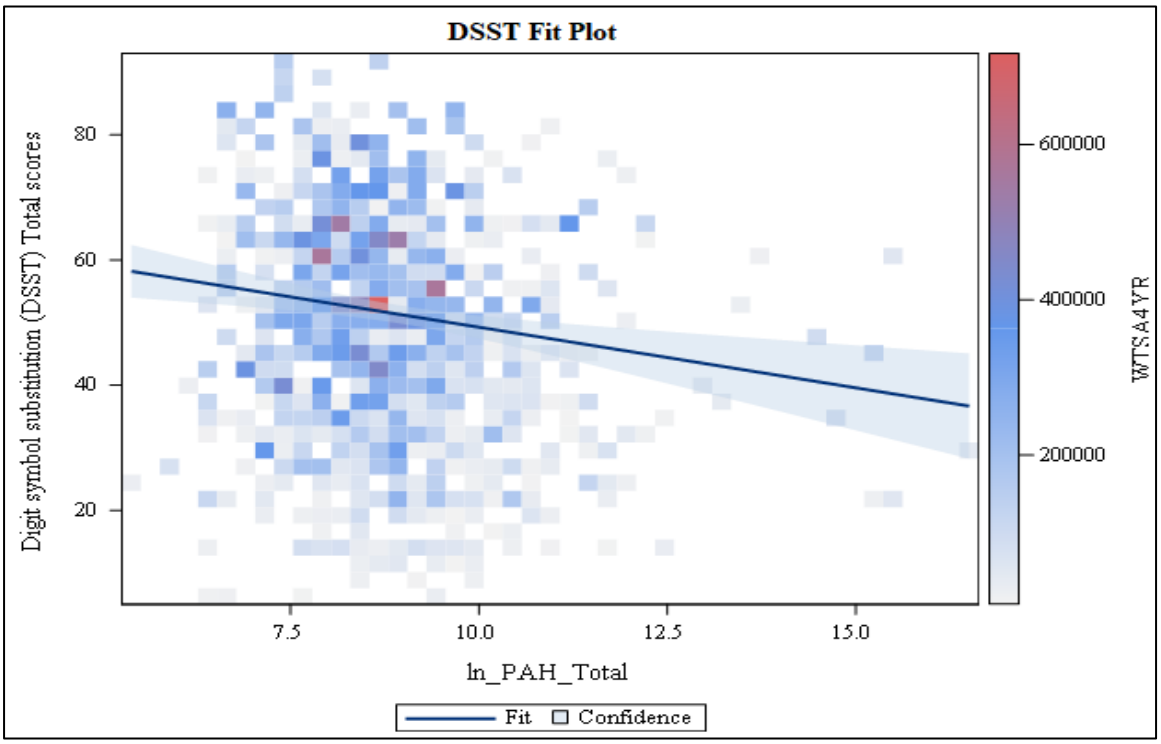


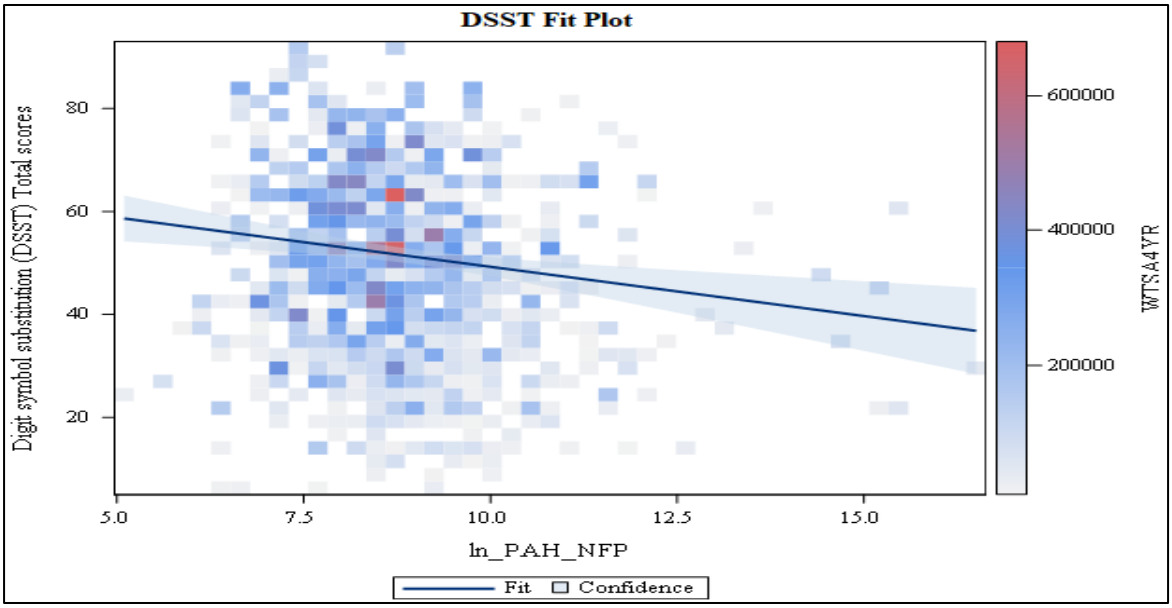

**Model 8. Multivariate model of the association between animal fluency test (AF), urinary PAH biomarker, and other covariates among 2011-2014 NHANES participants**

