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Exposure to Estrogenic Endocrine Disrupting Chemicals and Brain Health

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EXPOSURE TO ESTROGENIC ENDOCRINE DISRUPTING CHEMICALS AND BRAIN HEALTH

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by

Mark Vicera Preciados

2018

To: Dean Tomas R. Guilarte
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This dissertation, written by Mark Vicera Preciados, and entitled Exposure to Estrogenic Endocrine Disrupting Chemicals and Brain Health, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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DEDICATION

To my Mom and Dad, for always sacrificing and providing me with all the resources needed to succeed. As I have become older and wiser, I have learned to value your example and advice.

To my wife, Jaemy, your confidence, never give up attitude, and support is all I could ask for in a spouse. You are one of the great foundations in my life.

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ABSTRACT OF THE DISSERTATION

EXPOSURE TO ESTROGENIC ENDOCRINE DISRUPTING CHEMICALS AND BRAIN HEALTH

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Mark Vicera Preciados

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Professor Deodutta Roy, Major Professor

The overall objective of this dissertation was to examine exposures to the estrogenic endocrine disrupting chemicals (EEDCs), phthalates, bisphenol-A (BPA), and the metalloestrogens cadmium (Cd), arsenic (As), and manganese (Mn) in an older geriatric aged-population and examine associations with brain health. Given the evidence that EEDCs affect brain health and play a role in the development of cognitive dysfunction and neurodegenerative disease, and the constant environmental exposure through foods and everyday products has led this to becoming a great public health concern. Using a bioinformatic approach to find nuclear respiratory factor 1 (NRF1) gene targets involved in mitochondrial dysfunction, that are both estrogen and EEDC-sensitive, we found several genes involved in the gene pathways of Alzheimer's disease (AD): APBB2, EIF2S1, ENO1, MAPT, and PAXIP1. Using the Center for Disease Control and Prevention (CDC), National Health and Nutrition Examination Survey (NHANES) 2011-2014 datasets to assess EEDC bioburden and associations with surrogate indicators of brain health, which include cognitive scores, memory questions, and taste and smell data, we found phthalate bioburden to be significantly higher in those with adverse brain health

and significantly higher in females. In our logistic regression model when controlling for all known and suspected covariates in AD, in females, the phthalates in females ECP, MBP, MOH, MZP, and MIB in males and the phthalates COP, ECP, MBP, MC1, MEP, MHH, MOH, and MIB were significantly associated with poor cognitive test scores, poor memory, and taste and smell dysfunction. Among the metalloestrogens, Cd bioburden was higher in those with poor cognitive performance, poor memory, and taste and smell dysfunction, with the trend more significant in males. Among oral contraceptive (OC) and HRT (hormone replacement therapy) use, in our logistic regression model when controlling for all known and suspected covariates in AD, past OC and HRT use was associated with better cognitive test scores. The study provides further evidence of the complex role EEDCs play in overall brain health through other biological mechanisms and fills a gap in knowledge that demonstrates EEDCs effects on brain health in a geriatric age population.

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ABBREVIATIONS AND ACRONYMS

AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactive Disorder
ALS	Amyotrophic Lateral Sclerosis
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
AS	Arsenic
BPA	Bisphenol-A
CD	Cadmium
CDC	Center for Disease Control and Prevention
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Cognitive Impairment
CNP	Mono (carboxynonyl) Phthalate
COP	Mono (carboxyoctyl) Phthalate
DHNES	Division of Health and Nutritional Examination Surveys
DSST	Digit Symbol Substitution Test
ECP	Mono-(2-ethyl-5-carboxypentyl) Phthalate
EDC	Endocrine Disrupting Chemical
EE	Ethinyl Estradiol
EEDC	Estrogenic Endocrine Disrupting Chemical
EPA	Environmental Protection Agency
ER	Estrogen Receptors

HRT	Hormone Replacement Therapy
HT	Huntington's Disease
LOD	Limit of Detection
MBP	Mono-n-butyl Phthalate
MBzp	Mono-benzyl Phthalate
MC1	Mono-(3-carboxypropyl) Phthalate
MCI	Mild Cognitive Impairment
MEC	Mobile Evaluation Clinic
MEP	Mono-ethyl phthalate
MHH	Mono (2-ethyl-5-hydroxy-hexyl) Phthalate
MIB	Mono-isobutyl Phthalate
MN	Manganese
MOH	Mono-(2-ethyl-5-oxohexyl) Phthalate
MZP	Mono-benzyl Phthalate
NCHS	National Center for Health Statistics
NHANES	National Health and Nutritional Examination Survey
NMDA	N-Methyl-D-aspartate
NRF1	Nuclear Respiratory Factor 1
OC	Oral Contraceptive
PCB	Polychlorinated Biphenyl
PD	Parkinson's Disease
PSU	Primary Sampling Units

RR	Relative Risk
UPDRS	Unified Parkinson's Disease Rating Scale
WHIMS	Women's Health Initiative Memory Study
WHISCA	Women's Health Initiative Study of Cognitive Aging

CHAPTER I

INTRODUCTION

Endocrine disrupting chemicals (EDCs) are of important public health concern and are linked to diseases of all human systems [1]. They affect all the sensitive periods of human life: gestation, childhood, puberty, reproductive life, and old age [1]. EDCs include numerous chemicals found in our environment, both natural and man-made. These include industrial chemicals, plasticizers, pesticides, pharmaceutical drugs, and phytoestrogens [2]. EDCs affect the human body by imitating, blocking, and/or altering hormonal function [1]. EDCs exert their effects by being able to enter the body by dermal, ingestion, and inhalation routes[2]. There widespread distribution in our environment is due to their use in most manufacturing processes [1] and their production from e-wastes [3]. Estrogenic endocrine disrupting chemicals (EEDCs) are a specific type of EDC, which affect bodily process that are influenced and modulated by estrogen hormones [4].

EEDCs as a Brain Health Concern: EEDCs have been implicated as one of the causes of neurodegenerative disease and adverse brain health [1]. Adverse brain health can be defined by neurodegeneration that encompasses any pathological condition affecting neurons [5]. Neurodegenerative diseases, a product of adverse brain health, have varied symptoms which affect neurons from different parts of the brain, with the most publicized diseases being Alzheimer‘s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis, (ALS), and Huntington’s disease (HD) [5]. The ability of various EEDCs to mimic estrogen and affect its role in brain health, and their widespread dissemination in the environment makes this an important public health concern.

Estrogen's Role in Brain Health: Estrogen role in the brain is extensive. Estrogen has been shown to influence sexual differentiation [6], plays a role as a neuroprotectant and promote anti-inflammatory effects on the brain [7–12], promotes neuroplasticity and synaptogenesis [13–17], and regulates and protects mitochondrial function in the brain [18–20]. A majority of studies have focused on EEDCs effects on early human development and the brain, and there are few studies that look at an older geriatric aged population. Due to EEDCs ability to interact with estrogen and disrupt its role in brain development and protection, merits further study on its effects on the aging brain. Of the hundreds of EEDCs that human beings are exposed to, this dissertation focuses on a selection of the most prevalent EEDCs in our environment with proven estrogenic activity: Phthalates, bisphenol-A (BPA), cadmium (Cd), manganese (Mn), and arsenic (As).

Phthalates: Phthalates are class of estrogenic endocrine disrupting chemicals that have a role in the development of neurodegenerative disease. Phthalates, also known as plasticizers, are chemicals used in plastics to make them flexible and strong [21–23]. Exposure to phthalates comes through ingestion, inhalation, and to a lesser extent, dermal contact with phthalate-containing products [24]. Phthalates are found in most consumer products. These include the following: wall coverings, tablecloths, floor tiles, furniture, upholstery, shower curtains, garden hoses, baby products, toys, shoes, packing materials, medical devices, paints, glue, nail polish, hair spray, insect repellents, food packaging materials, cosmetics, insecticides, and drug products [21–23]. Phthalates have short biological half-lives and do not accumulate, with urine as the primary route of excretion [25]. Specific phthalates are also found in high levels among the US population. One study, found the body burden of the phthalates mono-ethyl phthalate (MEP), mono-n-butyl

phthalate (MBP) and and mono-benzyl phthalate (MBzp) in 97% of samples tested from the CDC NHANES 1999-2000 datasets [26]. As such, most of the US population has some measurable levels of phthalates in their bodies [25].

Phthalates have also been demonstrated to have estrogenic activity and affinity for estrogen receptors (ER) [27,28] and have been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [29].

Bisphenol-A (BPA): BPA is a synthetically created chemical that is used to create polycarbonate plastics and resins [30]. BPA is found in many consumer products and plastics. These products include the following: baby bottles, compact discs, impact-resistant safety equipment, medical devices, food cans and tops, water supply pipes, ATM receipts and dental sealants and composites [30]. Food storage containers that have BPA can cause it to leech into foods by the use of high heat [30]. It is of note that during the 2003-2004 NHANES data cycle, BPA was detected in 93% of urine samples collected from subjects 6 years of age and older [31].

BPA has been shown to be weakly estrogenic and have a low affinity for binding to ER receptors, but is speculated to exert its effects through other non-classical pathways [32]. BPA has also been shown to interact with estrogen-responsive genes that are implicated in neurodegenerative disease pathways [29].

Cadmium (Cd): Cd is a naturally occurring metal in the earth's crust and a natural part of water in the ocean [33]. People are exposed through eating food, cigarette smoke, drinking water, and air [33]. Cd is introduced into the food chain through soil and food contact surfaces, and through foods such as green vegetables, grains, legumes, and meats [33]. Occupation exposures are highest in occupations involving the manufacture of Cd-

containing products [33]. Inhalation and oral routes of exposure are predominant, followed by dermal exposure [33]. Current evidence supports the toxicity of Cd and its effects on the developing organism, reproductive toxicity, hepatic effects, hematological effects, and immunological effects [33]. Cd has also been demonstrated to have estrogenic properties [34] and has been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [29].

Arsenic (As): As is an element in the environment, found in the earth's crust, and is considered a metalloid [35]. Populations are usually exposed through the air, drinking water, and food, with food being the main source of As in a population, with some areas having naturally high levels of As [35]. Occupational exposure occurs through individuals working in metal working, wood treatment, and those in working in the production and application of pesticides [35]. As is also used in the animal and poultry feed as an antimicrobial compound [35]. The main routes of exposure are inhalation and oral, with dermal exposure being considered a minor route [35]. As has been associated with various health conditions and affects every organ system [35]. Genetic polymorphisms are suspected of causing some individuals to be more sensitive to As[35]. As has also been demonstrated to have estrogenic properties [34] and has been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [29].

Manganese (Mn): Mn is a metal that is an essential nutrient required as a cofactor for various enzymatic processes and is found as a naturally occurring element in grains and fruit [36]. Mn is used in industrial processes and products and exposure can occur through inhalation, oral, dermal, and occupational routes [36]. Mn has the potential to accumulate in organisms at the bottom tier of the food chain and has been linked to various health issues

that include neurological dysfunction [36]. Mn has also been demonstrated to have estrogenic properties [34] and has been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [29].

Oral Contraceptives (OC): Oral contraceptives containing specifically containing synthetic estrogens such as ethinyl estradiol are considered EEDCs due to its ability to mimic estrogen and influence the reproductive cycle. OC use has been shown to reduce the amount of available endogenous estrogen in the body [37]. OCs has varying effects brain structure, function, and cognition [38]. Most recent studies have shown varying effects; however, the studies do not differentiate between the various types of contraceptives, making it difficult to find out if the contraceptives used contained ethinyl estradiol and inconsistencies are found in the reporting of the type of OC used [39].

Hormonal Replacement Therapy (HRT): Hormone replacement therapy, or HRT, has been shown to be associated with the start of neurodegenerative disease, although this has been related to a time dependent response, which depends on when the HRT was initiated. Observation studies and analyses with women indicated the use of HRT's containing estrogen to be associated with a reduced risk of Alzheimer's disease. Studies suggest that the timing of HRT use during parts of the menopausal stage may dictate whether beneficial adverse effects are observed [40,41].

National Health and Nutrition Examination Survey (NHANES): NHANES is a continuous cross-sectional data collection carried out by the Center for Disease Control and Prevention (CDC) utilizing a complex multi-stage sampling design that creates a survey representative of the non-institutionalized population of the United States [42,43]. The survey has been conducted since 1999 and consists of an at-home questionnaires

followed by a standardized physical examination and specimen collection conducted in mobile examination centers (MEC) [42,43]. Eligibility is determined using preset selection probabilities for the desired demographic subdomains [43]. A household screener is performed before to determine if any household members are eligible for the interview and examination [43]. The interview collects demographic, health, nutrition, and household information, while the physical examination includes physical measurements, dental examination, and the collection of blood and urine specimens for laboratory testing [43]. Prior to any to interviews and examinations, informed consent was obtained and all procedures were approved by the CDC Institutional Review Board [44].