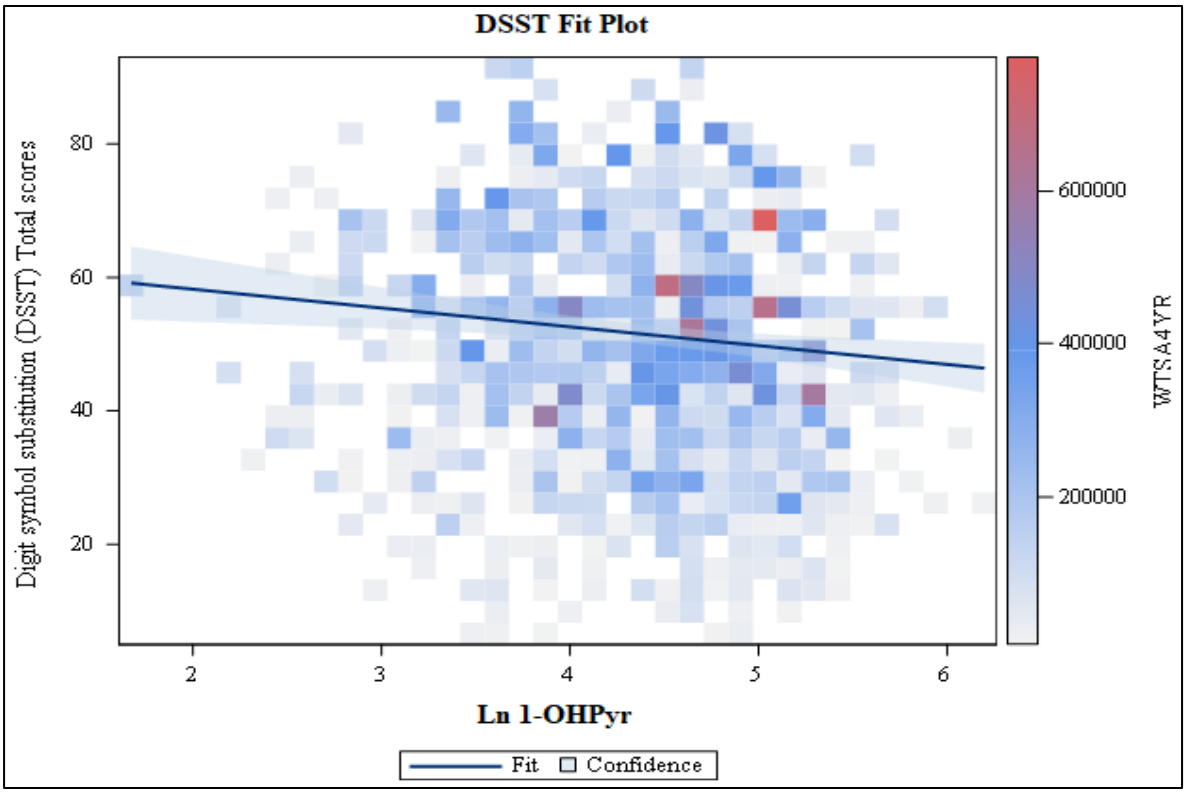


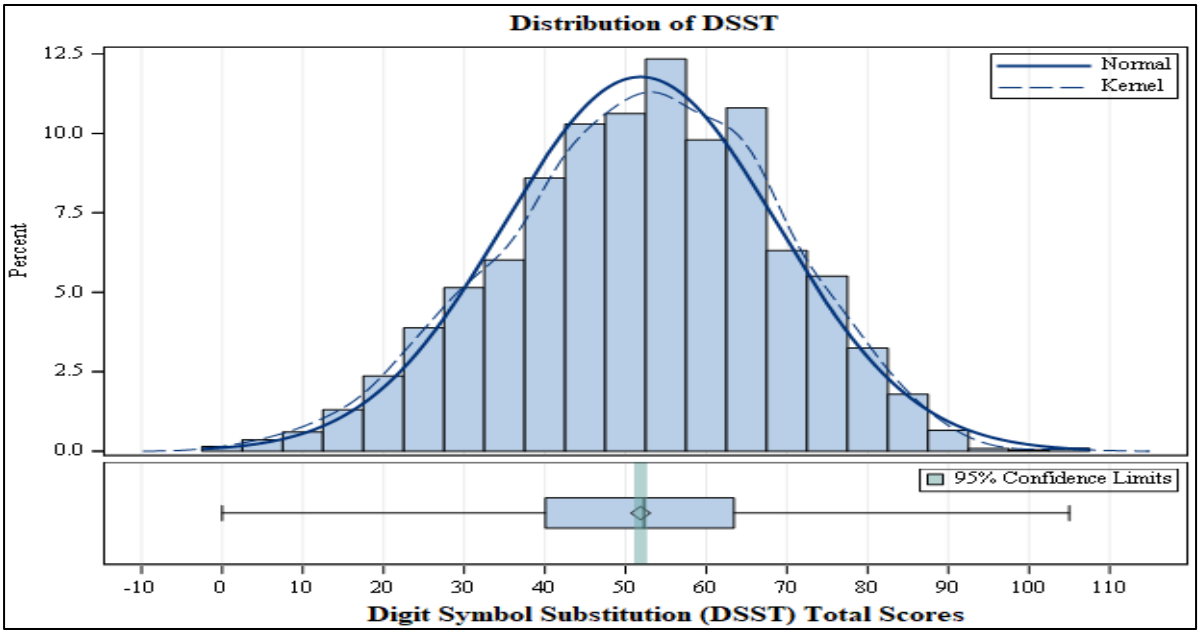
## Appendix A.3 Figures

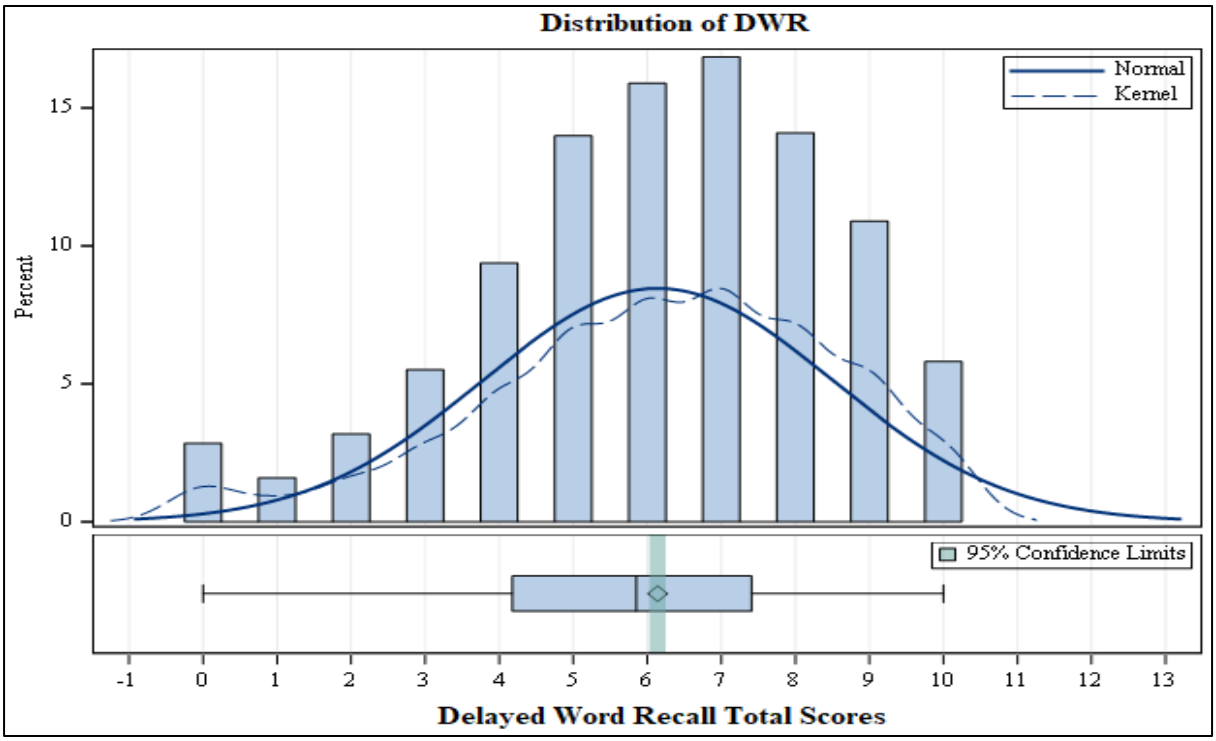
Appendix A.3 includes Residual plots and normal distribution charts for the outcome and primary exposure variables.

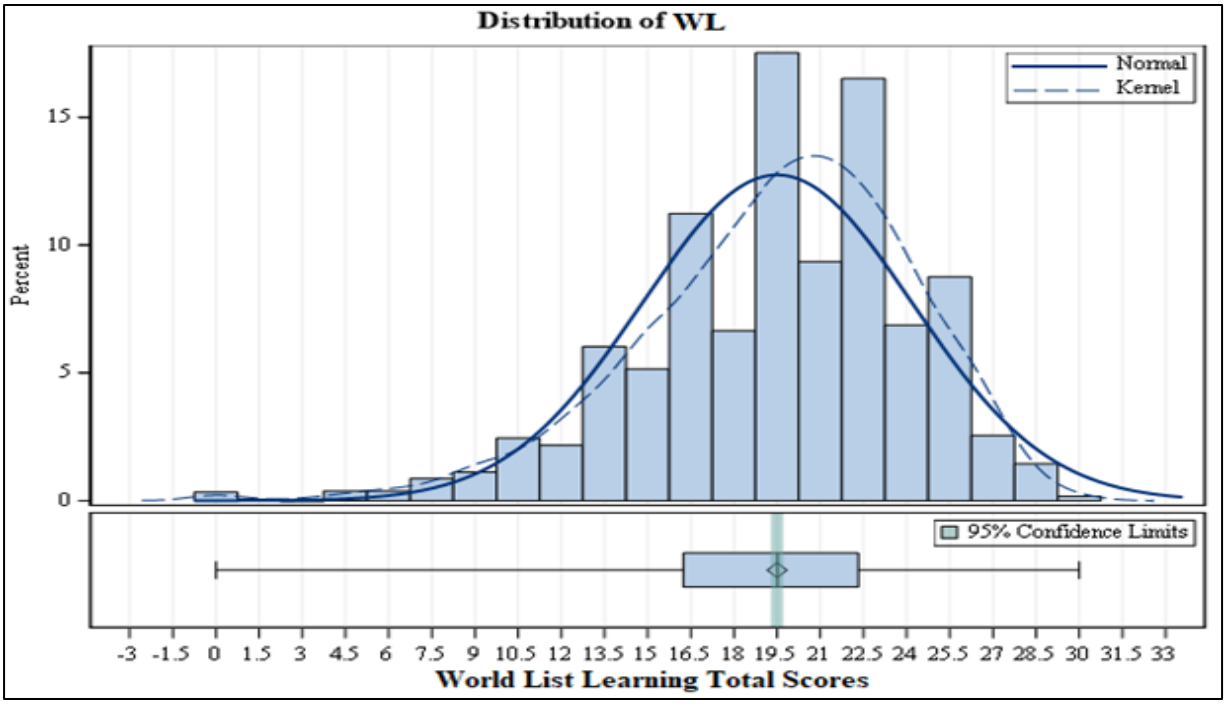


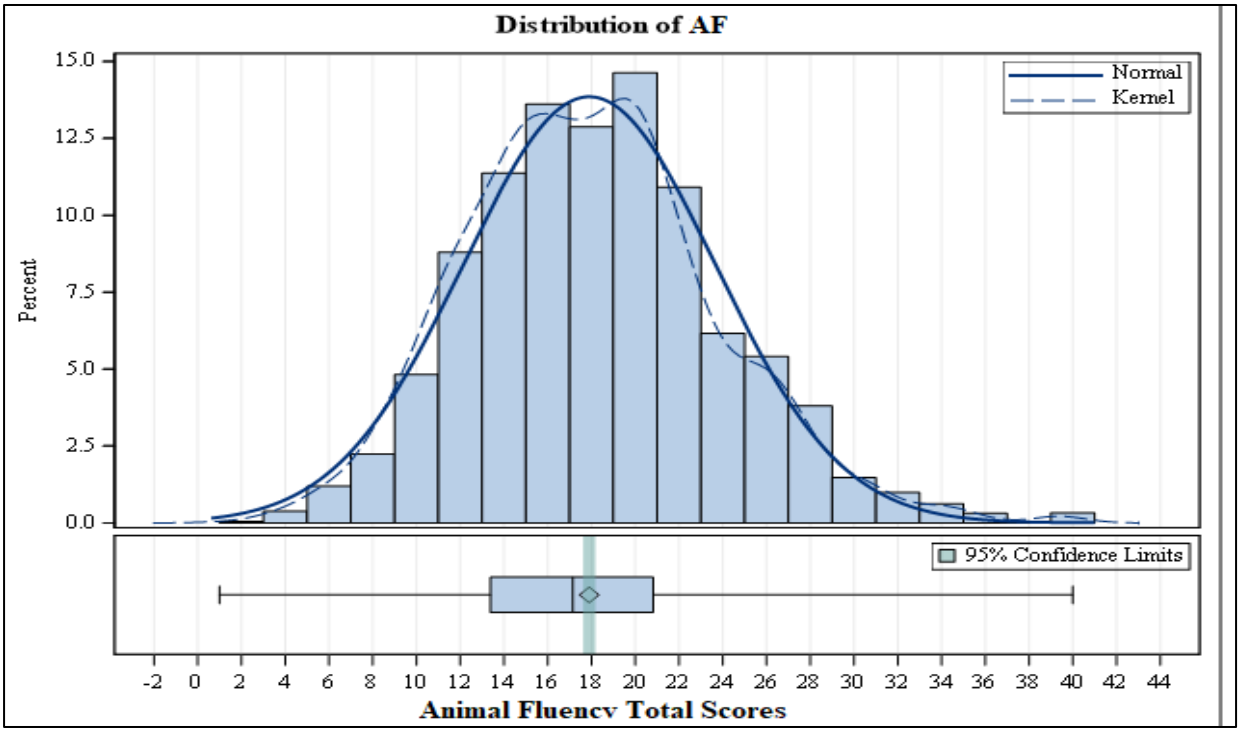

DSST Fit Plot
Digit symbol substitution (DSST) Total scores
80
60
40
20
5.0
7.5
10.0
12.5
15.0
ln_PAH_NFP
600000
400000
200000
WTSA4YR
Fit
Confidence

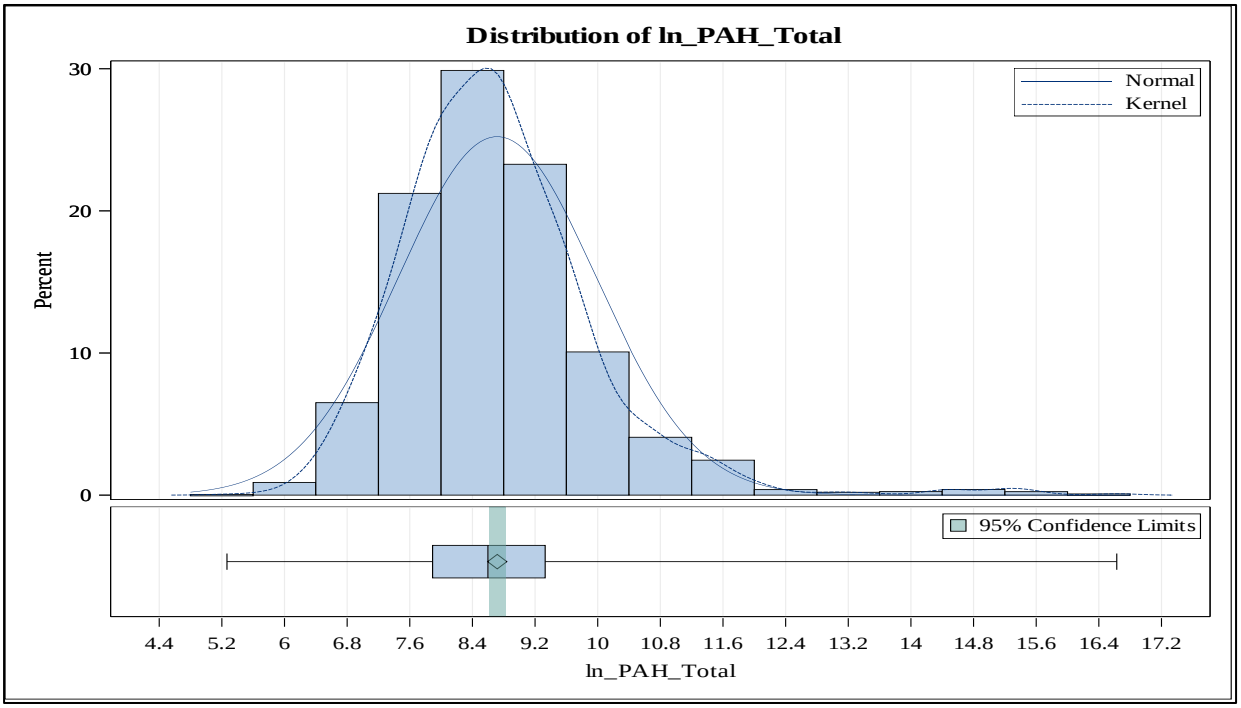

DSST Fit Plot
Digit symbol substitution (DSST) Total scores
80
60
40
20
2
3
4
5
6
Ln 1-OHPyr
600000
400000
200000
WTSA4YR
Fit
Confidence

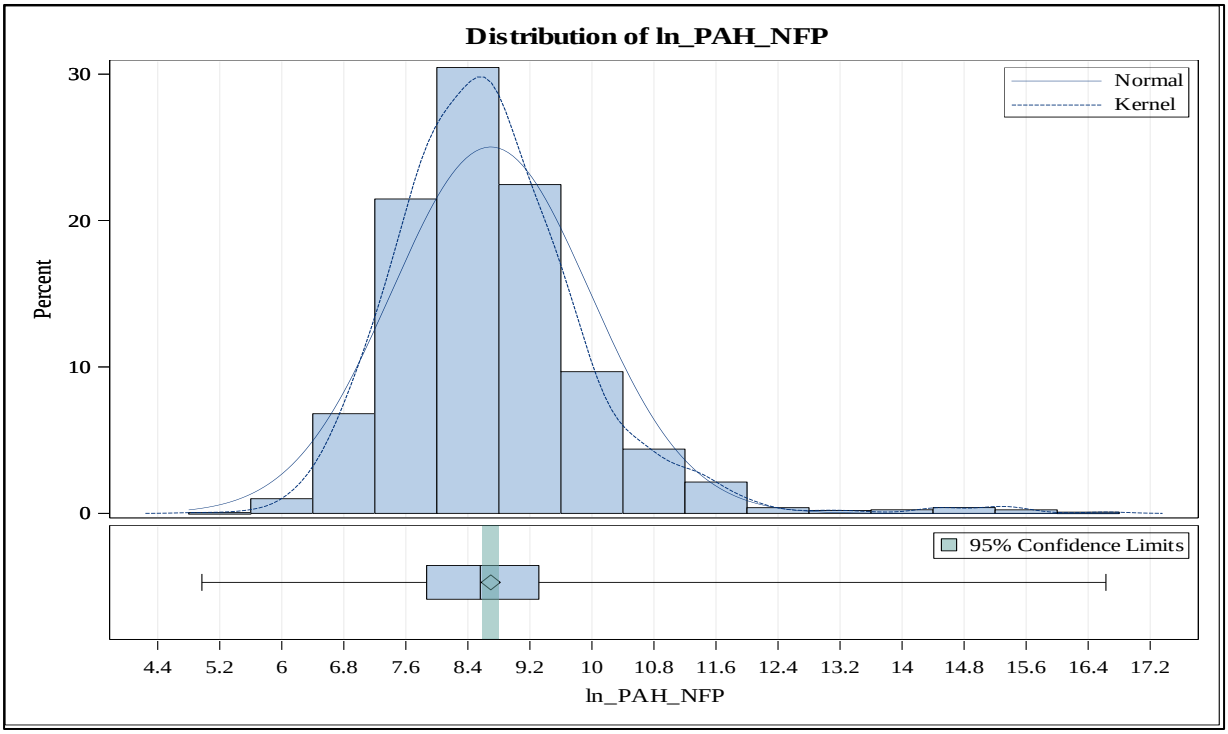

Distribution of DSST
Normal
Kernel
Percent
12.5
10.0
7.5
5.0
2.5
0.0
95% Confidence Limits
-10
0
10
20
30
40
50
60
70
80
90
100
110
Digit Symbol Substitution (DSST) Total Scores

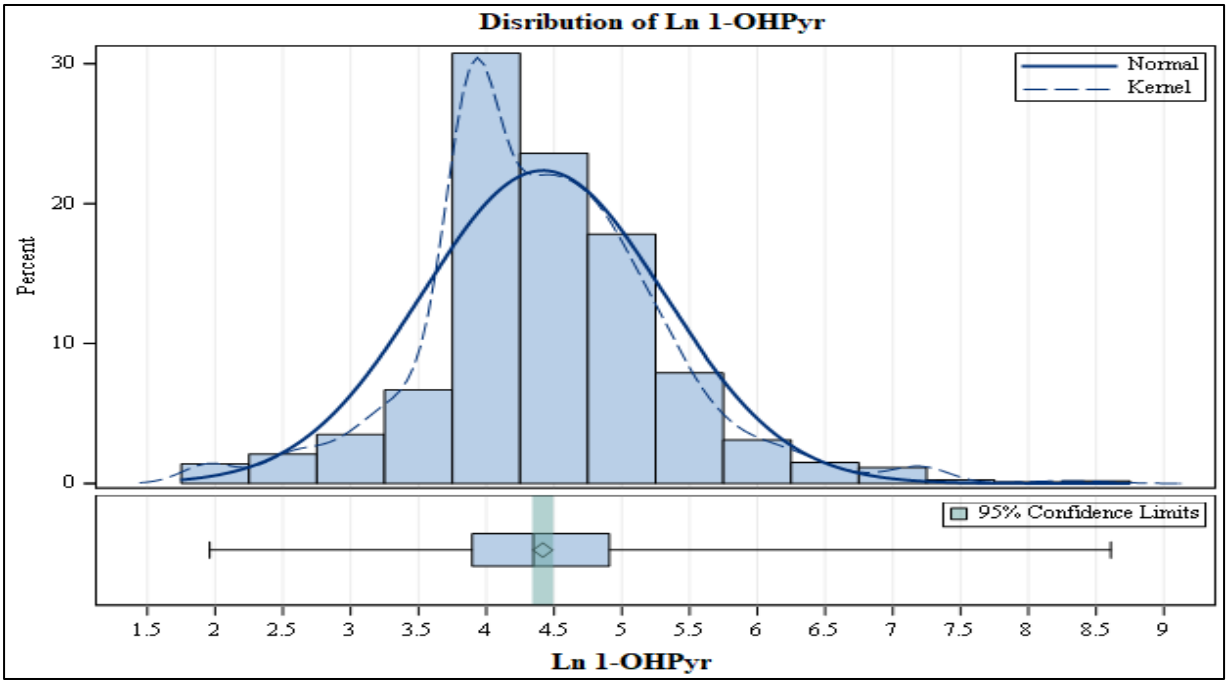

Distribution of DWR
Normal
Kernel
Percent
15
10
5
0
95% Confidence Limits
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Delayed Word Recall Total Scores


Distribution of WL
Normal
Kernel
Percent
15
10
5
0
95% Confidence Limits
-3 -1.5 0 1.5 3 4.5 6 7.5 9 10.5 12 13.5 15 16.5 18 19.5 21 22.5 24 25.5 27 28.5 30 31.5 33
World List Learning Total Scores


Distribution of AF
Normal
Kernel
Percent
15.0
12.5
10.0
7.5
5.0
2.5
0.0
95% Confidence Limits
-2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Animal Fluency Total Scores


Distribution of ln_PAH_Total
Normal
Kernel
Percent
30
20
10
0
95% Confidence Limits
4.4
5.2
6
6.8
7.6
8.4
9.2
10
10.8
11.6
12.4
13.2
14
14.8
15.6
16.4
17.2
ln_PAH_Total


Distribution of ln_PAH_NFP
Normal
Kernel
Percent
30
20
10
0
95% Confidence Limits
4.4
5.2
6
6.8
7.6
8.4
9.2
10
10.8
11.6
12.4
13.2
14
14.8
15.6
16.4
17.2
ln_PAH_NFP


Disribution of Ln 1-OHPyr
Normal
Kernel
Percent
30
20
10
0
95% Confidence Limits
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
8.5
9
Ln 1-OHPyr

**Bibliography**


Abboud, M., & Karam, S. (2021). Hypertension in the Middle East: current state, human factors, and barriers to control. *Journal of human hypertension*, 10.1038/s41371-021-00554-z. Advance online publication. https://doi.org/10.1038/s41371-021-00554-z

Abid, Z., Roy, A., Herbstman, J. B., & Ettinger, A. S. (2014). Urinary polycyclic aromatic hydrocarbon metabolites and attention/deficit hyperactivity disorder, learning disability, and special education in U.S. children aged 6 to 15. *Journal of environmental and public health*, *2014*, 628508. https://doi.org/10.1155/2014/628508

Agency for Toxic Substances and Disease Registry (ATSDR). (1995a). Polycyclic Aromatic Hydrocarbons (PAH). Available: https://www.atsdr.cdc.gov/toxprofiles/tp69.pdf

Agency for Toxic Substances and Disease Registry (ATSDR). (1995b). Toxicological profile for Polycyclic Aromatic Hydrocarbons Available: https://www.atsdr.cdc.gov/toxprofiles/tp69.pdf

Agency for Toxic Substances and Disease Registry (ATSDR). (2009a). Polycyclic Aromatic Hydrocarbons (PAH) Available: https://www.atsdr.cdc.gov/csem/csem.asp?csem=13&po=3

Agency for Toxic Substances and Disease Registry (ATSDR). (2009b). Toxicity of Polycyclic Aromatic Hydrocarbons (PAH) Available: https://www.atsdr.cdc.gov/csem/pah/docs/pah.pdf

Akhtar, W. Z., Andresen, E. M., Cannell, M. B., & Xu, X. (2013). Association of blood cotinine level with cognitive and physical performance in non-smoking older adults. Environmental research, 121, 64–70.