The goal of this research was to find out if exposure to EEDCs (phthalates, BPA, Cd, As, and Mn) are associated with adverse brain health. Using the CDC's NHANES 2011 to 2014 datasets, statistical analyses were performed on surrogates of brain health indicators, urinary EEDC levels, and associated variables.

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CHAPTER II

MANUSCRIPT I

EXPOSURE TO ESTROGENIC ENDOCRINE DISRUPTING CHEMICALS AND THEIR ROLE IN BRAIN HEALTH

LITERATURE REVIW

INTRODUCTION

Estrogenic endocrine disrupting chemicals (EEDCs) are endocrine disruptors that mimic and affect the function of estrogen [1]. They can affect the human body through every route of exposure and are found in almost all manufactured products [2]. The global increase in manufacturing and e-waste production have increased exposures [3]. The effects of these chemicals are far reaching since they affect every part of the human timeline, from birth to old age, and have even been demonstrated to produce adverse health effects in later generations [4].

These chemicals are of great concern to public health since they are linked to almost every disease of every human system including neurodegenerative diseases [4,5]. EEDCs have also been associated with other neurological disorders such as attention deficit and hyperactive disorder (ADHD) as well as learning disabilities and aggressiveness [6]. EEDCs have also been demonstrated to affect the young through maternal exposure, producing neurological issues such as abnormal rearing behavior, locomotion issues, anxiety disorder, learning difficulties, memory issues, and abnormal neuronal development [7,8].

Estrogens and Brain Health

Estrogens have many roles in the human brain. Estrogen plays a role in sexual differentiation in early brain development [9]. Estrogen has been found to potent neuroprotectant and decreases inflammation in the brain [10–15]. Estrogen has been demonstrated to stimulate the grown of neurons and synapses [16–20], and protect the function of mitochondria in the brain [21–23].

Epidemiological studies have shown the effects of estrogen on brain health. In the review of epidemiological studies pertaining to estrogen and brain health, exposure was assessed through serum or blood measures, or through a surrogate of exposure. The surrogate of exposure to estrogen was quantified as the start of menarche to the end of menopause. Studies were also only used if exogenous estrogen exposure was either controlled for, or excluded, as exogenous estrogen can affect the natural levels of estrogen in the body.

Cross-sectional studies have differing results. In a study of 393 postmenopausal geriatric-age women, no significant association was found between sex hormone levels and neuropsychological test performance [24]. Another study consisting of 760 post-menopausal women looking at life-long endogenous estrogen exposure and using a surrogate of estrogen exposure did not find any associations with cognitive tests [25]. A study of 11094 postmenopausal women found significant associations between surrogates of estrogen exposure and delayed recall scores (p-value=0.001, 95% CI, 0.008-0.02) and mini-mental state exam scores [26]. In a study of 181 geriatric-aged men, higher estrogen serum levels were associated with better verbal memory assessment scores (Beta=0.17, p-value<0.02)

[27]. In a cross-sectional study of 579 females, the age of Parkinson's disease (PD) onset was positively associated with surrogates of estrogen exposure (7.10,[3.31],P-value=0.032) [28].

Several case-control studies were identified that assessed the effects of endogenous estrogen exposure on brain health. In a case-control study of 50 Alzheimer's disease (AD) cases and 93 controls, women with the lowest endogenous estradiol levels were 4 times as likely to have AD compared to women with the highest estradiol levels (OR=4.2, 95% CI 1.1-15.6) [29]. In a case-control study of 131 amyotrophic lateral sclerosis (ALS) cases and 430 age-matched controls a longer reproductive time-span decrease ALS risk (OR=0.95, 95% CI 0.91-0.98) and longer endogenous estrogen exposure decreases ALS risk (OR=0.95, 95% CI 0.89-1.01) [30].

Several cohort studies were identified that assessed the effects of endogenous estrogen exposure on brain health. In a cohort of 3601 postmenopausal women, it was found after adjusting for covariates, women with longer reproductive spans had an increased risk of dementia compared to women with the shortest reproductive spans (RR=1.78, 95% CI 1.12-2.84) and an increased risk of AD (RR=1.51, 95% CI 0.91-2.50) with the risk was more pronounced in carriers of the APOE allele [31]. In a cohort study of 119 women with Down's syndrome, women with low bioavailable estrogen were more likely to develop AD (HR=4.1, 95% CI 1.2-13.9) [32]. A study of 133 postmenopausal females found longer duration of months with endogenous estrogen exposure had a protective effect against AD risk (p-value=0.0235, 96% CI 0.9907-0.9993) with the effect becoming stronger when subjects were over the total median number of months (p-value=0.00754, 96% CI 0.004118-0.005289) [33].

Oral Contraceptives (OC) and Brain Health

OCs containing synthetic estrogens, such as ethinyl estradiol (EE), are considered EEDCs since they imitate estrogen and cause changes to the human reproductive cycle. OC use has been demonstrated to reduce endogenous estrogen in the body [34]. Most studies do not differentiate if contraceptives do, or do not contain ethinyl estradiol and inconsistencies are found in the reporting of the type of OC used [35]

A cross-sectional study examined OC effects on spatial and verbal abilities found OC users to perform better on spatial ability and verbal tests [35]. Another cross-sectional study found OC users to have better cognitive scores compared to non-users [36]. Another study found OC use to negatively affect cognition and verbal fluency [34] A review by Warren et al. suggest an overall positive effect with OC use and verbal memory [37].

Hormonal Replacement Therapy (HRT) and Brain Health

Initial observation studies indicate the use of hormone replacement therapy (HRT) containing synthetic estrogen to be associated with a reduced risk of AD [38]. Studies suggest that the timing of HRT use during specific times during menopause may dictate whether beneficial effects are observed [38,39]. In the Women's Health Initiative Memory Study (WHIMS), a randomized, double-blind, placebo-controlled clinical trial, HRT treatment of estrogen with progestin increased the risk for dementia in postmenopausal women and did not prevent cognitive impairment [40]. In the same trial, it was found that estrogen-only HRT increased the risk for both dementia and cognitive impairment [41]. The Women's Health Initiative Study of Cognitive Aging (WHISCA) further supports HRT use and its' association with neurodegenerative disease, with mixed findings. One finding from the WHISCA study found conjugated equine estrogen with

medroxyprogesterone acetate (estrogen + progestin) appeared to negatively impact verbal memory, but positively affect figural memory among postmenopausal women, free of probable dementia compared to controls [42] Another study found estrogen alone, as conjugated equine estrogen, did not improve cognitive functioning and lowered certain cognitive functions in women with prior hysterectomy [43]. Other studies have indicated that no improvement in using estrogen only treatments for cognitive function [44–47].

Newer studies give mixed findings. One cohort study showed increased AD risk amongst women who used HRT more than five years after menopause but observed a decreased risk of AD if used within five years of menopause [48]. Another recent meta-analysis showed no association between postmenopausal HRT use and AD and dementia [49]. While another study found an increase in Parkinson's disease (PD) risk dependent on the type of HRT treatment [50].

Bisphenol-A (BPA) and Brain Health

BPA is a synthetically created chemical that is used to create polycarbonate plastics and resins [51]. BPA is found in many consumer products and plastics. These products include the following: baby bottles, compact discs, impact-resistant safety equipment, medical devices, food cans and tops, water supply pipes, ATM receipts and dental sealants and composites [51]. Food storage containers that have BPA can cause BPA to leech into foods by the use of high heat [51]. It is of note that during the 2003-2004 NHANES data cycle, BPA was detected in 93% of urine samples collected from subjects 6 years of age and older [52].

BPA has been shown to be weakly estrogenic and have a low affinity for binding to ER receptors, but is speculated to exert its effects through other non-classical pathways

[53]. BPA has also been shown to interact with estrogen-responsive genes that are implicated in neurodegenerative disease pathways [54]. BPA has been demonstrated to be able to cross the blood brain barrier [55,56].

Animal studies have demonstrated BPA to have negative effects on memory [57–72], negatively affect neurogenesis [62,72], negatively affect structure of dendritic spines and synaptogenesis [57,61,66,69,71,73], and negatively affect cellular processes, protein expression, and gene expression [60,64,66–68,70]. Other studies show BPA produces no negative effects on spatial and working memory [74–76].

BPA was found to cause hyperactivity in rats [77]. A single dose of BPA administered to neonatal mice was observed to affect cognitive function and alter adult spontaneous behavior, mid and high dosed mice [78]. In utero exposure to BPA in mice was shown to reduce dendritic spine densities in the hippocampal CA1 region and was not dose dependent [79]. BPA was shown to effect neural ectoderm specification and neural progenitor cells in mouse embryonic stem cells [80]. In an animal model using C.elegans, early embryogenesis exposure to BPA and BPS was shown to cause changes in behavior and learning into adulthood [81]. BPA was shown to decrease the proliferation of multipotent neural progenitor cells and produce cytotoxicity in F1 mice, and in low-doses stimulated neuronal differentiation which might disrupt brain development [82].

Animal studies have indicated bisphenol-A to affect various aspects of memory at lower than the US Environmental Protection Agency's (EPA) reference safe daily limit of 50 ug/kg/day [83]. The types of memory affected include spatial memory, visual memory, object recognition, working memory, reference memory and navigational memory [57,58,62,63,66,69,71–73,84]. Animal studies have also indicate affects to locomotor function [58,66].

In humans, prenatal BPA exposure has been demonstrated to cause aggressive and hyperactive behavior in offspring from mothers with higher BPA levels when compared to offspring with mothers that have lower BPA levels [85]. This human epidemiological study is consistent with animal studies that also show the same effect [86–93].

Prenatal urinary BPA concentrations in the human mother and child were associated with anxiety, depression, and hyperactivity [94]. In autistic children, plasma levels of BPA and phthalates were significantly higher compared to controls [95]. One study using cross-sectional data from the Canadian Health Measures Survey found children taking psychotropic medications was associated with urinary BPA (OR 1.59; 95% CI 1.05-2.40) [96]. Another study assessing prenatal exposure to bisphenol A and phthalates and infant neurobehavior at five weeks found no associations with bisphenol A and some associations with phthalate exposure and improved neurobehavior [97]. In a prospective cohort study following African-American and Dominican-American women from pregnancy to children's age of 7-9, it was found that among boys, high prenatal BPA concentrations was associated with increased internalizing and externalizing behaviors in boys, with a decrease in internalizing behavior in girls, and high postnatal BPA concentrations was associated with increased internalizing and externalizing behaviors in girls more than in boys [98]. Other studies have found were related to a decrease in hyperactivity symptoms in boys and an increase in anxiety, depression, and externalizing behavior in young girls [85,99]. Other studies have found no associations between maternal BPA levels and autism [100].

Phthalates and Brain Health

Phthalates are class of estrogenic endocrine disrupting chemicals that have a role in the development of neurodegenerative disease. Phthalates, also known as plasticizers, are chemicals used in plastics to make them flexible and strong [101–103]. Exposure to phthalates comes through ingestion, inhalation, and to a lesser extent, dermal contact with phthalate-containing products [104]. Phthalates are found in most consumer products. These include the following: wall coverings, tablecloths, floor tiles, furniture, upholstery, shower curtains, garden hoses, baby products, toys, shoes, packing materials, medical devices, paints, glue, nail polish, hair spray, insect repellents, food packaging materials, cosmetics, insecticides, and drug products [101–103]. Phthalates have short biological half-lives and do not accumulate, with urine as the primary route of excretion [105]. Specific phthalates are also found in high levels among the US population. One study, found the body burden of the phthalates mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MBP) and mono-benzyl phthalate (MBzp) in 97% of samples tested from the CDC NHANES 1999-2000 datasets [106]. As such, most of the US population has some measurable levels of phthalates in their bodies [105].

Phthalates have also been demonstrated to have estrogenic activity and affinity for estrogen receptors [107,108] and have been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [54]. Phthalates have also been demonstrated to cross the blood brain barrier [109,110]

Animal studies have shown phthalates to have adverse effects on brain health. Negative effects include adversely affecting learning [111,112], adversely affecting memory [111,113], interfering with locomotion [113]; negatively affecting social behavior [112], and

producing cellular effects such as cell death, synaptic loss, and synaptic dysfunction [114]. Some animal studies indicate improvement in memory [115] and possible dose-dependent effects, where memory improves with one dose, but degrades with another [116]. A recent review of phthalates and neuroplasticity suggests phthalates negatively affect neurogenesis and plasticity in animal models [114,117].

There are a group of studies that have found associations between phthalates and brain behavioral disorders such as autism spectrum disorder (ASD) and attention deficit hyperactive disorder (ADHD). One study examining exposure to EEDCs and autism and ADHD found intracranial exposure to several classes of EEDCs, which include phthalates, caused significant hyperactivity in neonatal rats with observable gene alteration [118]. A retrospective study followed children 1-6 years of age with a follow-up at 6-8 years of age and found the children with exposure to phthalates from PVC pipe dust were more likely to develop ASD [119]. Phthalates are suspected in the development of neurodegenerative diseases [110]. In rat model study, phthalate exposure was shown to impair cognition and increase the levels of phospho-Tau, a precursor of AD development, in exposed rat offspring [120]. Currently no definitive epidemiological studies have been conducted with phthalates and neurodegenerative diseases.