Akin, F. J., Snook, M. E., Severson, R. E., Chamberlain, W. J., & Walters, D. B. (1976). Identification of polynuclear aromatic hydrocarbons in cigarette smoke and their importance as tumorigens. Journal of the National Cancer Institute, 57(1), 191–195. https://doi.org/10.1093/jnci/57.1.191

Alemany, S., Vilor-Tejedor, N., García-Esteban, R., Bustamante, M., Dadvand, P., Esnaola, M., Mortamais, M., Forns, J., van Drooge, B. L., Álvarez-Pedrerol, M., Grimalt, J. O., Rivas, I., Querol, X., Pujol, J., & Sunyer, J. (2018). Traffic-Related Air Pollution, *APOE*ε4 Status, and Neurodevelopmental Outcomes among School Children Enrolled in the breath Project (Catalonia, Spain). *Environmental health perspectives*, *126*(8), 087001. https://doi.org/10.1289/EHP2246

Alexandrov, K., Rojas, M., and Satarug, S. (2010). The critical DNA damage by benzo(a)pyrene in lung tissues of smokers and approaches to preventing its formation. Toxicol. Lett., 198, 63–68.

Alzheimer's Association. (2018). Alzheimer's disease facts and figures. Alzheimer's Dementia. https://doi.org/10.1016/j.jalz.2018.02.001

American Conference of Governmental Industrial Hygienists (ACGIH). (2005). Polycyclic aromatic hydrocarbons (PAH) biologic exposure indices (BEI) Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Anderson, L. M., Jones, A. B., Miller, M. S., & Chauhan, D. P. (1989). Metabolism of transplacental carcinogens. IARC scientific publications, (96), 155–188.

Aranda, J. M., Jr, Calderon, R., & Aranda, J. M., Sr (2008). Clinical characteristics and outcomes in hypertensive patients of Hispanic descent. *Preventive cardiology*, *11*(2), 116–120. https://doi.org/10.1111/j.1751-7141.2008.08008.x

Aryal, A., Harmon, A. C., & Dugas, T. R. (2021). Particulate matter air pollutants and cardiovascular disease: Strategies for intervention. *Pharmacology & therapeutics*, *223*, 107890. https://doi.org/10.1016/j.pharmthera.2021.107890

Atkinson R, Arey J (1994). Atmospheric chemistry of gas-phase polycyclic aromatic hydrocarbons: formation of atmospheric mutagens. Environ Health Perspect. 102(Suppl 4):117–26.

Baccarelli, A., & Ghosh, S. (2012). Environmental exposures, epigenetics and cardiovascular disease. *Current opinion in clinical nutrition and metabolic care*, *15*(4), 323–329. https://doi.org/10.1097/MCO.0b013e328354bf5c

Bangia, K. S., Symanski, E., Strom, S. S., & Bondy, M. (2021). A cross-sectional analysis of polycyclic aromatic hydrocarbons and diesel particulate matter exposures and hypertension among individuals of Mexican origin. *Environmental health : a global access science source*, *14*, 51. https://doi.org/10.1186/s12940-015-0039-2

Bassan, H., Bassan, M., Pinhasov, A., Kariv, N., Giladi, E., Gozes, I., & Harel, S. (2005). The pregnant spontaneously hypertensive rat as a model of asymmetric intrauterine growth retardation and neurodevelopmental delay. *Hypertension in pregnancy*, *24*(3), 201–211. https://doi.org/10.1080/10641950500281142

Becher G, Bjorseth A. (1983). Determination of exposure to polycyclic aromatic hydrocarbons by analysis of human urine. Cancer letters 17:301–11

Berge, G., Mollerup, S., S, O. V., Hewer, A., Phillips, D. H., Eilertsen, E., and Haugen, A. (2004). Role of estrogen receptor in regulation of polycyclic aromatic hydrocarbon metabolic activation in lung. Lung Cancer, 45, 289–297.

Best, E. A., Juarez-Colunga, E., James, K., LeBlanc, W. G., & Serdar, B. (2016). Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons and Cognitive Function among Elderly in the United States (National Health and Nutrition Examination Survey: 2001-2002). PloS one, 11(2), e0147632. https://doi.org/10.1371/journal.pone.0147632

Beydoun, M. A., Beydoun, H. A., Gamaldo, A. A., Teel, A., Zonderman, A. B., & Wang, Y. (2014). Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC public health, 14, 643. https://doi.org/10.1186/1471-2458-14-643

Bouchard, M. F., Oulhote, Y., Sagiv, S. K., Saint-Amour, D., & Weuve, J. (2014). Polychlorinated biphenyl exposures and cognition in older U.S. adults: NHANES (1999-2002). Environmental health perspectives, 122(1), 73–78.

Brody, D. J., Kramarow, E. A., Taylor, C. A., & McGuire, L. C. (2019). Cognitive Performance in Adults Aged 60 and Over: National Health and Nutrition Examination Survey, 2011-2014. *National health statistics reports*, (126), 1–23.

Bronas, U. G., Puzantian, H., & Hannan, M. (2017). Cognitive Impairment in Chronic Kidney Disease: Vascular Milieu and the Potential Therapeutic Role of Exercise. *BioMed research international*, *2017*, 2726369. https://doi.org/10.1155/2017/2726369

Brook, R. D., & Rajagopalan, S. (2009). Particulate matter, air pollution, and blood pressure. *Journal of the American Society of Hypertension : JASH*, *3*(5), 332–350. https://doi.org/10.1016/j.jash.2009.08.005

Bruce, D. G., Casey, G. P., Grange, V., Clarnette, R. C., Almeida, O. P., Foster, J. K., Ives, F. J., Davis, T. M., & Fremantle Cognition in Diabetes Study (2003). Cognitive impairment, physical disability and depressive symptoms in older diabetic patients: the Fremantle Cognition in Diabetes Study. *Diabetes research and clinical practice*, *61*(1), 59–67. https://doi.org/10.1016/s0168-8227(03)00084-6

Burkauskas, J., Lang, P., Bunevičius, A., Neverauskas, J., Bučiūtė-Jankauskienė, M., & Mickuvienė, N. (2018). Cognitive function in patients with coronary artery disease: A literature review. The Journal of international medical research, 46(10), 4019–4031. https://doi.org/10.1177/0300060517751452

Burroughs Peña, M. S., & Rollins, A. (2017). Environmental Exposures and Cardiovascular Disease: A Challenge for Health and Development in Low- and Middle-Income Countries. *Cardiology clinics*, *35*(1), 71–86. https://doi.org/10.1016/j.ccl.2016.09.001

Burstyn, I., Kromhout, H., Partanen, T., Svane, O., Langård, S., Ahrens, W., Kauppinen, T., Stücker, I., Shaham, J., Heederik, D., Ferro, G., Heikkilä, P., Hooiveld, M., Johansen, C., Randem, B. G., & Boffetta, P. (2005). Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. Epidemiology (Cambridge, Mass.), 16(6), 744–750. https://doi.org/10.1097/01.ede.0000181310.65043.2f

Busbee DL, Normal JO, Ziprin RL. (1990). Comparative uptake, vascular transport and cellular internalization of aflatoxin B1 and benzo[a]pyrene. Arch Toxicology 64(4):285–90.

Caselli, R. J., Reiman, E. M., Osborne, D., Hentz, J. G., Baxter, L. C., Hernandez, J. L., & Alexander, G. G. (2004). Longitudinal changes in cognition and behavior in

asymptomatic carriers of the APOE e4 allele. Neurology, 62(11), 1990–1995. https://doi.org/10.1212/01.wnl.0000129533.26544.bf

Centers for Disease Control and Prevention (CDC) (2014a). National Health and Examination Survey. 2011–2012 Data Documentation, Codebook, and Frequencies. Cognitive Functioning. Available: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/CFQ_G.htm

Centers for Disease Control and Prevention (CDC) (2014b). National Health and Examination Survey. 2011–2012 Data Documentation, Codebook, and Frequencies. Polyaromatic Hydrocarbons (PAH) - Urine. Available: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/PAH_G.htm

Centers for Disease Control and Prevention (CDC) (2016). National Health and Examination Survey. 2013–2014 Data Documentation, Codebook, and Frequencies. Polyaromatic Hydrocarbons (PAH) - Urine. Available: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/PAH_H.htm

Centers for Disease Control and Prevention (CDC) (2020). Hypertension Prevalence Among Adults Aged 18 and Over: United States, 2017–2018. April, 2020. Available: https://www.cdc.gov/nchs/products/databriefs/db364.htm

Centers for Disease Control and Prevention (CDC). (2009). Cognitive Impairment. Retrieved from https://www.cdc.gov/aging/pdf/cognitive_impairment/cogimp_poilicy_final.pdf

Centers for Disease Control and Prevention (CDC). (2011). Cognitive Impairment: A call for action now. Retrieved from https://www.cdc.gov/aging/pdf/cognitive_impairment/cogimp_poilicy_final.pdf

Centers for Disease Control and Prevention (CDC). (2017). Alzheimer's Disease and Healthy Aging. Retrieved from http://www.cdc.gov/aging/healthybrain/

Chen, J. C., & Schwartz, J. (2009). Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. Neurotoxicology, 30(2), 231–239.

Chen, Y. Y., Kao, T. W., Wang, C. C., Chen, Y. J., Wu, C. J., Lai, C. H., & Chen, W. L. (2021). Polycyclic aromatic hydrocarbon metabolites and mortality risk in an adult population. Environmental geochemistry and health, 43(1), 37–45. https://doi.org/10.1007/s10653-020-00663-7

Cho, J., Sohn, J., Noh, J., Jang, H., Kim, W., Cho, S. K., Seo, H., Seo, G., Lee, S. K., Noh, Y., Seo, S., Koh, S. B., Oh, S. S., Kim, H. J., Seo, S. W., Shin, D. S., Kim, N., Kim, H. H., Lee, J. I., Kim, S. Y., Kim, C. (2020). Association between exposure to polycyclic aromatic hydrocarbons and brain cortical thinning: The Environmental Pollution-Induced Neurological Effects (EPINEF) study. The Science of the total environment, 737, 140097.

Choi H, Harrison R, Komulainen H, Delgado Saborit JM (2010). Polycyclic aromatic hydrocarbons. In: WHO guidelines for indoor air quality: selected pollutants. Geneva,

Switzerland: World Health Organization. Available from: http://www.ncbi.nlm.nih.gov/books/NBK138709/.