Polychlorinated Biphenyls (PCBs) and Brain Health

PCBs are synthetic organic chemicals composed in different combinations of 209 different chlorinated compounds, or congeners [121]. PCBs have been used as coolant and lubricants in transformers, and its manufacture was banned in 1977 because of harmful health effects, however, old products may still contain them [121]. PCBs have been found to cause cancer in animals [121]. Routes of exposure included occupational exposure,

breathing air near contaminated areas, using older products manufactured before and around 1977, and eating contaminated food [121]. PCBs bio accumulate in the food chain and remain active in the environment for extended periods of time [121].

Recent animal and cell studies have shown PCBs to adversely affect brain health. Animal studies have shown exposure to PCBs affect brain health by affecting social behavior[122], increased hyperactivity [123], reduction in learning ability [124], and physiological effects on the brain such as neuronal degradation [123,125], neuronal loss and damage [126], and susceptibility to amyloid stress and reduced expression of synaptic proteins [125].

Recent cell studies have shown PCBs to cause cellular death [127] and interfere with estrogen's neuroprotective effects on neurons and brain cells [128].

Cross-sectional studies have shown the effects of PCBs on brain health. In children, PCB exposure is associated with lower IQ [129] and lower visual memory function [130]. In older populations, PCB exposure is associated with lower verbal learning and memory [131], lower verbal memory and depressive symptoms [132], lower score on memory and learning measures [133], and attenuation of emotional wellbeing and attentional functioning [134].

In a nested case-control study in Finland, serum PCBs were not associated with PD development [135]. In a retrospective mortality study examining PCB exposure amongst workers in capacitor plants, sex-specific analyses found higher deaths from PD amongst exposed women [136]. In a case-control study examining post-mortem brain tissue from PD, AD, and control patients, PCB levels were higher in PD groups, and when stratified by age, were higher amongst women [137].

Cadmium (Cd) and Brain Health

Cd is a naturally occurring metal in the earth's crust and a natural part of water in the ocean [138]. People are exposed through eating food, cigarette smoke, drinking water, and air [138]. Cd is introduced into the food chain through soil and food contact surfaces, and through foods such as green vegetables, grains, legumes, and meats [138]. Occupation exposures are highest in occupations involving the manufacture of Cd-containing products [138]. Inhalation and oral routes of exposure are predominant, followed by dermal exposure [138]. Current evidence supports the toxicity of Cd and its effects on the developing organism, reproductive toxicity, hepatic effects, hematological effects, and immunological effects [138]. Cd has also been demonstrated to have estrogenic properties [139] and has been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [54].

In a study using hippocampal CA1 neurons, cadmium was shown to negatively affect synaptic transmission and neural plasticity [140]. In a study using neural PC12 and SH-SY5Y cells, cadmium induced apoptosis in the neural cells [141,142]. In a zebrafish animal model, cadmium has been shown to inhibit neurogenesis in embryonic development [143]. Cadmium has been shown to cause cell death in rat cerebellum cortical neurons by affecting calcium homeostasis [144] and also cause cell death by damaging mitochondria in rat oligodendrocytes [145]. Cadmium has been shown to interact with beta amyloid peptides which is involved in the development of AD [146].

A study that examined the cerebrospinal fluid of ALS patients observed higher levels of various metals, including cadmium [147]. A case-control study examining heavy metal levels in hair samples from a group of Mongolian people found elevated cadmium,

as well as other heavy metals in those with Parkinson-like symptoms [148]. In a study of boiler workers and occupational exposure, exposure to various heavy metals, including cadmium was associated with conditions similar to PD and AD [149].

Arsenic (As) and Brain Health

As is an element in the environment, found in the earth's crust, and is considered a metalloid [150]. Populations are usually exposed through the air, drinking water, and food, with food being the main source of As in a population, with some areas having naturally high levels of As [150]. Occupational exposure occurs through individuals working in metal working, wood treatment, and those in working in the production and application of pesticides [150]. As is also used in the animal and poultry feed as an antimicrobial compound [150]. The main routes of exposure are inhalation and oral, with dermal exposure being considered a minor route [150]. As has been associated with various health conditions and affects every organ system [150]. Genetic polymorphisms are suspected of causing some individuals to be more sensitive to As[150]. As has also been demonstrated to have estrogenic properties [139] and has been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [54].

In animal studies using rats, arsenic exposure through ingest water has been shown to impair neurogenesis, worsened spatial memory, and promote abnormal neural synapses growth. [151]. Animal studies in rats have demonstrated arsenic exposure to affect synaptic plasticity, by affecting the expression of NDMA receptors [152,153] and downregulating the PTEN-Akt-Creb signaling pathway and damaging cerebral neurons [154]. Arsenic was demonstrated to cause oxidative stress and cell death in cultured neuronal cells, when administered with dopamine [155]. In a study using a cholinergic

neuronal cell line overexpressing amyloid precursor protein (APP) and exposing it to sodium arsenite and its metabolite, dimethyl arsenic acid, increased APP production was observed [156].

In a cohort study consisting of 133 men and 201 women, long-term low level exposure to arsenic from groundwater was found to be associated with poorer scores in language, visuospatial skills, and executive functioning, global cognition, processing speed, and immediate memory [157]. In another study, consisting of 526 subjects genotyped according to the AS3MT gene, exposure to higher low level arsenic in groundwater reduced cognitive functioning, but the results differed with amongst the different SNPs [158]. In a case-control study measuring heavy metal serum levels in 89 Ad patients and 188 cognitively normal controls, there was no difference in serum arsenic levels between the AD group and controls [159]. Another study with a cohort consisting of 733 AD patients, 127 individuals with mild cognitive impairment (CI), and 530 individuals of normal cognition, found that exposure to low level arsenic exposure from groundwater was found to be associated with poorer neuropsychological performance [160].

Manganese (Mn) and Brain Health

Mn is a metal that is an essential nutrient required as a cofactor for various enzymatic processes and is found as a naturally occurring element in grains and fruit [161]. Mn is used in industrial processes and products and exposure can occur through inhalation, oral, dermal, and occupational routes [161]. Mn has the potential to accumulate in organisms at the bottom tier of the food chain and has been linked to various health issues that include neurological dysfunction [161]. Mn has also been demonstrated to have

estrogenic properties [139] and has been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [54].

Recent epidemiological studies have assessed the effects of manganese on brain health. A cross-sectional study by Hozumi et al. [162], analyzed the cerebrospinal fluid of various neurodegenerative disease patients and found a higher level of manganese among PD patients (p-value <0.05). In another cross-sectional study assessing children's intellectual functioning and arsenic and manganese exposure, blood manganese levels were negatively associated with full scale IQ test scores (p-value<0.05), working memory (p-value<0.05), and perceptual memory (p-value<0.05) [163]. A cross-sectional study by Kim et al.[164] examining low-level manganese exposure in adults of a Ohio community found subtle subclinical effects in Unified Parkinson's Disease Rating Scale (UPDRS) and postural sway test for PD. A cross-sectional study of school-aged children in Brazil found inverse scores on executive function and attention tests with manganese levels [165]. A study amongst school-children in Canada found low-level manganese exposure in drinking water was associated with poorer neurobehavioral functions [166]. Koc et al. [167] found higher levels of metal, including manganese, in hair samples of AD patients compared to controls.

A case-control study Miyake et al. [168], assessing dietary intake of heavy metals amongst PD patients found no association with manganese intake. A case-control study by Roos et al. [147] found elevated manganese levels in cerebrospinal fluid of ALS patients. A study by Kumudini et al.[169] found not correlation between manganese blood levels in PD patients compared to controls. A case control study by Garzillo et al.[170] found no association between manganese levels in ALS patients vs controls. A study by Kihira et

al. [171] found elevated manganese levels in ALS patients vs controls from hair samples. Another study by Arain et al. [172] found higher levels of manganese and aluminum in hair samples of patients suffering from neurodegenerative disease.

A small cohort study that followed 26 welders exposed to manganese found after a 3.5-year follow-up found worsened olfactory, extrapyramidal, and mood disturbances [173]. A cohort study following asymptomatic welder trainees with no previous manganese exposure found low-level exposure to cause sub-clinical brain changes in subjects before any measurable learning deficits may occur [174].

Evidence suggests manganese having a role in neurotoxicity. Chronic manganese exposure has been shown to promote the build-up of the metal in the basal ganglia, white matter, and cortical structures of the brain [175]. manganese has also been shown to cause an inhibitory effect on NMDA receptors [176] Although manganese is an essential nutrient and has beneficial uses in the human body, increased levels of manganese in the body can lead to PD-like symptoms and developmental exposure has been shown to negatively affect neurological development [177]. Manganese appears to interfere with dopaminergic synaptic transmission, by possibly impairing presynaptic dopamine release[177]. A study using a monkey model showed manganese exposure caused neurotoxicity by inhibiting dopamine neurotransmission [178].

Mechanisms of Action of EEDCs and Brain Health

From our review, it is demonstrated that physiologic pharmacologic, and chemical forms of estrogen and EEDCs affect brain health. The exact molecular mechanisms are not clear. Estrogens have a clear gender difference as they regulate the both men and women's sexual development. In females, they are produced mainly by the ovaries, in the

testis in males, but are produced in both men and women from the adrenal gland, brain, and fat cells. In the brain, estrogen is produced by both neurons and glial cells through the aromatization of testosterone [20,179]. Early animal studies in rhesus monkeys found circulating estrogen in the brains of in the fetal and postnatal stages of development [180]. Circulating estrogen produced in the hypothalamus may also play a role in the release of gonadotropin releasing hormone (GnRH), further adding to the complexity of estrogen's role in the brain. There is evidence to suggest that phthalates, BPA, PCBs, Cd, As, and Mn influence GnRH regulation through the hypothalamic-pituitary-ovarian axis since they also bind to estrogen receptors [4,181–183] and have been demonstrated to cross the blood brain barrier [110,117,184–186] and have shown estrogenic activity [53,107,108,139]. The most widely research idea regarding estrogen and the brain estrogens and EEDCs effects are mediated through estrogen receptors which are all expressed in the brain [8]. There is also evidence that suggests EEDC's adverse effects in the brain area results of reactive oxygen species (ROS) production and oxidative stress in the brain. Studies suggest phthalate metabolites, BPA, and metalloestrogns are associated oxidative stress and ROS production [141,148,155,184,187,188].

Nuclear Respiratory Factor 1 (NRF1) Genes, EEDCs, and Brain Health

Nuclear respiratory factor 1 is a transcription factor that acts on genes encoding for mitochondrial respiratory subunits, heme biosynthetic enzymes, and regulatory factors involved in the creation and transcription of mitochondrial DNA [189]. Other possible extra-mitochondrial processes that are affected by NRF-1 include RNA metabolism, splicing, cell cycle, DNA damage repair, protein translation initiation, and ubiquitin-mediated protein degradation [190]. Since mitochondrial dysfunction has been

implicated as a possible pathway for neurodegenerative diseases [191], gene targets of NRF-1 directly affect brain health and may provide insight into mechanisms of these diseases. NRF-1 mediate oxidative stress responses by regulating the expression of genes involved in cell cycle, DNA repair, cell apoptosis and mitochondrial biogenesis. NRF1 is highly expressed in human fetal brain [192].

A recent study based on data from SK-N-SH human neuroblastoma cells showed that NRF1 DNA motif(s) are present in the promoters of 2470 genes [190]. The study speculates that NRF1 targets may be involved in the development of adverse brain health and neurodegenerative disease [190]. The study stated that seven out of 2470 NRF1 target genes have significant relationships with several neurodegenerative conditions. The NRF1 target genes- PARK2, PARK6 (PINK1), PARK7, PAELR (GPR37) are associated with Parkinson's disease. NRF1 target genes -PSENEN AND MAPT are involved in Alzheimer's disease. TAF4, a NRF1 target gene, is associated with Huntington's disease [190].

Bioinformatic Method: Estrogen and NRF1 responsive Genes and EEDCs

We used the Comparative Toxicogenomics Database (CTD), which contains gene information based on curated information about chemical–gene/protein interactions, chemical–disease and gene–disease relationships. Using a bioinformatics approach, we examined the gene-EDC interactions associated with both estrogen and NRF1 signaling pathways, and neurodegenerative diseases. Findings of EDCs-modified estrogen signaling and NRF1 signaling genes with exposure to natural estrogen, pharmacological estrogen, PCBs, phthalate, BPA, As, Cd, or Mn are summarized in Tables 1 and 2.