Choi, H., Rauh, V., Garfinkel, R., Tu, Y., & Perera, F. P. (2008). Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. *Environmental health perspectives*, *116*(5), 658–665. https://doi.org/10.1289/ehp.10958

Chu, S., Zhang, H., Maher, C., McDonald, J. D., Zhang, X., Ho, S. M., Yan, B., Chillrud, S., Perera, F., Factor, P., & Miller, R. L. (2013). Prenatal and postnatal polycyclic aromatic hydrocarbon exposure, airway hyperreactivity, and Beta-2 adrenergic receptor function in sensitized mouse offspring. *Journal of toxicology*, *2013*, 603581. https://doi.org/10.1155/2013/603581

Coresh, J., Selvin, E., Stevens, L. A., Manzi, J., Kusek, J. W., Eggers, P., Van Lente, F., & Levey, A. S. (2007). Prevalence of chronic kidney disease in the United States. JAMA, 298(17), 2038–2047. https://doi.org/10.1001/jama.298.17.2038

Cukierman, T., Gerstein, H. C., & Williamson, J. D. (2005). Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. *Diabetologia*, *48*(12), 2460–2469. https://doi.org/10.1007/s00125-005-0023-4

Das, L., Patel, B., & Patri, M. (2019). Adolescence benzo[a]pyrene treatment induces learning and memory impairment and anxiolytic like behavioral response altering neuronal morphology of hippocampus in adult male Wistar rats. Toxicology reports, 6, 1104–1113.

Das, S. K., Patel, B., & Patri, M. (2016). Neurotoxic Effect of Benzo[a]pyrene and Its Possible Association with 6-Hydroxydopamine Induced Neurobehavioral Changes during Early Adolescence Period in Rats. Journal of toxicology, 2016, 8606410.

Dayal, H., Gupta, S., Trieff, N., Maierson, D., & Reich, D. (1995). Symptom clusters in a community with chronic exposure to chemicals in two superfund sites. Archives of environmental health, 50(2), 108–111. https://doi.org/10.1080/00039896.1995.9940887

DeGuire, J., Clarke, J., Rouleau, K., Roy, J., & Bushnik, T. (2019). Blood pressure and hypertension. Health reports, 30(2), 14–21. https://doi.org/10.25318/82-003-x201900200002

Dejmek, J., Solanský, I., Benes, I., Lenícek, J., & Srám, R. J. (2000). The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. *Environmental health perspectives*, *108*(12), 1159–1164. https://doi.org/10.1289/ehp.001081159

Díaz-Venegas, C., Downer, B., Langa, K. M., & Wong, R. (2016). Racial and ethnic differences in cognitive function among older adults in the USA. *International journal of geriatric psychiatry*, *31*(9), 1004–1012. https://doi.org/10.1002/gps.4410

Dong, G. H., Qian, Z. M., Xaverius, P. K., Trevathan, E., Maalouf, S., Parker, J., Yang, L., Liu, M. M., Wang, D., Ren, W. H., Ma, W., Wang, J., Zelicoff, A., Fu, Q., & Simckes, M.

(2013). Association between long-term air pollution and increased blood pressure and hypertension in China. Hypertension (Dallas, Tex.: 1979), 61(3), 578–584. https://doi.org/10.1161/HYPERTENSIONAHA.111.00003

Du, J., Pan, B., Cao, X., Li, J., Yang, J., & Nie, J. (2020). Urinary polycyclic aromatic hydrocarbon metabolites, peripheral blood mitochondrial DNA copy number, and neurobehavioral function in coke oven workers. Chemosphere, 261, 127628. https://doi.org/10.1016/j.chemosphere.2020.127628

Eggermont, L. H., de Boer, K., Muller, M., Jaschke, A. C., Kamp, O., & Scherder, E. J. (2012). Cardiac disease and cognitive impairment: a systematic review. Heart (British Cardiac Society), 98(18), 1334–1340. https://doi.org/10.1136/heartjnl-2012-301682

Emrani, S., Arain, H. A., DeMarshall, C., & Nuriel, T. (2020). APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer's disease: a systematic review. Alzheimer's research & therapy, 12(1), 141. https://doi.org/10.1186/s13195-020-00712-4

Environmental Pollution Centers (2017). What is Air Pollution. Retrieved from https://www.environmentalpollutioncenters.org/air/

Evans, S. M., & Levin, F. R. (2004). Differential response to alcohol in light and moderate female social drinkers. Behavioural pharmacology, 15(3), 167–181.

Fillenbaum, G. G., van Belle, G., Morris, J. C., Mohs, R. C., Mirra, S. S., Davis, P. C., Tariot, P. N., Silverman, J. M., Clark, C. M., Welsh-Bohmer, K. A., & Heyman, A. (2008). Consortium to Establish a Registry for Alzheimer's Disease (CERAD): the first twenty years. Alzheimer's & dementia: the journal of the Alzheimer's Association, 4(2), 96–109.

Food and Drug Administration (FDA) (2012). Harmful and potentially harmful constituents in tobacco products and tobacco smoke; Established list. Federal registration. 77(64):20034–20037.

Foth, H., Kahl, R., & Kahl, G.F. (1988). Pharmacokinetics of low doses of benzo[a]pyrene in the rat. Food chemistry and toxicology, 26: 45–51.

Gatto, N. M., Henderson, V. W., Hodis, H. N., St John, J. A., Lurmann, F., Chen, J. C., & Mack, W. J. (2014). Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology, 40, 1–7.

Giorgini, P., Di Giosia, P., Grassi, D., Rubenfire, M., Brook, R. D., & Ferri, C. (2016). Air Pollution Exposure and Blood Pressure: An Updated Review of the Literature. *Current pharmaceutical design*, *22*(1), 28–51. https://doi.org/10.2174/1381612822666151109111712

Goldman, R., Enewold, L., Pellizzari, E., Beach, J. B., Bowman, E. D., Krishnan, S. S., & Shields, P. G. (2001). Smoking increases carcinogenic polycyclic aromatic hydrocarbons in human lung tissue. Cancer research, 61(17), 6367–6371.

Gräslund, A., & Jernström, B. (1989). DNA-carcinogen interaction: covalent DNA-adducts of benzo(a)pyrene 7,8-dihydrodiol 9,10-epoxides studied by biochemical and biophysical techniques. Quarterly reviews of biophysics, 22(1), 1–37.

Gregg, E. W., Yaffe, K., Cauley, J. A., Rolka, D. B., Blackwell, T. L., Narayan, K. M., & Cummings, S. R. (2000). Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Archives of internal medicine*, *160*(2), 174–180. https://doi.org/10.1001/archinte.160.2.174

Grimmer, G., Brune, H., Dettbarn, G., Naujack, K. W., Mohr, U., and Wenzel-Hartung, R. (1988). Contribution of polycyclic aromatic compounds to the carcinogenicity of sidestream smoke of cigarettes evaluated by implantation into the lungs of rats. Cancer Lett., 43, 173–177.

Gupta S. (2021). Racial and ethnic disparities in subjective cognitive decline: a closer look, United States, 2015-2018. *BMC public health*, *21*(1), 1173. https://doi.org/10.1186/s12889-021-11068-1

Ha, M., Kwon, H., Cheong, HK., Lim, S., Yoo, SJ., Kim, EJ., Park, SG., Lee, J., Chung, BC. (2012). Urinary metabolites before and after clean-up and subjective symptoms in volunteer participants in clean-up of the Hebei Spirit oil spill. Science of the Total Environment 429,167-173.

Hall, M., Forrester, L., Parker, D., Grover, P., & Wolf, C.R. (1989). Relative contribution of various forms of cytochrome P450 to the metabolism of benzo[a]pyrene by human liver microsomes. Carcinogenesis, 10 10, 1815-21.

Haritash, A. K., & Kaushik, C. P. (2009). Biodegradation aspects of polycyclic aromatic hydrocarbons (PAH): a review. Journal of hazardous materials, 169(1-3), 1–15.

Hawley GG. (1987). The condensed chemical dictionary. New York, NY: Van Nostrand Reinhold Company.

Hazardous Substances Data Bank (HSDB). (1994). National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD.

Hendrie, H. C., Albert, M. S., Butters, M. A., Gao, S., Knopman, D. S., Launer, L. J., Yaffe, K., Cuthbert, B. N., Edwards, E., & Wagster, M. V. (2006). The NIH Cognitive and Emotional Health Project. Report of the Critical Evaluation Study Committee. Alzheimer's & dementia: the journal of the Alzheimer's Association, 2(1), 12–32. https://www.alz.org/national/documents/report_alzfactsfigures2009.pdf https://www.euro.who.int/data/assets/pdf_file/0015/123063/AQG2ndEd59PAH.pdf?ua=1

Humphreys, J., & Valdés Hernández, M.D.C. (2021). Impact of Polycyclic Aromatic Hydrocarbon Exposure on Cognitive Function and Neurodegeneration in Humans. A Systematic Review and Meta-Analysis. 2021050692 (doi: 10.20944/05. 0692.v1)

International Agency for Research on Cancer (IARC). (1983). Polynuclear aromatic compounds, Part 1, Chemical, environmental and experimental data. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, 32, 1–453.

International Agency for Research on Cancer (IARC). (2010). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum. 92:1–853. Available from: http://publications.iarc.fr/110 PMID:21141735

Jaeger J. (2018). Digit Symbol Substitution Test: The Case for Sensitivity Over Specificity in Neuropsychological Testing. Journal of clinical psychopharmacology, 38(5), 513–519.

Jameson, C. (2019). Polycyclic aromatic hydrocarbons and associated occupational exposures. Chapter 7. Retrieved from https://publications.iarc.fr/

Jarup, L. (2003). Hazards of heavy metal contamination. Br. Med. Bullet., 68, 167–182.

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K. A., van der Flier, W. M., Glodzik, L., van Harten, A. C., de Leon, M. J., McHugh, P., Mielke, M. M., Molinuevo, J. L., Mosconi, L., Osorio, R. S., Perrotin, A., Petersen, R. C., Subjective Cognitive Decline Initiative (SCD-I) Working Group (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association, 10(6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001

Johnsen, A. R., Wick, L. Y., & Harms, H. (2005). Principles of microbial PAH-degradation in soil. Environmental pollution (Barking, Essex: 1987), 133(1), 71–84.

Kafferlein, H. U., Marczynski, B., Mensing, T., and Bruning, T. (2010). Albumin and hemoglobin adducts of benzo[a]pyrene in humans—analytical methods, exposure assessment, and recommendations for future directions. Crit. Rev. Toxicol., 40, 126–150.

Karel, M. J., Gatz, M., & Smyer, M. A. (2012). Aging and mental health in the decade ahead: what psychologists need to know. The American psychologist, 67(3), 184–198.

Kilanowicz, A., Wiaderna, D., Lutz, P., & Szymczak, W. (2012). Behavioral effects following repeated exposure to hexachloronaphthalene in rats. Neurotoxicology, 33(3), 361–369.

Killin, L. O., Starr, J. M., Shiue, I. J., & Russ, T. C. (2016). Environmental risk factors for dementia: a systematic review. BMC geriatrics, 16(1), 175.