Results

17-Beta Estradiol interacting genes which are also NRF1 target genes: The CTD search results showed that there were 6695 genes related to 17-beta estradiol (E2) (Figure 1). The 724 genes out of the 6695 E2 modified genes are NRF1 target genes (Figure 1). Three of the common E2 and NRF1 target genes, GPR37, MAPT, and PSENEN are associated with neurodegenerative disease [190]. Table 1 showing enriched pathway analysis revealed the top pathways associated with E2 responsive NRF1 target genes, that included:1) Disease (86 genes), 2) Metabolism (86 genes),3) Gene Expression (77 genes), 4) Signal Transduction (72 genes), 5) Immune System (67 genes), 6) Cell Cycle (62 genes), 7) Metabolic pathways (62 genes), 8) Metabolism of proteins (48 genes), 9) Developmental Biology (43 genes), and 10) Mitotic M-M/G1 phases (35 genes).

Ethinyl Estradiol Interacting genes common to both E2 and NRF1 target genes: The CTD search revealed that there were 6049 genes related to the active estrogenic chemical in oral contraceptives, ethinyl estradiol (EE) (Figure 1). Out of the 6049 EE modified genes, 800 genes are NRF1 target genes and 331 genes are target genes of both E2 and NRF1 (Figure 1). Two of the genes, MAPT and PSENEN, observed interacting with all three EE, E2 and NRF1 are associated with neurodegenerative disease [190]. Table 1 showing enriched pathway analysis revealed the top pathways associated with the number of common E2, E2 and NRF1 target genes, that included: 1) Metabolism (49 genes), 2) Disease (48 genes), 3) Gene Expression (43 genes), 4) Immune System (36 genes), 5) Cell Cycle (35 genes), 6) Metabolic pathways (33 genes), 7) Signal

Transduction (33 genes), 8) Metabolism of Proteins (28 genes), 9) Developmental Biology (25 genes), and 10) Cancer Pathways (22 genes).

Bisphenol A and Interactions with NRF1 Target Genes: The CTD search revealed there are 19113 genes related to BPA. Out of the 19113 interacting genes, 2113 are NRF1 target genes, and 673 are target genes of both BPA and E2 (Figure 1). Three of the genes, GPR37, MAPT and PSENEN observed interacting with all three BPA, E2, and NRF1 are associated with neurodegenerative disease [190]. Enriched pathway analysis revealed the top pathways associated with number of common BPA/E2/NRF1 target genes, that included: 1) Metabolism (85 genes), 2) Disease (84 genes), 3) Gene Expression (71 genes), 4) Signal Transduction (68 genes), 5) Immune System (66 genes), 6) Cell Cycle (61 genes), 7) Metabolic Pathways (58 genes), 8) Metabolism of Proteins (47 genes), 9) Developmental Biology (41 genes), and Cancer Pathways (34 genes) (Table 1).

Phthalates and Interactions with NRF1 Target Genes: The CTD search revealed there were 4816 genes interacting with dibutyl phthalate (DBP) and 1344 genes with diethylhexyl phthalate (DEHP). The 756 DBP interacting genes are NRF1 target genes, whereas 149 DEHP interacting genes are NRF1 target genes. Among DBP responsive genes, there are 309 genes common E2 and NRF1 target genes and 86 DEHP associated genes are common E2 and NRF1 target genes (Figure 1). MAPT, a common DEHP, E2 and NRF1 target genes are associated with neurodegenerative disease [190]. Enriched pathway analysis revealed the top pathways associated with number of common DBP/E2/NRF1 target genes, that included: 1) Metabolism (56 genes), 2) Disease (45 genes), 3) Gene Expression (39 genes), 4) Metabolic Pathways (38 genes), 5)

Cell Cycle (34 genes), 6) Signal Transduction (32 genes), 7) Immune System (31 genes), 8) Metabolism of Proteins (25 genes), 9) Mitotic M-M/G1 phases (23 genes), and Developmental Biology (21 genes). Enriched pathway analysis of E2/NRF1/DEHP-responsive genes revealed the top pathways for gene involvement that includes: 1) Metabolism (21 genes), 2) Metabolic pathways (15 genes), 3) Disease (15 genes), 4) Immune System (12 genes), 5) Metabolism of proteins (11 genes), 6) Cell Cycle (9 genes), 7) Cellular response to stress (8 genes), 8) Cancer Pathways (8 genes), 9) Developmental Biology (8 genes), and 10) Cell cycle (5 genes) (Table 1).

Polychlorinated Biphenyls (PCBs) and Interactions with NRF1 Target Genes: There were 648 genes interacting with polychlorinated biphenyls (PCBs). The 433 PCBs genes are NRF1 target genes, and the 53 PCBs genes are common E2 and NRF1 target genes (Figure 1). Enriched pathway analysis of common PCBs/E2/NRF1-associated genes revealed the top pathways for gene involvement that included: 1) Cell Cycle (13 genes), 2) Mitotic M-M/G1 phases (9 genes), 3) DNA replication (4 genes), 4) Cell Cycle (4 genes), 5) DNA replication and repair (3 genes), and 6) Pancreatic cancer (3 genes) (Table 1).

Cadmium and Interactions with NRF1 Target Genes: Using CTD search we found 2458 genes interacting with cadmium (Cd). The 263 Cd interacting genes are NRF1 target genes and 143 interacting genes are common E2 and NRF1 target genes (Figure 1). GPR37 gene, a common Cd/E2/NRF1 gene, is associated with neurodegenerative disease [190]. Enriched pathway analysis of Cd/E2/NRF1 common genes revealed the top pathways that included: 1) Metabolism (26 genes), 2) Gene Expression (25 genes), 3) Disease (24 genes), 4) Signal Transduction (21 genes), 5) Metabolic

pathways (20 genes), 6) Immune System (18 genes), 7) Cell Cycle (17 genes), 8) Cancer Pathways (15 genes), 9) Developmental Biology (15 genes), 10) Metabolism of proteins (12 genes) (Table 1).

Arsenic and Interactions with NRF1 Target Genes: The CTD search revealed there were 4037 genes related to arsenic (As). The 520 As interacting genes are NRF1 target genes and the 190 As interacting genes are common E2 and NRF1 target genes (Figure 1). Enriched pathway analysis of As/E2/NRF1 common genes revealed the top pathways that included: 1) Metabolism (33 genes), 2) Immune System (30 genes), 3) Disease (27 genes), 4) Signal Transduction (24 genes), 5) Developmental Biology (22 genes), 6) Metabolic pathways (20 genes), 7) Cell Cycle (19 genes), 8) Gene Expression (19 genes), 9) Cancer Pathways (17 genes), and 10) Cellular responses to stress (16 genes) (Table 1).

Manganese and Interactions with NRF1 Target Genes: Using CTD search we found 462 genes interacting with manganese (Mn). The 50 Mn interacting genes are NRF1 target genes and the 30 Mn interacting genes are common E2 and NRF1 target genes (Figure 1). Enriched pathway analysis of common Mn/E2/NRF1 genes revealed the top pathways that included: 1) Cellular responses to stress (6 genes), 2) Developmental Biology (5 genes), 3) Tuberculosis (4 genes), 4) p53 signaling pathway (3 genes), Small cell lung cancer (3 genes), Apoptosis (3 genes), Cell cycle (3 genes) (Table 1).

Association of EDC interacting genes common to both E2- and NRF1 targets with Neurodegenerative Diseases: Table 2 summarizes EEDs modified genes, which are common E2 and NRF1 target genes and their involvement with the specific type of brain disease, such as AD, PD, HD, ALS, Autism Spectrum Disorder, and Brain

Neoplasms. Out of the 6643 E2 interacting genes, there were 1413 genes associated with nervous system disease.

The CTD search of E2 interacting genes in AD revealed 61 genes: ACE, ACHE, AMFR, **APBB2,** APOE, APP, ARC, ATP5A1, BAX, BCHE, BCL2, BDNF, BIN1,CALM1,CASP3,CHRNA7,CHRNB2,CLU,CRH,CYP46A1,DHCR24,**DPYSL2,EIF2S1,ENO1,**EPHA1,ESR1,F2,GAPDHS,GSK3B,HFE,HMOX1,IGF1,IGF1R,IGF2,IGF2R,IL1B,INS,INSR,LEP,MAOB,**MAPT,**MIR146A,MPO,NOS3,NPY,**PAXIP1,**PICALM,PLAU,PPARG,PRNP,**PSEN2**,SLC2A4,**SOD2,**SORL1,TF,**TFAM,TNF,**TPI1,TREM2,VEGFA,**VSNL**.The bold indicates E2 interacting genes which are NRF1 target genes. With AD, the six E2-responsive genes are NRF1 target genes: *APBB2, DPYSL2, EIF2S1, ENO1, MAPT, AND PAXIP1.* These genes are also responsive to the following EEDCs: ethinyl estradiol (*APBB2, DPYSL2, EIF2S1, ENO1, MAPT, and PAXIP1*), bisphenol-A (*APBB2, EIF2S1, ENO1, MAPT, and PAXIP1*), dibutyl phthalate (*DPYSL2, EIF2S1, ENO1),* diethylhexyl phthalate (*DPYSL2 and MAPT*), dibutyl phthalate (*DPYSL2, EIF2S1, ENO1*), cadmium (*ENO1*), arsenic (*ENO1 and MAPT*), and manganese (*MAPT*) (Table 5).

With PD, the eight E2-responsive NRF1 target genes are: *GAK, HSPA9, MAPT, PARK2, PARK7, PINK1, RPL14, AND VPS35*. These genes are also responsive to the following EEDCs: ethinyl estradiol (*HSPA9, MAPT*), bisphenol-A (*HSPA9, MAPT, RPL14),* dibutyl phthalate (*HSPA9, RPL14*), diethylhexyl phthalate (*HSPA9, MAPT*), cadmium (*RPL14*), and arsenic *(HSPA9* and *MAPT*) (Table 5). The CTD search revealed that PCBs-interacting nine genes: HMOX1, IL6, NQO1, RPS8, SLC18A2, SNCA,

SOD1, SOD2, TNF are associated with Parkinson Disease. Both SOD and TNF E2 interacting genes are NRF1 target genes.

With HD, the two E2-responsive NRF1 target genes are: *AIFM1* and *IP6K2*. These genes are also responsive to the following EEDCs: ethinyl estradiol (*AIFM1*), bisphenol-A (*AIFM1* and *IP6K2*), dibutyl phthalate (*IP6K2*), cadmium (*AIFM1*), and arsenic (*IP6K2*) (Table 2).

With ALS, the E2-responsive NRF1 target genes are *CHMP2B* and *GSR*. These genes are also responsive to the following EEDCs: ethinyl estradiol (*GSR*), bisphenol-A (*GSR* and *CHMP2B*), dibutyl phthalate (*GSR*), diethylhexyl phthalate (*GSR*), cadmium (*GSR*), and arsenic (*GSR*) (Table 2).

With ASD, the E2-responsive NRF1 target genes are *CIRBP*, *PCDH9*, and *GTF2I*. These genes are also responsive to the following EEDCs: ethinyl estradiol (*CIRBP and GTF2I*), bisphenol-A (*CIRBP, GTF2I, and PCDH9*), polychlorinated biphenyls (*CIRBP*), cadmium (*CIRBP*), and arsenic (*PCDH9*) (Table 2).

With brain neoplasms, the E2-responsive NRF1 target genes are *PCNA*, *PTCH1*, and *RELA*. These genes are also responsive to the following EEDCs: ethinyl estradiol (*PCNA and PTCH1),* bisphenol-A (*PCNA and RELA*), dibutyl phthalate (*PCNA and PTCH1*), cadmium (*RELA*), arsenic (PCNA and PTCH1), and manganese (*RELA*) (Table 2).

NRF1, Mitochondrial Dysfunction, and Neurodegenerative Disease

Mitochondria are known as the powerhouses of cells. They are important for cell viability and function [193]. They control cell process such as energy production, calcium signaling, and apoptosis [193]. Research has suggested that mitochondrial dysfunction is a

cause and not a result of neurodegenerative diseases [191] It is suggested mitochondrial dysfunction plays a major role, in AD, PD, HD, and ALS through the oxidative phosphorylation dysfunction [191]. Mitochondrial dysfunction may also increase ROS generation, cause abnormal protein-protein interactions, and may lead to loss of cellular integrity and cell death [194]. There is also evidence to suggest mitochondrial dysfunction may play a role in neuronal plasticity and maintenance [194]. Sex steroid have been observed to regulate mitochondrial function [195], and provide targets for estrogenic endocrine disruptors such as bisphenol-A, phthalates, polychlorinated biphenyls, metals, oral contraceptives, and hormonal replacement therapies [1]. NRF1 regulates the expression of nuclear genes that encode that encode mitochondrial proteins that function in metabolic pathways such as the trichloroacetic acid cycle (TCA), oxidative phosphorylation, heme synthesis, and in mitochondrial DNA replication and transcription (eg, mitochondrial transcription factor A [Tfam] [189,190]. Since mitochondrial dysfunction has been implicated as a possible pathway for neurodegenerative diseases [191], gene targets of NRF-1 directly affect brain health and may provide insight into mechanisms of these diseases.

NRF1-mediated Regulation of Neurogenesis and Synaptogenesis

Estrogen has been demonstrated to have a significant role in controlling neural progenitors in the developing embryonic brain. Estrogen has been shown to induce proliferation and differentiation of neural progenitor [196–198]. Neural progenitors have also been demonstrated to express estrogen receptors [197,198], which provide a site in EEDCs to exert their effects. EEDCs have been shown to cross the placental and blood brain barrier [6], but the mechanisms regarding the effects on the early stages of neural development are

largely not known. Studies suggest neural development is affected by exposures to EEDCs. Low-dose exposure to bisphenol-A and S has been shown to induce hypothalamic neurogenesis in an embryonic zebrafish at a point in time analogous to the second trimester of human development [199]. Several classes of phthalates were shown to prevent neural stem cell proliferation in a rat mesencephalic stem cell model [200]. Polychlorinated biphenyls have also been demonstrated to interfere with neuronal cell differentiation in a rat embryonic neural stem cell model [201]. Arsenic was shown to substantially inhibited neuronal differentiation in human embryonic neural stem cells [202]. Manganese has also been demonstrated to cause cell death in a rat neural stem cell model through a mitochondrial-mediated pathway [203]. The generation of new neurons from neural progenitor stem cells, the growth of axons and dendrites and the formation and reorganization of synapses are examples of neuroplasticity. All these processes seem to be regulated by nuclear respiratory factor 1 (NRF1) target network genes. For example, recently, it has been shown that NRF1 regulates neurite outgrowth - a critical process in neuronal development in neuroblastoma cells and hippocampal neurons by regulating its target gene, Synapsin 1[204]. Another fifteen genes involved in different biological processes of neurons, cell cycle-related genes- MAPRE3, NPDC1, SUV39H2, SKA3, transport-related genes- RAB3IP, TRAPPC3, signal transduction-related genes- SMAD5, PIP5K1A, USP10, SPRY4, transcription-related genes- GTF2F2, NR1D1, and regulation of GTPase activity-related genes- RHOA, RAPGEF6, SMAP1, have been reported to contain NRF1 binding motif(s) in their promoters and mRNA levels of 12 of these genes are regulated by NRF1 [205]. Overexpression or knockdown of MAPRE3, NPDC1, SMAD5, USP10, SPRY4, GTF2F2, SKA3, RAPGEF6 positively regulates, where as

RHOA and SMAP1 negatively regulates neurite outgrowth. Three hypothetical genes - FAM134C, C3orf10, and ENOX1 involved in neurite outgrowth are regulated by NRF1. FAM134C positively regulates and C3orf10 negatively regulates neurite outgrowth [206] In summary, it appears that NRF1 regulates neurite outgrowth through cell cycle-, transport-, signal transduction-, transcription-, regulation of GTPase activity-related genes and hypothetical genes. This suggests that NRF1 regulates neuronal differentiation through a variety of biological processes.

Gender Bias and NRF1 Regulated Genes-EEDC Interactions in AD

Sex differences in nervous system diseases, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease, exist in prevalence, severity, and progression of pathologies and consequently has become a major obstacle for the treatment. Cognitive disturbances are frequent in brain health deficit-related disease. Men show greater cognitive impairment in schizophrenia, whereas women show more severe dementia and cognitive decline with Alzheimer's disease. Alzheimer's disease (AD) disproportionally affects women (F:M ≈2:1) and the total number of Americans aged 65 years and older with AD is projected to increase from 5.1 million to 13.8 million by 2050 [207]Despite tremendous progress in understanding the pathogenesis of AD, the molecular basis underlying the sex-dependent differences in AD remains largely unknown. and consequently, has become a major obstacle for the development of new sex-based molecular targets of AD.

NRF1 and Estrogen Responsive Genes in the AD Pathway

Many genes modified by EEDs are common targets of both (E2) and NRF1 and some of these genes are involved with the specified brain diseases. Therefore, using

NRF1-EDC interacting genes identified from CTD (Table 4), we focused our efforts on AD and conducted enrichment pathway analysis, which revealed that many of the NRF1 target genes interacting with each specific EEDC and they are part of pathway of AD (Figures 2–7). Enrichment pathway analysis was performed using Cytoscape and Genemania. The search of enriched pathways showed that top 10 E2 interacting genes in AD: *APOE, APP, ATP5A1, CALM1, CASP3, GSK3B, IL1B, MAPT, PSEN2* and *TNF* underlie the enrichment of the Kyoto Encyclopedia of Genes and Genomes (KEGG) Alzheimer's disease pathway. With AD, the six E2-responsive genes are NRF1 target genes: *APBB2, DPYSL2, EIF2S1, ENO1, MAPT, AND PAXIP1*. These genes are also responsive to the following EEDs: ethinyl estradiol (*APBB2, DPYSL2, EIF2S1, ENO1, MAPT,* and *PAXIP1) BPA (APBB2, EIF2S1, ENO1, MAPT,* and *PAXIP1*), dibutyl phthalate (*DPYSL2, EIF2S1, ENO1*), diethylhexyl phthalate (*DPYSL2* and *MAPT*), dibutyl phthalate (*DPYSL2, EIF2S1, ENO1*) (Figures 2–7, Table 2). GO annotations of E2 and NRF1 enrichment network genes of EEDs revealed multiple common E2 and NRF1 genes associated with carbohydrate metabolic pathways, which was common among all EEDCs (Figures 2–7). Other two biological process pathways showing association with multiple common E2 and NRF1 genes interacting with E2, EE, BPA or phthalates were translation (translation initiation, translation initiation factory activity and translation factory activity, nucleic acid binding) and glial/oligodendrocytes growth and differentiation (Figures 2–7). To validate our CTD findings, we used Bayesian network (BN) analysis [208] of microarray data of 79 subjects from the Gene Expression Omnibus (GEO) database [209], which showed the female NRF1 gene network is different from the male network. It was also observed that both NRF1 expression and gender were

associated with AD (Figure 8). Genes associated with AD – APLP1, APP, GRIN1, GRIN2B, MAPT, PSEN2, PEN2, and IDE are also NRF1-regulated and E2-responsive and may contribute to NRF1 gender differences and may play a role in the prevention of AD by E2.

Conclusions

Estrogenic endocrine disrupting chemicals go further than the known novel mechanisms of endocrine disruption. Gene-gene and gene-environment provide alternative paths for endocrine disruption. Bioinformatics analysis of gene-EEDCs interactions and brain disease associations identified numerous NRF1 regulated genes that were altered by exposure to estrogen, phthalate, BPA, and metalloestrogens. EEDC-modified genes in brain health deficits are part of estrogen and nuclear respiratory factor 1 signaling pathways. Our findings suggest that in addition to estrogen signaling, these chemicals influence NRF1 factor regulated communities of genes across genomic and epigenomic multiple networks may contribute in the development of complex chronic human brain health deficits.

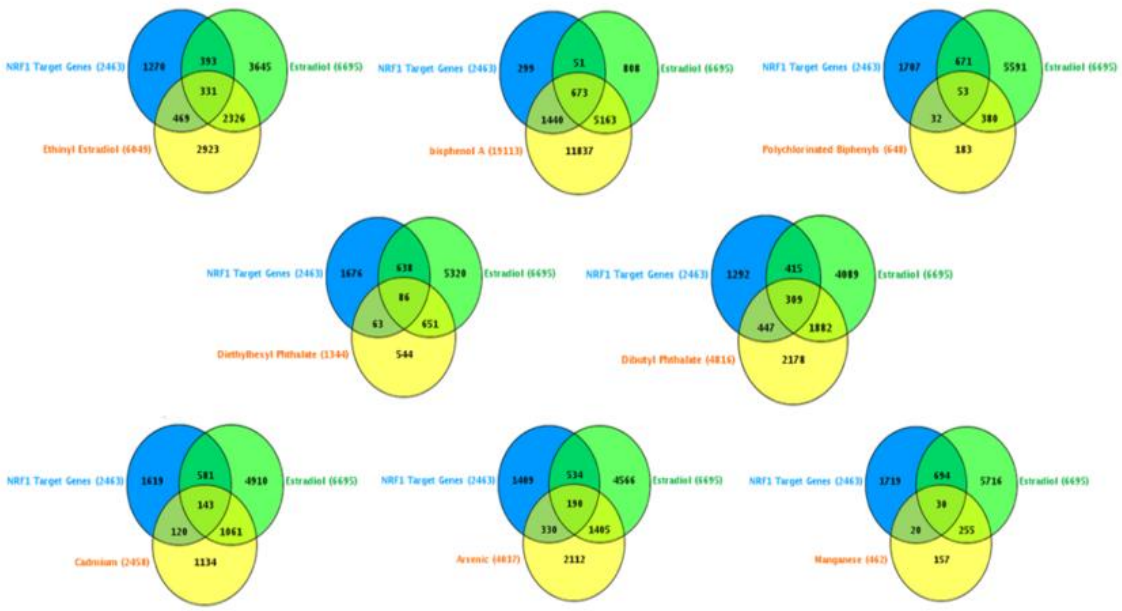
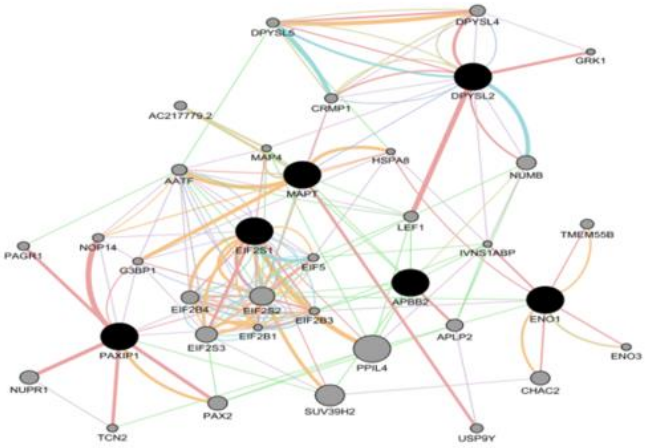
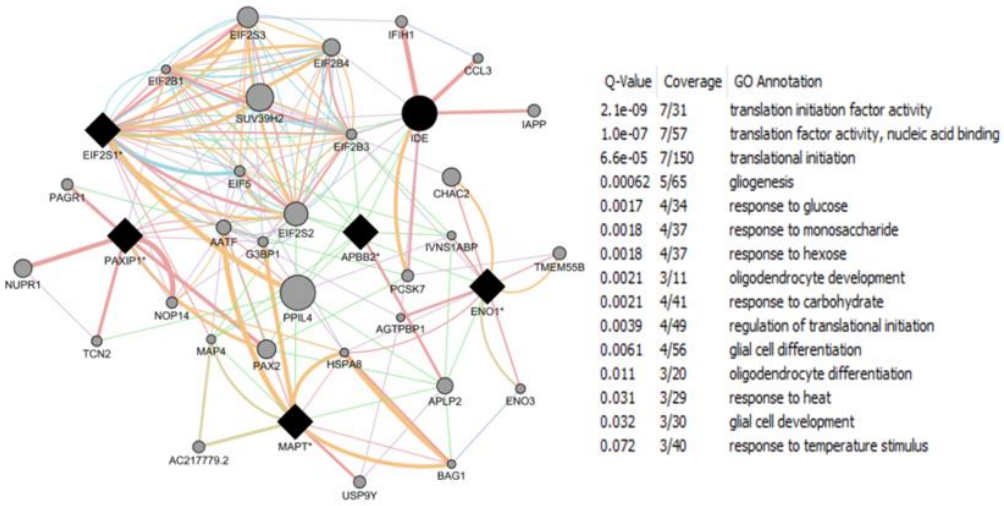


Figure 1: A Venn diagram showing the individual pharmacological estrogen or estrogenic Endocrine Disruptor (EED) modified genes common to both NRF1 and/or estrogen signaling pathways. NRF1 target genes were mapped between 17-beta estradiol (E2) and pharmacological estrogen ethinyl estradiol or PCBs or BPA or phthalates or Cd or As or Mn.