Kim, K. H., Jahan, S. A., Kabir, E., & Brown, R. J. (2013). A review of airborne polycyclic aromatic hydrocarbons (PAH) and their human health effects. Environment international, 60, 71–80. https://doi.org/10.1016/j.envint.2013.07.019

Kim, S. A., Lee, Y. M., Lee, H. W., Jacobs, D. R., Jr, & Lee, D. H. (2015). Greater cognitive decline with aging among elders with high serum concentrations of organochlorine pesticides. PloS one, 10(6), e0130623.

Kirkwood, T. (2008). A systematic look at an old problem. Nature 451, 644–647.

Kodl, C. T., & Seaquist, E. R. (2008). Cognitive dysfunction and diabetes mellitus. *Endocrine reviews*, *29*(4), 494–511. https://doi.org/10.1210/er.2007-0034

Kreutz, R., Dobrowolski, P., Prejbisz, A., Algharably, E., Bilo, G., Creutzig, F., Grassi, G., Kotsis, V., Lovic, D., Lurbe, E., Modesti, P. A., Pappaccogli, M., Parati, G., Persu, A., Polonia, J., Rajzer, M., de Timary, P., Weber, T., Weisser, B., Tsioufis, K., … European Society of Hypertension COVID-19 Task Force Review (2021). Lifestyle, psychological, socioeconomic and environmental factors and their impact on hypertension during the coronavirus disease 2019 pandemic. *Journal of hypertension*, *39*(6), 1077–1089. https://doi.org/10.1097/HJH.0000000000002770

Kuang, D., Zhang, W., Deng, Q., Zhang, X., Huang, K., Guan, L., Hu, D., Wu, T., & Guo, H. (2013). Dose-response relationships of polycyclic aromatic hydrocarbons exposure and oxidative damage to DNA and lipid in coke oven workers. Environmental science & technology, 47(13), 7446–7456. https://doi.org/10.1021/es401639x

Kwack, S. J., and Lee, B. M. (2000). Correlation between DNA or protein adducts and benzo[a]pyrene diol epoxide I-triglyceride adduct detected in vitro and in vivo. Carcinogenesis, 21, 629–632.

Lau, H. H., & Baird, W. M. (1992). The co-carcinogen benzo[e]pyrene increases the binding of a low dose of the carcinogen benzo[a]pyrene to DNA in Sencar mouse epidermis. Cancer letters, 63(3), 229–236. https://doi.org/10.1016/0304-3835(92)90265-w

Lau, W. L., Huisa, B. N., & Fisher, M. (2017). The Cerebrovascular-Chronic Kidney Disease Connection: Perspectives and Mechanisms. *Translational stroke research*, *8*(1), 67–76. https://doi.org/10.1007/s12975-016-0499-x

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., Greenop, K. R., & Almeida, O. P. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*, *300*(9), 1027–1037. https://doi.org/10.1001/jama.300.9.1027

Lee, B. J., Kim, B., & Lee, K. (2014). Air pollution exposure and cardiovascular disease. *Toxicological research*, *30*(2), 71–75. https://doi.org/10.5487/TR.2014.30.2.071

Leitner, Y., Fattal-Valevski, A., Geva, R., Eshel, R., Toledano-Alhadef, H., Rotstein, M., Bassan, H., Radianu, B., Bitchonsky, O., Jaffa, A. J., & Harel, S. (2007). Neurodevelopmental outcome of children with intrauterine growth retardation: a longitudinal, 10-year prospective study. *Journal of child neurology*, *22*(5), 580–587. https://doi.org/10.1177/0883073807302605

Levin, W., Wood, A., Chang, R., Ryan, D., Thomas, P., Yagi, H., Thakker, D., Vyas, K., Boyd, C., Chu, S. Y., Conney, A., & Jerina, D. (1982). Oxidative metabolism of polycyclic aromatic hydrocarbons to ultimate carcinogens. Drug metabolism reviews, 13(4), 555–580. https://doi.org/10.3109/03602538209011087

Li, Z., Romanoff, L. C., Lewin, M. D., Porter, E. N., Trinidad, D. A., Needham, L. L., Patterson, D. G., Jr, & Sjödin, A. (2010). Variability of urinary concentrations of polycyclic aromatic hydrocarbon metabolite in general population and comparison of spot, first-morning, and 24-h void sampling. *Journal of exposure science & environmental epidemiology*, *20*(6), 526–535. https://doi.org/10.1038/jes.2009.41

Liu, B., Xue, Z., Zhu, X., & Jia, C. (2017). Long-term trends (1990-2014), health risks, and sources of atmospheric polycyclic aromatic hydrocarbons (PAH) in the U.S. Environmental pollution (Barking, Essex: 1987), 220(Pt B), 1171–1179. https://doi.org/10.1016/j.envpol.2016.11.018

Liu, Y., Vinje, J., Pacifico, C., Natile, G., and Sletten, E. (2002). Formation of adenine-N3/guanine-N7 cross-link in the reaction of trans-oriented platinum substrates with dinucleotides. J. Am. Chem. Soc., 124, 12854–12862.

Loop, M. S., Kent, S. T., Al-Hamdan, M. Z., Crosson, W. L., Estes, S. M., Estes, M. G., Jr, Quattrochi, D. A., Hemmings, S. N., Wadley, V. G., & McClure, L. A. (2013). Fine particulate matter and incident cognitive impairment in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. PloS one, 8(9), e75001.

Luchsinger, J. A., Tang, M. X., Stern, Y., Shea, S., & Mayeux, R. (2001). Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *American journal of epidemiology*, *154*(7), 635–641. https://doi.org/10.1093/aje/154.7.635

Lyness, S. A., Lee, A. Y., Zarow, C., Teng, E. L., & Chui, H. C. (2014). 10-minute delayed recall from the modified mini-mental state test predicts Alzheimer's disease pathology. Journal of Alzheimer's disease: JAD, 39(3), 575–582.

Mackay D, Callcott D (1998). Partitioning and physical chemical properties of PAH. In: Neilson A, editor. PAH and related compounds. The handbook of environmental chemistry, Volume 3. Berlin, Germany: Springer-Verlag; pp. 325–45. http://dx.doi. org/10.1007/978-3-540-49697-7_8

Majchrzak, R., Sroczyński, J., and Chełmecka, E. (1990). Evaluation of the nervous system in workers in the furnace and coal divisions of the coke-producing plants. Med. Pr. 41: 108–113.

Mayo Clinic. High blood pressure (hypertension) (2021). Available at https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/symptoms-causes/syc-20373410

Mehlman M. J. (2004). Cognition-enhancing drugs. The Milbank quarterly, 82(3), 483–506. https://doi.org/10.1111/j.0887-378X.2004.00319.x

Millán-Calenti, J. C., Tubío, J., Pita-Fernández, S., González-Abraldes, I., Lorenzo, T., & Maseda, A. (2009). Prevalence of cognitive impairment: effects of level of education, age, sex and associated factors. Dementia and geriatric cognitive disorders, 28(5), 455–460. https://doi.org/10.1159/000257086

Miller, R. L., Yan, Z., Maher, C., Zhang, H., Gudsnuk, K., McDonald, J., & Champagne, F. A. (2016). Impact of prenatal polycyclic aromatic hydrocarbon exposure on behavior, cortical gene expression and DNA methylation of the *Bdnf* gene. *Neuroepigenetics*, *5*, 11–18. https://doi.org/10.1016/j.nepig.2016.02.001

Modica, R., Fiume, M., Guaitani, A., & Bartosek, I. (1983). Comparative kinetics of benz(a)anthracene, chrysene and triphenylene in rats after oral administration. I. Study with single compounds. Toxicology letters, 18(1-2), 103–109.

Moorthy, B., Chu, C., & Carlin, D. J. (2015). Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. Toxicological sciences: an official journal of the Society of Toxicology, 145(1), 5–15. https://doi.org/10.1093/toxsci/kfv040

Moorthy, B., Chu, C., & Carlin, D. J. (2015). Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. Toxicological sciences: an official journal of the Society of Toxicology, 145(1), 5–15. https://doi.org/10.1093/toxsci/kfv040

Mortamais, M., Pujol, J., van Drooge, B. L., Macià, D., Martínez-Vilavella, G., Reynes, C., Sabatier, R., Rivas, I., Grimalt, J., Forns, J., Alvarez-Pedrerol, M., Querol, X., & Sunyer, J. (2017). Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary school children. *Environment international*, *105*, 12–19. https://doi.org/10.1016/j.envint.2017.04.011

Mutlu, U., Colijn, J. M., Ikram, M. A., Bonnemaijer, P., Licher, S., Wolters, F. J., Tiemeier, H., Koudstaal, P. J., Klaver, C., & Ikram, M. K. (2018). Association of Retinal Neurodegeneration on Optical Coherence Tomography with Dementia: A Population-Based Study. JAMA neurology, 75(10), 1256–1263. https://doi.org/10.1001/jamaneurol.2018.1563

Myers M. G. (2007). Kaplan's Clinical Hypertension, 9th edn (2005). The Canadian Journal of Cardiology, 23(7), 605.

National Research Council (NRC). (1983). Polycyclic aromatic hydrocarbons: Evaluation of sources and effects. Washington, D.C, National Academy Press, ES/l-ES/7.

National Toxicology Program (2014). Polycyclic Aromatic Compounds. Available: https://ntp.niehs.nih.gov/whatwestudy/topics/pacs/index.html

Nebert, D. W., Puga, A., & Vasiliou, V. (1993). Role of the Ah receptor and the dioxin-inducible [Ah] gene battery in toxicity, cancer, and signal transduction. Annals of the New York Academy of Sciences, 685, 624–640.

Nebert, D. W., Shi, Z., Galvez-Peralta, M., Uno, S., and Dragin, N. (2013). Oral benzo[a]pyrene: understanding pharmacokinetics, detoxication and consequences—Cyp1 knockout mouse lines as a paradigm. Mol. Pharmacol.

Neubert, D., & Tapken, S. (1988). Transfer of benzo(a)pyrene into mouse embryos and fetuses. Archives of toxicology, 62(2-3), 236–239.

Nguyen, V. K., Kahana, A., Heidt, J., Polemi, K., Kvasnicka, J., Jolliet, O., & Colacino, J. A. (2020). A comprehensive analysis of racial disparities in chemical biomarker concentrations in United States women, 1999-2014. *Environment international*, *137*, 105496. https://doi.org/10.1016/j.envint.2020.105496

Nie, J., Li, J., Cheng, L., Deng, Y., Li, Y., Yan, Z., Duan, L., Niu, Q., & Tang, D. (2019). Prenatal polycyclic aromatic hydrocarbons metabolites, cord blood telomere length, and neonatal neurobehavioral development. Environmental research, 174, 105–113. https://doi.org/10.1016/j.envres.2019.04.024

Otto, D., Skalik, I., and Bahboli, R. (1997). Neurobehavioral performance of Czech school children born in years of maximal air pollution. Neurotoxicology 18: 903.