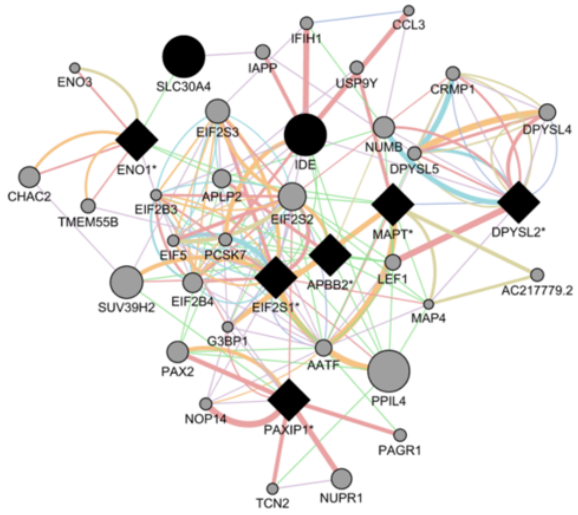
Q-Value	Coverage	GO Annotation
2.1e-09	7/31	translation initiation factor activity
1.0e-07	7/57	translation factor activity, nucleic acid binding
6.6e-05	7/150	translational initiation
0.00029	5/56	glial cell differentiation
0.00050	5/65	gliogenesis
0.0015	4/34	response to glucose
0.0015	4/37	response to monosaccharide
0.0015	4/37	response to hexose
0.0019	3/11	oligodendrocyte development
0.0019	4/41	response to carbohydrate
0.0036	4/49	regulation of translational initiation
0.011	3/20	oligodendrocyte differentiation
0.031	3/29	response to heat
0.032	3/30	glial cell development
0.057	4/106	positive regulation of cell development
0.068	3/40	response to temperature stimulus

Figure 2. Gene set pathway enrichment analysis of 17-beta estradiol (E2) responsive NRF1 target genes associated with Alzheimer Disease (AD). E2 responsive NRF1 genes are in black. The network includes the top 30 related genes. Right panel show GO annotations of NRF1 enrichment network genes of E2 associated with biological process pathways involving multiple E2 and NRF1 genes and Q-value as a probability showing number of genes out of the total genes annotated to each GO term.



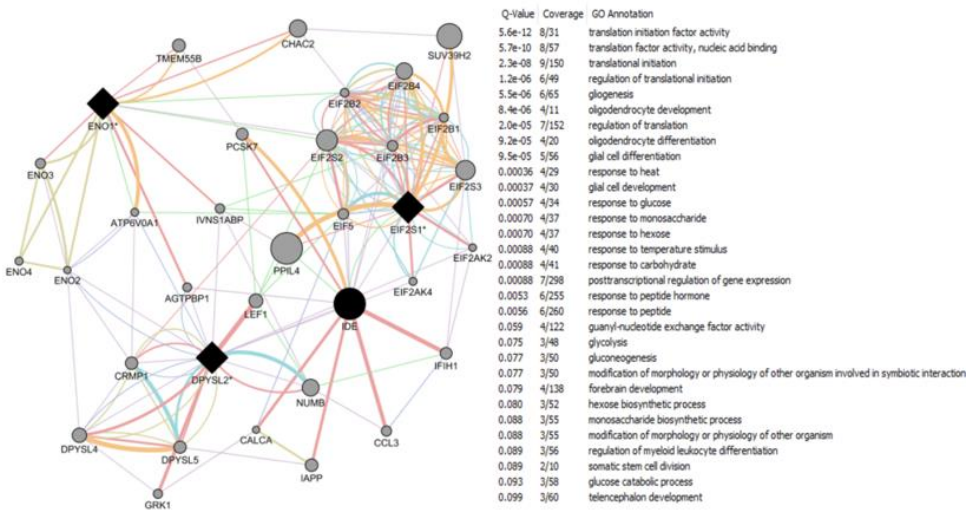
Q-Value	Coverage	GO Annotation
2.1e-09	7/31	translation initiation factor activity
1.0e-07	7/57	translation factor activity, nucleic acid binding
6.6e-05	7/150	translational initiation
0.00062	5/65	gliogenesis
0.0017	4/34	response to glucose
0.0018	4/37	response to monosaccharide
0.0018	4/37	response to hexose
0.0021	3/11	oligodendrocyte development
0.0021	4/41	response to carbohydrate
0.0039	4/49	regulation of translational initiation
0.0061	4/56	glial cell differentiation
0.011	3/20	oligodendrocyte differentiation
0.031	3/29	response to heat
0.032	3/30	glial cell development
0.072	3/40	response to temperature stimulus

Figure 3. Gene set pathway enrichment analysis of ethinyl estradiol responsive E2 and NRF1 common target genes associated with Alzheimer Disease (AD). Ethinyl estradiol responsive NRF1 genes are in black. Genes denoted by a diamond-shaped node are E2 and NRF1. The network includes the top 30 related genes. Right panel show GO annotations of E2 and NRF1 enrichment network genes of ethinyl estradiol associated with biological process pathways involving multiple E2 and NRF1 genes and Q-value as a probability showing number of genes out of the total genes annotated to each GO term.



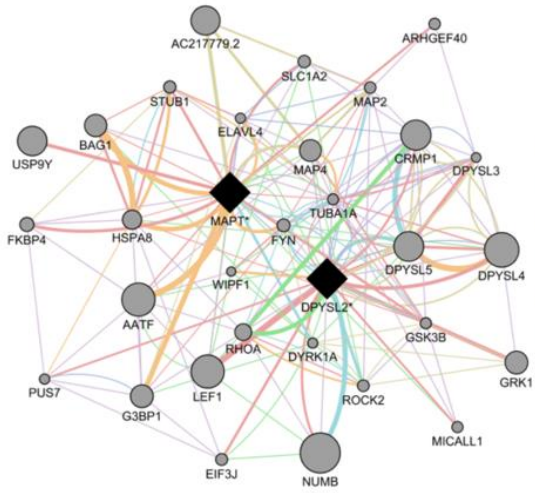
Q-Value	Coverage	GO Annotation
5.2e-07	6/31	translation initiation factor activity
1.2e-05	6/57	translation factor activity, nucleic acid binding
0.0011	5/65	gliogenesis
0.0022	6/150	translational initiation
0.017	4/56	glial cell differentiation
0.12	3/37	response to monosaccharide
0.12	3/34	response to glucose
0.12	4/106	positive regulation of cell development
0.12	3/37	response to hexose
0.14	3/41	response to carbohydrate

Figure 4. Gene set pathway enrichment analysis of bisphenol-A (BPA) responsive R2 and NRF1common target genes associated with Alzheimer Disease (AD). Bisphenol-A responsive NRF1 genes are in black. Genes denoted by a diamond-shaped node are E2 and NRF1 responsive. The network includes the top 30 related genes. Right panel show GO annotations of E2 and NRF1 enrichment network genes of BPA associated with biological process pathways involving multiple E2 and NRF1 genes and Q-value as a probability showing number of genes out of the total genes annotated to each GO term.



Q-Value	Coverage	GO Annotation
5.6e-12	8/31	translation initiation factor activity
5.7e-10	8/57	translation factor activity, nucleic acid binding
2.3e-08	9/150	translational initiation
1.2e-06	6/49	regulation of translational initiation
5.5e-06	6/65	gliogenesis
8.4e-06	4/11	oligodendrocyte development
2.0e-05	7/152	regulation of translation
9.2e-05	4/20	oligodendrocyte differentiation
9.5e-05	5/56	glial cell differentiation
0.00036	4/29	response to heat
0.00037	4/30	glial cell development
0.00057	4/34	response to glucose
0.00070	4/37	response to monosaccharide
0.00070	4/37	response to hexose
0.00088	4/40	response to temperature stimulus
0.00088	4/41	response to carbohydrate
0.00088	7/298	posttranscriptional regulation of gene expression
0.0053	6/255	response to peptide hormone
0.0056	6/260	response to peptide
0.059	4/122	guanyl-nucleotide exchange factor activity
0.075	3/48	glycolysis
0.077	3/50	gluconeogenesis
0.077	3/50	modification of morphology or physiology of other organism involved in symbiotic interaction
0.079	4/138	forebrain development
0.080	3/52	hexose biosynthetic process
0.088	3/55	monosaccharide biosynthetic process
0.088	3/55	modification of morphology or physiology of other organism
0.089	3/56	regulation of myeloid leukocyte differentiation
0.089	2/10	somatic stem cell division
0.093	3/58	glucose catabolic process
0.099	3/60	telencephalon development

Figure 5. Gene set pathway enrichment analysis of dibutyl phthalate modified E2 and NRF1 common target genes associated with Alzheimer Disease (AD). Dibutyl phthalate responsive NRF1 genes are in black. Genes denoted by a diamond-shaped node are E2 and NRF1 responsive. The network includes the top 30 related genes. Right panel show GO annotations of E2 and NRF1 enrichment network genes of dibutyl phthalate associated with biological process pathways involving multiple E2 and NRF1 genes and Q-value as a probability showing number of genes out of the total genes annotated to each GO term.



Q-Value	Coverage	GO Annotation
0.17	3/45	growth cone
0.17	4/138	forebrain development
0.17	5/255	regulation of nervous system development
0.17	3/47	site of polarized growth
0.17	4/106	positive regulation of cell development
0.17	5/218	microtubule cytoskeleton organization
0.17	4/144	regulation of neuron projection development
0.17	4/124	protein folding
0.17	5/227	regulation of neurogenesis
0.17	3/52	negative regulation of cell projection organization

Figure 6. Gene set pathway enrichment analysis of diethylhexyl phthalate responsive E2 and NRF1 common target genes associated with Alzheimer Disease (AD). Diethylhexyl phthalate responsive NRF1 genes are in black. Genes denoted by a diamond-shaped node are E2 and NRF1 responsive. The network includes the top 30 related genes. Right panel show GO annotations of E2 and NRF1 enrichment network genes of diethylhexyl phthalate associated with biological process pathways involving multiple E2 and NRF1 genes and Q-value as a probability showing number of genes out of the total genes annotated to each GO term.

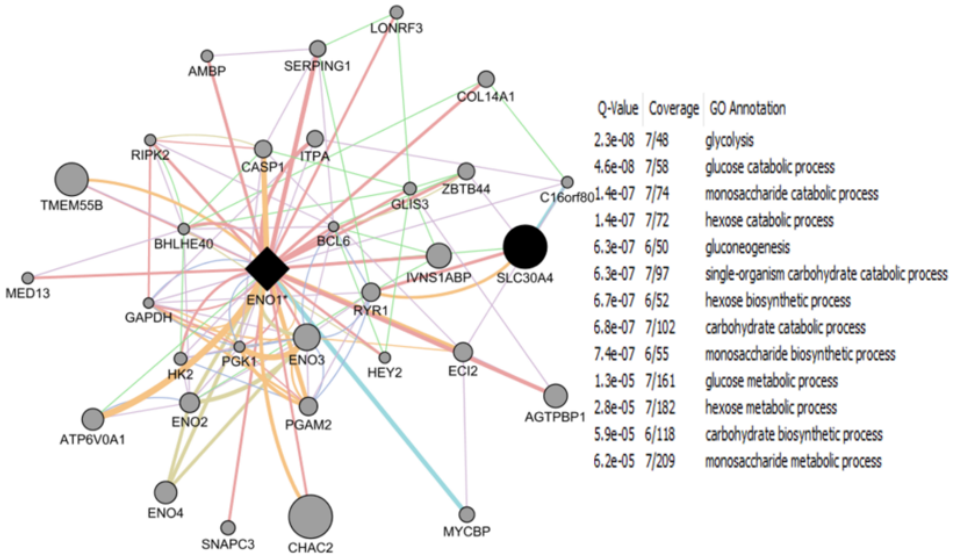


Figure 7. Gene set pathway enrichment analysis of cadmium responsive E2 and NRF1 common target genes associated with Alzheimer Disease (AD). Cadmium responsive NRF1 genes are in black. Genes denoted by a diamond-shaped node are E2-and NRF1 responsive. The network includes the top 30 related genes. Right panel show GO annotations of E2 and NRF1 enrichment network genes of cadmium associated with biological process pathways involving multiple E2 and NRF1 genes and Q-value as a probability showing number of genes out of the total genes annotated to each GO term.

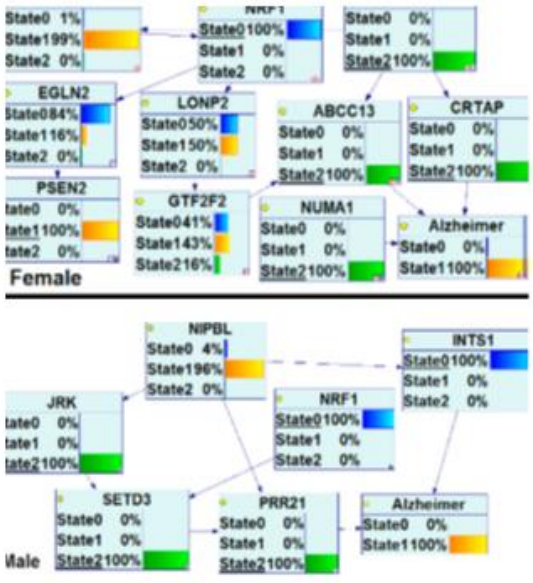


Figure 8. Gender differences in the NRF1 network from brain microarray data of 79 male and female AD subjects and controls from the GEO database.

Table 1: Top 10 enriched pathways for E2 and NRF1-Target Genes Associated with Estrogenic Endocrine Disruptors – BPA, PCB, Phthalates, As, Cd, and Mn		
17 Beta-estradiol (E2) interacting NRF1 target genes		
KEGG Pathway	**Number of genes:**	**Annotated Genes**
Disease	86	ADCY9|AKT2|ALDOA|AP1S1|CCNT2|CDC42|CDK1|CDKN2B|CHMP2A|CHMP2B|CHMP5|CREB1|CSK|CSNK1A1|CTBP1|CYB5A|ENO1|EPS15L1|ERCC2|EXT2|FASN|FZD4|GLB1|GTF2E2|HDAC2|HDAC3|HDAC4|HMMR|HRAS|HSP90AA1|IRS1|MAP2K7|MKNK1|MMADHC|MTHFD1|NAMPT|NPM1|NUP107|NUP50|OS9|P4HB|PAPSS1|PFKFB4|PIP5K1B|PLCG1|POLR2A|POM121|PPIA|PRKAR2A|PSENEN|PYGL|RAC1|RAE1|RAF1|RAN|RBX1|RHOA|RPL10|RPL13A|RPL14|RPL36|RPS13|RPS16|RPS21|RPS29|RPS9|SHC1|SLC25A10|SLC37A4|SMARCA4|SNW1|SOS1|SRC|STUB1|STX1A|TAF12|TAF5|TCEB2|TGIF1|TNKS2|TPR|UBA52|WNT5A|XRCC5|XRCC6|YWHAZ
Metabolism	86	ACADM|ADCY9|ADI1|AGPAT5|AKR7A2|ALAS1|ALDOA|AMACR|ATP5O|AUH|BCAT1|BCAT2|BSG|CBR1|COX5B|COX6C|CTPS1|CYB5A|CYCS|DTYMK|ELOVL4|ENO1|ERCC2|ETFB|ETFDH|EXT2|FASN|FDPS|GCLC|GLB1|GNG5|GPD1L|GSR|GSS|GSTM3|HDAC3|HMMR|HSD17B4|HSP90AA1|INPP5A|INPP5K|IP6K2|LDHA|LPCAT3|LSS|MGST3|MMADHC|MPC2|MTHFD1|NAMPT|NDUFA3|NDUFB4|NUBP1|NUP107|NUP50|OAZ2|ODC1|P4HB|PAICS|PAPSS1|PDHB|PFKFB4|PIP5K1B|PLA2G12A|PLCG1|PLD1|POM121|PPAT|PRKAR2A|PSAP|PYGL|RAE1|RAN|SDHA|SGMS1|SIN3B|SLC16A1|SLC25A10|SLC37A4|SLC44A2|STX1A|SUCLA2|TPMT|TPR|UBA52|VAPB
Gene Expression	77	CCNT2|CDKN2B|CNOT1|DHX9|DNMT1|EEF1A1|EEF1D|EEF1G|EIF2S1|EIF2S2|EIF3K|EIF4E|EIF4G1|ERCC2|ESRRA|EXOSC2|EZH2|FARSB|GEMIN4|GTF2E2|HARS|HDAC2|HNRNPA1|HNRNPH1|HNRNPU|HSPA8|LSM2|MARS2|MED20|MED4|NR1D1|PCBP2|POLR1A|POLR2A|POLRMT|PPA1|PTBP1|RAN|RBBP4|RBBP7|RNPS1|RPL10|RPL13A|RPL14|RPL36|RPS13|RPS16|RPS21|RPS29|RPS9|RUNX2|SAP18|SARS|SEC61G|SET|SIN3B|SNW1|SRRM1|SRSF1|TAF12|TAF5|TARS|TCEB2|TGIF1|THRA|TRAM1|U2AF1|UBA52|UPF1|UPF2|VARS2|XPO5|YWHAZ|ZNF610|ZNF658|ZNF711|ZNF750
Signal Transduction	72	ABI1|ADCY9|AKT2|ARHGDIA|BRK1|CASP2|CCNT2|CDC42|CDK1|CDKN2B|CREB1|CRK|CRKL|CSK|CSNK1A1|CTBP1|DAAM1|DGKH|E2F1|EIF4E|EIF4G1|EPS15L1|FSTL3|FZD4|GNG5|GPR37|HDAC2|HDAC3|HDAC4|HRAS|HSP90AA1|IRS1|JAK2|LFNG|MAPK7|MEF2A|MKNK1|OS9|P4HB|PFN1|PIP5K1B|PLCG1|PRDM4|PRKAR2A|PSAP|PSENEN|PTCH1|PTK2|RAC1|RAF1|RBX1|RELA|RHOA|RIPK2|ROCK1|RPS6KA5|RPS6KB1|SHC1|SMARCA4|SNW1|SOCS1|SOS1|SRC|STARD13|STUB1|TGIF1|THBS2|TNKS2|TRIO|UBA52|WNT5A|YWHAZ
Immune System	67	ABI1|ADCY9|AKT2|ANAPC1|ANAPC11|AP1S1|ARPC2|ARPC5|BRK1|CASP2|CDC34|CDC42|CDK1|CREB1|CRK|CRKL|CSK|CTSD|DHX9|DYNLL1|EIF4E|EIF4G1|FADD|FZR1|HRAS|HSP90AA1|IP6K2|IRS1|JAK2|KIF18A|KIF4A|MAP2K7|MAPK7|MEF2A|NUP107|NUP50|PCBP2|PELI1|PLCG1|PLD1|POM121|PRKAR2A|PRKDC|PTK2|PVR|RAC1|RAE1|RAF1|RBX1|RELA|RIPK2|RNF19B|RPS6KA5|SEC61G|SHC1|SOCS1|SOS1|SRC|STUB1|TCEB2|TPR|TUBB4B|UBA52|UBE2D4|XRCC5|XRCC6|YWHAZ
Cell Cycle	62	ANAPC1|ANAPC11|APITD1|ATM|AURKA|AURKB|BUB1|CCNB1|CCNE1|CDC7|CDK1|CDKN2B|CDKN2D|CDT1|CENPN|CKS1B|CLASP2|DKC1|DSN1|DYNLL1|E2F1|ERCC6L|FBXO5|FZR1|GOLGA2|HSP90AA1|KIF18A|LIN37|MAD2L1|MCM2|MCM4|MCM6|MLH3|NEK2|NPM1|NUP107|NUP50|OIP5|ORC6|PCNA|PLK4|POLA1|POM121|PPP1R

		12A|RAB1B|RAD50|RAE1|RBBP4|RBBP7|RBBP8|RBL2|RSF1|SDCCAG8|SET|SMC4|SPC24|SPDL1|TPR|TUBB|TUBB4B|UBA52|ZWINT
Metabolic pathways	62	: ACADM|ADI1|ALAS1|ALDOA|AMACR|ATP5O|AUH|BCAT1|BCAT2|CBR1|COX5B|COX6A2|COX6C|CTPS1|HAD1|DGKH|DNMT1|DTYMK|ENO1|EXT2|FASN|FBL|FDPS|FUT8|GAA|GCLC|GFPT1|GLB1|GSS|HSD17B4|INPP5A|INPP5K|LAP3|LDHA|LSS|MECR|MTHFD1|NDUFA3|NDUFB4|ODC1|PAICS|PAPSS1|PDHB|PGAM5|PGAP1|PIGA|PIP5K1B|PLA2G12A|PLCG1|PLD1|POLA1|POLE4|POLG2|POLR1A|POLR2A|PPAT|SDHA|SGMS1|SHMT2|SUCLA2|SUFU|TGDS
Metabolism of proteins	48	B3GNTL1|CCT3|CCT6A|CCT8|CTSD|HAD1|DDIT3|DNAJB9|DNAJC3|DOHH|EEF1A1|EEF1D|EEF1G|EIF2S1|EIF2S2|EIF3K|EIF4E|EIF4G1|EIF5A|FBXW5|FUT8|GFPT1|GLB1|GRPEL2|HSPA9|HSPD1|IGFBP3|MANEA|PFDN1|PGAP1|PIGA|RPL10|RPL13A|RPL14|RPL36|RPS13|RPS16|RPS21|RPS29|RPS9|SEC61G|SHC1|STX1A|THBS2|TRAM1|TSPYL2|TUBB4B|UBA52
Developmental Biology	42	ABLIM2|AKT2|ARPC2|ARPC5|CDC42|CDK1|CLASP2|CREB1|CRMP1|CTNNA2|DPYSL2|HDAC3|HRAS|HSP90AA1|HSPA8|ITGA1|KIF4A|MED11|MED18|MED20|MED4|MEF2A|MYH10|MYH14|NRTN|PFN1|PLCG1|PSENEN|PTK2|RAC1|RAF1|RHOA|ROCK1|RPS6KA5|RPS6KA6|SCN3B|SDCBP|SIAH2|SOS1|SPTAN1|SRC|TRIO|TUBB4B
Mitotic M-M/G1 phases	35	ANAPC1|ANAPC11|APITD1|AURKB|BUB1|CCNB1|CDC7|CDK1|CDT1|CENPN|CLASP2|DSN1|ERCC6L|FBXO5|GOLGA2|KIF18A|MAD2L1|MCM2|MCM4|MCM6|NUP107|NUP50|ORC6|POLA1|POM121|RAB1B|RAE1|SET|SMC4|SPC24|SPDL1|TPR|TUBB4B|UBA52|ZWINT
Ethinyl estradiol interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of Genes:**	**Annotated Genes**
Metabolism	49	ACADM|ADCY9|AGPAT5|ALAS1|ALDOA|ATP5O|BCAT1|BSG|CBR1|COX5B|COX6C|CTPS1|CYB5A|CYCS|ENO1|ERCC2|ETFDH|EXT2|FASN|FDPS|GCLC|GLB1|GSR|GSS|GSTM3|HDAC3|HSD17B4|HSP90AA1|INPP5A|LDHA|LSS|MGST3|MTHFD1|NAMPT|NUP50|ODC1|P4HB|PAPSS1|PDHB|PPAT|PSAP|PYGL|RAE1|RAN|SGMS1|SIN3B|SLC16A1|SLC25A10|SLC37A4
Disease	48	:ADCY9|AKT2|ALDOA|AP1S1|CDC42|CDK1|CHMP2A|CREB1|CSK|CSNK1A1|CYB5A|ENO1|ERCC2|EXT2|FASN|GLB1|GTF2E2|HDAC2|HDAC3|HRAS|HSP90AA1|MAP2K7|MTHFD1|NAMPT|NPM1|NUP50|OS9|P4HB|PAPSS1|PSENEN|PYGL|RAE1|RAN|RBX1|RHOA|RPL36|RPS16|RPS9|SLC25A10|SLC37A4|SMARCA4|STUB1|TAF12|TAF5|TCEB2|WNT5A|XRCC5|YWHAZ
Gene Expression	43	DNMT1|EEF1A1|EEF1G|EIF2S1|EIF2S2|EIF3K|EIF4E|ERCC2|EZH2|FARSB|GTF2E2|HARS|HDAC2|HNRNPA1|HNRNPH1|HNRNPU|HSPA8|MED4|NR1D1|PCBP2|POLR1A|POLRMT|RAN|RBBP4|RBBP7|RNPS1|RPL36|RPS16|RPS9|SAP18|SARS|SEC61G|SET|SIN3B|SRSF1|TAF12|TAF5|TARS|TCEB2|THRA|UPF1|VARS2|YWHAZ
Immune System	36	ABI1|ADCY9|AKT2|ANAPC1|ANAPC11|AP1S1|ARPC2|ARPC5|CASP2|CDC42|CDK1|CREB1|CRK|CSK|CTSD|DYNLL1|EIF4E|FADD|FZR1|HRAS|HSP90AA1|MAP2K7|MAPK7|NUP50|PCBP2|PTK2|PVR|RAE1|RBX1|SEC61G|SOCS1|STUB1|TCEB2|TUBB4B|XRCC5|YWHAZ
Cell Cycle	35	