Pagliaccio, D., Herbstman, J. B., Perera, F., Tang, D., Goldsmith, J., Peterson, B. S., Rauh, V., & Margolis, A. E. (2020). Prenatal exposure to polycyclic aromatic hydrocarbons modifies the effects of early life stress on attention and Thought Problems in late childhood. *Journal of child psychology and psychiatry, and allied disciplines*, *61*(11), 1253–1265. https://doi.org/10.1111/jcpp.13189

Paúl, C., Ribeiro, O., & Santos, P. (2010). Cognitive impairment in old people living in the community. Archives of gerontology and geriatrics, 51(2), 121–124. https://doi.org/10.1016/j.archger.2009.09.037

Peiffer, J., Cosnier, F., Grova, N., Nunge, H., Salquèbre, G., Decret, M. J., Cossec, B., Rychen, G., Appenzeller, B. M., & Schroeder, H. (2013). Neurobehavioral toxicity of a repeated exposure (14 days) to the airborne polycyclic aromatic hydrocarbon fluorene in adult Wistar male rats. PloS one, 8(8), e71413.

Pereira, M., Lunet, N., Azevedo, A., & Barros, H. (2009). Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. Journal of hypertension, 27(5), 963–975. https://doi.org/10.1097/hjh.0b013e3283282f65

Perera, F. P., Li, Z., Whyatt, R., Hoepner, L., Wang, S., Camann, D., & Rauh, V. (2009). Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics*, *124*(2), e195–e202. https://doi.org/10.1542/peds.2008-3506

Perera, F. P., Rauh, V., Whyatt, R. M., Tsai, W. Y., Tang, D., Diaz, D., Hoepner, L., Barr, D., Tu, Y. H., Camann, D., & Kinney, P. (2006). Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environmental health perspectives*, *114*(8), 1287–1292. https://doi.org/10.1289/ehp.9084

Perera, F. P., Tang, D., Wang, S., Vishnevetsky, J., Zhang, B., Diaz, D., Camann, D., & Rauh, V. (2012). Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at

age 6-7 years. *Environmental health perspectives*, *120*(6), 921–926. https://doi.org/10.1289/ehp.1104315

Perera, F. P., Wang, S., Vishnevetsky, J., Zhang, B., Cole, K. J., Tang, D., Rauh, V., & Phillips, D. H. (2011). Polycyclic aromatic hydrocarbons-aromatic DNA adducts in cord blood and behavior scores in New York city children. *Environmental health perspectives*, *119*(8), 1176–1181. https://doi.org/10.1289/ehp.1002705

Perera, F. P., Wheelock, K., Wang, Y., Tang, D., Margolis, A. E., Badia, G., Cowell, W., Miller, R. L., Rauh, V., Wang, S., & Herbstman, J. B. (2018). Combined effects of prenatal exposure to polycyclic aromatic hydrocarbons and material hardship on child ADHD behavior problems. *Environmental research*, *160*, 506–513. https://doi.org/10.1016/j.envres.2017.09.002

Perera, F., Tang, D., Whyatt, R., Lederman, S. A., & Jedrychowski, W. (2005). DNA damage from polycyclic aromatic hydrocarbons measured by benzo[a]pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center Area, Poland, and China. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, *14*(3), 709–714. https://doi.org/10.1158/1055-9965.EPI-04-0457

Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., & Anstey, K. J. (2019). Air Pollution and Dementia: A Systematic Review. Journal of Alzheimer's disease: JAD, 70(s1), S145–S163.

Piccardo, M. T., Stella, A., and Valerio, F. (2010). Is the smokers exposure to environmental tobacco smoke negligible? Environ. Health, 9, 5.

Polanska, K., Dettbarn, G., Jurewicz, J., Sobala, W., Magnus, P., Seidel, A., & Hanke, W. (2014). Effect of prenatal polycyclic aromatic hydrocarbons exposure on birth outcomes: the Polish mother and child cohort study. BioMed research international, 2014, 408939. https://doi.org/10.1155/2014/408939

Polańska, K., Hanke, W., Sobala, W., Brzeźnicki, S., & Ligocka, D. (2010). Exposure to polycyclic aromatic hydrocarbons and newborn biometric indicators. *International journal of occupational medicine and environmental health*, *23*(4), 339–346. https://doi.org/10.2478/v10001-010-0028-1

Proust-Lima, C., Amieva, H., Dartigues, J. F., & Jacqmin-Gadda, H. (2007). Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. American journal of epidemiology, 165(3), 344–350.

Ramesh, A., Archibong, A., Hood, D., Guo, Z., & Loganathan, B. (2016). Global Environmental Distribution and Human Health Effects of Polycyclic Aromatic Hydrocarbons. http://dx.doi.org/10.1201/b11098-7

Ramesh, A., Archibong, A., Hood, D., Guo, Z., & Loganathan, B. (2011). Global Environmental Distribution and Human Health Effects of Polycyclic Aromatic Hydrocarbons. http://dx.doi.org/10.1201/b11098-7

Ramesh, A., Walker, S. A., Hood, D. B., Guillén, M. D., Schneider, K., & Weyand, E. H. (2004). Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. *International journal of toxicology*, *23*(5), 301–333. https://doi.org/10.1080/10915810490517063

Ranjbar, M., Rotondi, M. A., Ardern, C. I., & Kuk, J. L. (2015). Urinary Biomarkers of Polycyclic Aromatic Hydrocarbons Are Associated with Cardiometabolic Health Risk. *PloS one*, *10*(9), e0137536. https://doi.org/10.1371/journal.pone.0137536

Rawle, M. J., Davis, D., Bendayan, R., Wong, A., Kuh, D., & Richards, M. (2018). Apolipoprotein-E (Apoe) ε4 and cognitive decline over the adult life course. Translational psychiatry, 8(1), 18. https://doi.org/10.1038/s41398-017-0064-8

Reaven, G. M., Thompson, L. W., Nahum, D., & Haskins, E. (1990). Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes care*, *13*(1), 16–21. https://doi.org/10.2337/diacare.13.1.16

Rice JE, Hosted TJ Jr, Lavoie EJ. Fluoranthene and pyrene enhance benzo[a]pyrene--DNA adduct formation in vivo in mouse skin. Cancer Lett. 1984 Oct;24(3):327-33. doi: 10.1016/0304-3835(84)90030-2. PMID: 6437667.

Rodgman A., and Perfetti TA. (2009). The chemical components of tobacco and tobacco smoke. Boca Raton, FL: CRC Press. pp. 1–110.

Rosano, C., Perera, S., Inzitari, M., Newman, A. B., Longstreth, W. T., & Studenski, S. (2016). Digit Symbol Substitution test and future clinical and subclinical disorders of cognition, mobility and mood in older adults. Age and ageing, 45(5), 688–695.

Rozman, K. K., and Klaassen, C. D. (2007). Absorption, distribution and excretion of toxicants. In Casarett and Doull´s Toxicology: The Basic Science of Poisons (C. D. Klaassen, Ed.), pp.107–132. McGraw-Hill, New York.

Sakata, N., & Okumura, Y. (2017). Job Loss After Diagnosis of Early-Onset Dementia: A Matched Cohort Study. Journal of Alzheimer's disease: JAD, 60(4), 1231–1235. https://doi.org/10.3233/JAD-170478

Salthouse T. A. (2009). When does age-related cognitive decline begin? Neurobiology of aging, 30(4), 507–514.

Sancini, A., Caciari, T., Sinibaldi, F., Sacco, C., Boscolo, P., Giubilati, R., Scala, B., Tomei, G., Tomei, F., & Rosati, M. V. (2014). Blood pressure changes and polycyclic aromatic hydrocarbons in outdoor workers. *La Clinica terapeutica*, *165*(4), e295–e303. https://doi.org/10.7417/CT.2014.1746

Saunders, C. R., Das, S. K., Ramesh, A., Shockley, D. C., & Mukherjee, S. (2006). Benzo(a)pyrene-induced acute neurotoxicity in the F-344 rat: role of oxidative stress. Journal of applied toxicology: JAT, 26(5), 427–438.

Schlede E, Kuntzman R, Conney AH. (1970). Stimulatory effect of benzo(alpha)pyrene and phenobarbital pretreatment on the biliary excretion of benzo(alpha)pyrene metabolites in the rat. Cancer Res. (12) 2898-2904. PMID: 5494574.

Schmand, B., Smit, J. H., Geerlings, M. I., & Lindeboom, J. (1997). The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychological medicine, 27(6), 1337–1344. https://doi.org/10.1017/s0033291797005461

Shiue I. (2015). Are urinary polyaromatic hydrocarbons associated with adult hypertension, heart attack, and cancer? USA NHANES, 2011-2012. *Environmental science and pollution research international*, *22*(21), 16962–16968. https://doi.org/10.1007/s11356-015-4922-8

Silvaggi, F., Leonardi, M., Tiraboschi, P., Muscio, C., Toppo, C., & Raggi, A. (2020). Keeping People with Dementia or Mild Cognitive Impairment in Employment: A Literature Review on Its Determinants. International journal of environmental research and public health, 17(3), 842. https://doi.org/10.3390/ijerph17030842

Sisinno, C. L., Pereira Netto, A. D., Rego, E. C., & Lima, G. (2003). Polycyclic aromatic hydrocarbons in industrial solid waste: a preliminary evaluation of the potential risk of environmental and human contamination in waste disposal areas]. Cadernos de saude publica, 19(2), 671–676. https://doi.org/10.1590/s0102-311x2003000200035

Song, L., Smith, G. S., Adar, S. D., Post, W. S., Guallar, E., Navas-Acien, A., Kaufman, J. D., & Jones, M. R. (2020). Ambient air pollution as a mediator in the pathway linking race/ethnicity to blood pressure elevation: The multi-ethnic study of atherosclerosis (MESA). *Environmental research*, *180*, 108776. https://doi.org/10.1016/j.envres.2019.108776

Srogi K (2007). Monitoring of environmental exposure to polycyclic aromatic hydrocarbons: a review. Environmental Chemistry Letters. 5(4):169–95.

Sun, J.D., Wolff, R., Kanapilly, G., & Mcclellan, R. (1984). Lung retention and metabolic fate of inhaled benzo(a)pyrene associated with diesel exhaust particles. Toxicology and applied pharmacology, 73 1, 48-59.

Sun, K., Song, Y., He, F., Jing, M., Tang, J., & Liu, R. (2021). A review of human and animals' exposure to polycyclic aromatic hydrocarbons: Health risk and adverse effects, photo-induced toxicity and regulating effect of microplastics. The Science of the total environment, 773, 145403. https://doi.org/10.1016/j.scitotenv.2021.145403

Suter, M. K., Karr, C. J., John-Stewart, G. C., Gómez, L. A., Moraa, H., Nyatika, D., Wamalwa, D., Paulsen, M., Simpson, C. D., Ghodsian, N., Boivin, M. J., Bangirana, P., & Benki-Nugent, S. (2018). Implications of Combined Exposure to Household Air Pollution and HIV on Neurocognition in Children. *International journal of environmental research and public health*, *15*(1), 163. https://doi.org/10.3390/ijerph15010163

Thyssen, J., Althoff, J., Kimmerle, G., & Mohr, U. (1981). Inhalation studies with benzo[a]pyrene in Syrian golden hamsters. Journal of the National Cancer Institute, 66(3), 575–577.

Tibuakuu, M., Michos, E. D., Navas-Acien, A., & Jones, M. R. (2018). Air Pollution and Cardiovascular Disease: A Focus on Vulnerable Populations Worldwide. *Current epidemiology reports*, *5*(4), 370–378. https://doi.org/10.1007/s40471-018-0166-8

Todd, M., Schneper, L., Vasunilashorn, S. M., Notterman, D., Ullman, M. T., & Goldman, N. (2018). Apolipoprotein E, cognitive function, and cognitive decline among older Taiwanese adults. PloS one, 13(10), e0206118. https://doi.org/10.1371/journal.pone.0206118

Törnquist, S., Wiklund, L., & Toftgård, R. (1985). Investigation of absorption, metabolism kinetics and DNA-binding of intratracheally administered benzo[a]pyrene in the isolated, perfused rat lung: a comparative study between microcrystalline and particulate adsorbed benzo[a]pyrene. Chemico-biological interactions, 54 2, 185-98.

United States Environmental Protection Agency (USEPA), 2015. Air Quality System Data Mart. US Environmental Protection Agency, Washington, D.C [internet Database] available at: http://www.epa.gov/ttn/airs/aqsdatamart

United States Environmental Protection Agency (USEPA). (1980). Ambient water quality criteria document for polynuclear aromatic hydrocarbons. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA 440/5-8-069.

University Health System. (2012). Dementia and Cognitive Impairment Diagnosis and Treatment Guideline. Retrieved from: https://www.universityhealthsystem.com/~/media/files/clinical-pathways/dementia-cognitive-impairment-guideline-2012.pdf?la=en

Valentine, G., & Sofuoglu, M. (2018). Cognitive Effects of Nicotine: Recent Progress. Current neuropharmacology, 16(4), 403–414.

Van Duuren, B. L., Katz, C., & Goldschmidt, B. M. (1973). Cocarcinogenic agents in tobacco carcinogenesis. Journal of the National Cancer Institute, 51(2), 703–705.

Van Duuren, B. L., Langseth, L., Goldschmidt, B. M., & Orris, L. (1976). Carcnogenicity of epoxides, lactones, and peroxy compounds. VI. Structure and carcinogenic activity. Journal of the National Cancer Institute, 39(6), 1217–1228.

Vu, A. T., Taylor, K. M., Holman, M. R., Ding, Y. S., Hearn, B., & Watson, C. H. (2015). Polycyclic Aromatic Hydrocarbons in the Mainstream Smoke of Popular U.S. Cigarettes. Chemical research in toxicology, 28(8), 1616–1626. https://doi.org/10.1021/acs.chemrestox.5b00190

Wang, J., Ke, T., Zhang, X., Chen, Y., Liu, M., Chen, J., & Luo, W. (2013). Effects of acetazolamide on cognitive performance during high-altitude exposure. Neurotoxicology and teratology, 35, 28–33.

Wang, S., Chanock, S., Tang, D., Li, Z., Edwards, S., Jedrychowski, W., & Perera, F. P. (2010). Effect of gene-environment Interactions on mental development in African American, Dominican, and Caucasian mothers and newborns. *Annals of human genetics*, *74*(1), 46–56. https://doi.org/10.1111/j.1469-1809.2009.00550.x

Wang, S., Chanock, S., Tang, D., Li, Z., Jedrychowski, W., & Perera, F. P. (2008). Assessment of interactions between PAH exposure and genetic polymorphisms on PAH-DNA adducts in African American, Dominican, and Whites mothers and newborns. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 17(2), 405–413.

Wee, L. E., Yeo, W. X., Yang, G. R., Hannan, N., Lim, K., Chua, C., Tan, M. Y., Fong, N., Yeap, A., Chen, L., Koh, G. C., & Shen, H. M. (2012). Individual and Area Level Socioeconomic Status and Its Association with Cognitive Function and Cognitive Impairment (Low MMSE) among Community-Dwelling Elderly in Singapore. Dementia and geriatric cognitive disorders extra, 2(1), 529–542. https://doi.org/10.1159/000345036

Wellenius, G. A., Wilhelm-Benartzi, C. S., Wilker, E. H., Coull, B. A., Suh, H. H., Koutrakis, P., & Lipsitz, L. A. (2012). Ambient particulate matter and the response to orthostatic challenge in the elderly: the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) of Boston study. Hypertension (Dallas, Tex.: 1979), 59(3), 558–563. https://doi.org/10.1161/HYPERTENSIONAHA.111.180778

Weuve, J., Puett, R. C., Schwartz, J., Yanosky, J. D., Laden, F., & Grodstein, F. (2012). Exposure to particulate air pollution and cognitive decline in older women. Archives of internal medicine, 172(3), 219–227.

Wiel, J.A., Fijneman, P., Duijf, C.M., Anzion, R., Theuws, J., & Bos, R. (1993). Excretion of benzo[a]pyrene and metabolites in urine and feces of rats: influence of route of administration, sex and long-term ethanol treatment. Toxicology, 80 2-3, 103-15.

Wiersma, D. A., & Roth, R. A. (1983). Total body clearance of circulating benzo(a)pyrene in conscious rats: effect of pretreatment with 3-methylcholanthrene and the role of liver and lung. The Journal of pharmacology and experimental therapeutics, 226(3), 661–667.

Windholz M. (1983). The Merck index. 10th ed. Rahway, NJ: Merck and Co.

Withey, J. R., Law, F. C., & Endrenyi, L. (1991). Pharmacokinetics and bioavailability of pyrene in the rat. Journal of toxicology and environmental health, 32(4), 429–447.

Withey, J. R., Shedden, J., Law, F. C., & Abedini, S. (1993). Distribution of benzo[a]pyrene in pregnant rats following inhalation exposure and a comparison with similar data obtained with pyrene. Journal of applied toxicology: JAT, 13(3), 193–202.

Withey, J. R., Shedden, J., Law, F. P., & Abedini, S. (1992). Distribution to the fetus and major organs of the rat following inhalation exposure to pyrene. Journal of applied toxicology: JAT, 12(3), 223–231.

Wolff, R., Bond, J., Sun, J.D., Henderson, R., Harkema, J., Griffith, W., Mauderly, J., & Mcclellan, R. (1989). Effects of adsorption of benzo[a]pyrene onto carbon black particles on levels of DNA adducts in lungs of rats exposed by inhalation. Toxicology and applied pharmacology, 97 2, 289-99.

World Health Organization (2004). Top ten leading causes of death by broad income group. Retrieved from: http://www.who.int/mediacentre/factsheets/fs310_2008.pdf. Accessed 10 Mar 2011.

World Health Organization (2012). Dementia: A Public Health Priority. Retrieved from: https://www.cabdirect.org/cabdirect/abstract/20133159231

World Health Organization (2020). Dementia. Retrieved from: http://www.who.int/mediacentre/factsheets/fs362/en/.

World Health Organization (WHO) Regional Office for Europe. (2000). Polynuclear aromatic hydrocarbons (PAH). In: Air quality guidelines for Europe. Copenhagen. pp. 105–117. Retrieved from https://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf

World Health Organization (WHO). (2018). Chapter 5.9 Polycyclic aromatic hydrocarbons (PAH). Retrieved from https://pdf4pro.com/view/chapter-5-9-polycyclic-aromatic-hydrocarbons-PAH-7ca9e.html

Wormley, D. D., Ramesh, A., & Hood, D. B. (2004). Environmental contaminant-mixture effects on CNS development, plasticity, and behavior. Toxicology and applied pharmacology, 197(1), 49–65. https://doi.org/10.1016/j.taap.2004.01.016

Wu, F., Guo, Y., Zheng, Y., Ma, W., Kowal, P., Chatterji, S., & Wang, L. (2016). Social-Economic Status and Cognitive Performance among Chinese Aged 50 Years and Older. PloS one, 11(11), e0166986. https://doi.org/10.1371/journal.pone.0166986.

Wu, M. S., Lan, T. H., Chen, C. M., Chiu, H. C., & Lan, T. Y. (2011). Socio-demographic and health-related factors associated with cognitive impairment in the elderly in Taiwan. BMC public health, 11, 22. https://doi.org/10.1186/1471-2458-11-22

Xu, X., Liang, J., Bennett, J., Botoseneanu, A., & Allore, H. (2015). Socioeconomic stratification and multidimensional health trajectories: evidence of convergence in later old age. The journals of gerontology. Series B, Psychological sciences and social sciences, 70 4, 661-71.

Yan, Z., Zhang, H., Maher, C., Arteaga-Solis, E., Champagne, F. A., Wu, L., McDonald, J. D., Yan, B., Schwartz, G. J., & Miller, R. L. (2014). Prenatal polycyclic aromatic hydrocarbon, adiposity, peroxisome proliferator-activated receptor (PPAR) γ methylation in offspring, grand-offspring mice. PloS one, 9(10), e110706. https://doi.org/10.1371/journal.pone.0110706

Yang, P., Ma, J., Zhang, B., Duan, H., He, Z., Zeng, J., Zeng, X., Li, D., Wang, Q., Xiao, Y., et al. (2012). CpG site-specific hypermethylation of p16INK4alpha in peripheral blood lymphocytes of PAH-exposed workers. Cancer Epidemiol. Biomarkers Prev., 21, 182–190.

Zhang, M., Gale, S. D., Erickson, L. D., Brown, B. L., Woody, P., & Hedges, D. W. (2015). Cognitive function in older adults according to current socioeconomic status. Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition, 22(5), 534–543.

Zhang, Y., Fan, X., Li, S., Wang, Y., Shi, S., Lu, H., Yan, F., & Ma, Y. (2021). Prevalence and risk factors of hypertension among Hui population in China: A systematic review and meta-analysis based on 30,565 study participants. *Medicine*, *100*(18), e25192. https://doi.org/10.1097/MD.0000000000025192