		ANAPC1|ANAPC11|AURKB|BUB1|CCNB1|CCNE1|CDC7|CDK1|CDT1|CKS1B|DYNLL1|E2F1|FZR1|GOLGA2|HSP90AA1|LIN37|MAD2L1|MCM2|MCM4|MCM6|NPM1|NUP50|ORC6|PCNA|PLK4|PPP1R12A|RAE1|RBBP4|RBBP7|RBBP8|RSF1|SET|SPC24|SPDL1|TUBB4B
Metabolic pathways	33	ACADM|ALAS1|ALDOA|ATP5O|BCAT1|CBR1|COX5B|COX6C|CTPS1|DNMT1|ENO1|EXT2|FASN|FDPS|GCLC|GLB1|GSS|HSD17B4|INPP5A|LDHA|LSS|MECR|MTHFD1|ODC1|PAPSS1|PDHB|PGAM5|PIGA|POLE4|POLG2|POLR1A|PPAT|SGMS1
Signal Transduction	33	ABI1|ADCY9|AKT2|CASP2|CDC42|CDK1|CREB1|CRK|CSK|CSNK1A1|E2F1|EIF4E|HDAC2|HDAC3|HRAS|HSP90AA1|MAPK7|OS9|P4HB|PFN1|PRDM4|PSAP|PSENEN|PTCH1|PTK2|RBX1|RHOA|SMARCA4|SOCS1|STUB1|TRIO|WNT5A|YWHAZ
Metabolism of proteins	28	B3GNTL1|CCT3|CCT6A|CCT8|CTSD|DDIT3|DNAJC3|EEF1A1|EEF1G|EIF2S1|EIF2S2|EIF3K|EIF4E|EIF5A|FBXW5|GLB1|GRPEL2|HSPA9|HSPD1|IGFBP3|PFDN1|PIGA|RPL36|RPS16|RPS9|SEC61G|TSPYL2|TUBB4B
Developmental Biology	25	AKT2|ARPC2|ARPC5|CDC42|CDK1|CREB1|CTNNA2|HDAC3|HRAS|HSP90AA1|HSPA8|ITGA1|MED11|MED4|MYH10|NRTN|PFN1|PSENEN|PTK2|RHOA|RPS6KA6|SDCBP|SIAH2|TRIO|TUBB4B
Bisphenol A interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of genes:**	**Annotated Genes**
Metabolism	85	ACADM|ADCY9|ADI1|AGPAT5|AKR7A2|ALAS1|ALDOA|AMACR|ATP5O|BCAT1|BCAT2|BSG|CBR1|COX5B|COX6C|CTPS1|CYB5A|CYCS|DTYMK|ELOVL4|ENO1|ERCC2|ETFB|ETFDH|EXT2|FASN|FDPS|GCLC|GLB1|GNG5|GPD1L|GSR|GSS|GSTM3|HDAC3|HMMR|HSD17B4|HSP90AA1|INPP5A|INPP5K|IP6K2|LDHA|LPCAT3|LSS|MGST3|MMADHC|MPC2|MTHFD1|NAMPT|NDUFA3|NDUFB4|NUBP1|NUP107|NUP50|OAZ2|ODC1|P4HB|PAICS|PAPSS1|PDHB|PFKFB4|PIP5K1B|PLA2G12A|PLCG1|PLD1|POM121|PPAT|PRKAR2A|PSAP|PYGL|RAE1|RAN|SDHA|SGMS1|SIN3B|SLC16A1|SLC25A10|SLC37A4|SLC44A2|STX1A|SUCLA2|TPMT|TPR|UBA52|VAPB
Disease	84	ADCY9|AKT2|ALDOA|AP1S1|CCNT2|CDC42|CDK1|CDKN2B|CHMP2A|CHMP2B|CHMP5|CREB1|CSK|CSNK1A1|CTBP1|CYB5A|ENO1|ERCC2|EXT2|FASN|FZD4|GLB1|GTF2E2|HDAC2|HDAC3|HDAC4|HMMR|HRAS|HSP90AA1|IRS1|MAP2K7|MKNK1|MMADHC|MTHFD1|NAMPT|NPM1|NUP107|NUP50|OS9|P4HB|PAPSS1|PFKFB4|PIP5K1B|PLCG1|POLR2A|POM121|PPIA|PRKAR2A|PSENEN|PYGL|RAC1|RAE1|RAF1|RAN|RBX1|RHOA|RPL13A|RPL14|RPL36|RPS13|RPS16|RPS21|RPS29|RPS9|SHC1|SLC25A10|SLC37A4|SMARCA4|SNW1|SOS1|SRC|STUB1|STX1A|TAF12|TAF5|TCEB2|TGIF1|TNKS2|TPR|UBA52|WNT5A|XRCC5|XRCC6|YWHAZ
Gene Expression	71	CCNT2|CDKN2B|CNOT1|DHX9|DNMT1|EEF1A1|EEF1D|EEF1G|EIF2S1|EIF2S2|EIF3K|EIF4E|EIF4G1|ERCC2|ESRRA|EXOSC2|EZH2|FARSB|GEMIN4|GTF2E2|HARS|HDAC2|HNRNPA1|HNRNPH1|HNRNPU|HSPA8|LSM2|MARS2|MED20|MED4|NR1D1|PCBP2|POLR1A|POLR2A|PPA1|PTBP1|RAN|RBBP4|RBBP7|RNPS1|RPL13A|RPL14|RPL36|RPS13|RPS16|RPS21|RPS29|RPS9|RUNX2|SAP18|SARS|SEC61G|SET|SIN3B|SNW1|SRRM1|SRSF1|TAF12|TAF5|TARS|TCEB2|TGIF1|THRA|TRAM1|U2AF1|UBA52|UPF1|UPF2|XPO5|YWHAZ|ZNF711
Signal Transduction	68	ABI1|ADCY9|AKT2|ARHGDIA|BRK1|CASP2|CCNT2|CDC42|CDK1|CDKN2B|CREB1|CRK|CRKL|CSK|CSNK1A1|CTBP1|DAAM1|DGKH|E2F1|EIF4E|EIF4G1|FSTL3|FZD4|GNG5|GPR37|HDAC2|HDAC3|HDAC4|HRAS|HSP90AA1|IRS1|JAK2|LFNG|MAPK7|MKNK1|OS9|P4HB|PFN1|PIP5K1B|PLCG1|PRKAR2A|PSAP|PSENEN|PTCH1|PTK2|RAC1|RAF1|RBX1|RELA|RHOA|RIPK2|ROCK1|RPS6KA5|RPS6KB1|SHC1|SMARCA4|SNW1|SOCS1|SOS1|SRC|STARD13|STUB1|TGIF1|THBS2|TNKS2|UBA52|WNT5A|YWHAZ

Immune System	66	ABI1|ADCY9|AKT2|ANAPC1|ANAPC11|AP1S1|ARPC2|ARPC5|BRK1|CASP2|CDC34|CDC42|CDK1|CREB1|CRK|CRKL|CSK|CTSD|DHX9|DYNLL1|EIF4E|EIF4G1|FADD|FZR1|HRAS|HSP90AA1|IP6K2|IRS1|JAK2|KIF18A|KIF4A|MAP2K7|MAPK7|NUP107|NUP50|PCBP2|PELI1|PLCG1|PLD1|POM121|PRKAR2A|PRKDC|PTK2|PVR|RAC1|RAE1|RAF1|RBX1|RELA|RIPK2|RNF19B|RPS6KA5|SEC61G|SHC1|SOCS1|SOS1|SRC|STUB1|TCEB2|TPR|TUBB4B|UBA52|UBE2D4|XRCC5|XRCC6|YWHAZ
Cell Cycle	61	ANAPC1|ANAPC11|ATM|AURKA|AURKB|BUB1|CCNB1|CCNE1|CDC7|CDK1|CDKN2B|CDKN2D|CDT1|CENPN|CKS1B|CLASP2|DKC1|DSN1|DYNLL1|E2F1|ERCC6L|FBXO5|FZR1|GOLGA2|HSP90AA1|KIF18A|LIN37|MAD2L1|MCM2|MCM4|MCM6|MLH3|NEK2|NPM1|NUP107|NUP50|OIP5|ORC6|PCNA|PLK4|POLA1|POM121|PPP1R12A|RAB1B|RAD50|RAE1|RBBP4|RBBP7|RBBP8|RBL2|RSF1|SDCCAG8|SET|SMC4|SPC24|SPDL1|TPR|TUBB|TUBB4B|UBA52|ZWINT
Metabolic pathways	58	ACADM|ADI1|ALAS1|ALDOA|AMACR|ATP5O|BCAT1|BCAT2|CBR1|COX5B|COX6C|CTPS1|HAD1|DGKH|DNMT1|DTYMK|ENO1|EXT2|FASN|FBL|FDPS|FUT8|GAA|GCLC|GFPT1|GLB1|GSS|HSD17B4|INPP5A|INPP5K|LDHA|LSS|MECR|MTHFD1|NDUFA3|NDUFB4|ODC1|PAICS|PAPSS1|PDHB|PGAM5|PGAP1|PIGA|PIP5K1B|PLA2G12A|PLCG1|PLD1|POLA1|POLG2|POLR1A|POLR2A|PPAT|SDHA|SGMS1|SHMT2|SUCLA2|SUFU|TGDS
Metabolism of proteins	47	B3GNTL1|CCT3|CCT6A|CCT8|CTSD|HAD1|DDIT3|DNAJB9|DNAJC3|DOHH|EEF1A1|EEF1D|EEF1G|EIF2S1|EIF2S2|EIF3K|EIF4E|EIF4G1|EIF5A|FBXW5|FUT8|GFPT1|GLB1|GRPEL2|HSPA9|HSPD1|IGFBP3|MANEA|PFDN1|PGAP1|PIGA|RPL13A|RPL14|RPL36|RPS13|RPS16|RPS21|RPS29|RPS9|SEC61G|SHC1|STX1A|THBS2|TRAM1|TSPYL2|TUBB4B|UBA52
Developmental Biology	41	ABLIM2|AKT2|ARPC2|ARPC5|CDC42|CDK1|CLASP2|CREB1|CRMP1|CTNNA2|DPYSL2|HDAC3|HRAS|HSP90AA1|HSPA8|ITGA1|KIF4A|MED11|MED18|MED20|MED4|MYH10|MYH14|NRTN|PFN1|PLCG1|PSENEN|PTK2|RAC1|RAF1|RHOA|ROCK1|RPS6KA5|RPS6KA6|SCN3B|SDCBP|SIAH2|SOS1|SPTAN1|SRC|TUBB4B
Pathways in cancer	34	AKT2|ARAF|CCNE1|CDC42|CDKN2B|CKS1B|CKS2|CRK|CRKL|CTBP1|CTNNA2|CYCS|E2F1|FADD|FZD4|HDAC2|HRAS|HSP90AA1|MSH2|PLCG1|PLD1|PTCH1|PTK2|RAC1|RAF1|RASSF1|RBX1|RELA|RHOA|SOS1|SUFU|TCEB2|TPR|WNT5A
Dibutyl Phthalate interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of genes:**	**Annotated Genes**
Metabolism	56	ACADM|ADCY9|ADI1|AKR7A2|ALAS1|ALDOA|AMACR|ATP5O|BCAT1|BCAT2|BSG|CBR1|CYB5A|CYCS|DTYMK|ENO1|ETFB|ETFDH|EXT2|FASN|FDPS|GCLC|GLB1|GNG5|GSR|GSS|HDAC3|HMMR|HSD17B4|HSP90AA1|INPP5A|IP6K2|LDHA|LPCAT3|LSS|MGST3|MTHFD1|NAMPT|NDUFA3|NDUFB4|NUBP1|NUP50|OAZ2|ODC1|PAPSS1|PLA2G12A|PLD1|POM121|PRKAR2A|PYGL|RAE1|RAN|SDHA|SGMS1|SLC25A10|UBA52
Disease	45	ADCY9|ALDOA|CCNT2|CDK1|CREB1|CSNK1A1|CTBP1|CYB5A|ENO1|EXT2|FASN|GLB1|HDAC3|HMMR|HSP90AA1|MTHFD1|NAMPT|NPM1|NUP50|PAPSS1|POLR2A|POM121|PRKAR2A|PYGL|RAE1|RAF1|RAN|RHOA|RPL13A|RPL14|RPL36|RPS13|RPS21|RPS29|SLC25A10|SMARCA4|SNW1|SRC|STUB1|TCEB2|TGIF1|TNKS2|UBA52|WNT5A|XRCC5

Gene Expression	39	CCNT2|DNMT1|EEF1A1|EEF1D|EIF2S1|EIF2S2|EIF4E|EIF4G1|ESRRA|EXOSC2|EZH2|GEMIN4|HNRNPA1|HNRNPU|HSPA8|LSM2|MED20|POLR1A|POLR2A|PTBP1|RAN|RBBP4|RNPS1|RPL13A|RPL14|RPL36|RPS13|RPS21|RPS29|SET|SNW1|SRSF1|TARS|TCEB2|TGIF1|THRA|U2AF1|UBA52|XPO5
Metabolic pathways	38	ACADM|ADI1|ALAS1|ALDOA|AMACR|ATP5O|BCAT1|BCAT2|CBR1|COX6A2|DNMT1|DTYMK|ENO1|EXT2|FASN|FBL|FDPS|GCLC|GFPT1|GLB1|GSS|HSD17B4|INPP5A|LDHA|LSS|MTHFD1|NDUFA3|NDUFB4|ODC1|PAPSS1|PGAM5|PLA2G12A|PLD1|POLE4|POLR1A|POLR2A|SDHA|SGMS1
Cell Cycle	34	ANAPC1|ANAPC11|APITD1|ATM|AURKB|CCNB1|CCNE1|CDC7|CDK1|CDKN2D|CDT1|CENPN|CKS1B|CLASP2|FBXO5|FZR1|HSP90AA1|MCM2|MCM4|MCM6|NPM1|NUP50|OIP5|ORC6|PCNA|POM121|PPP1R12A|RAE1|RBBP4|SET|SPC24|SPDL1|UBA52|ZWINT
Signal Transduction	32	ADCY9|ARHGDIA|CCNT2|CDK1|CREB1|CSNK1A1|CTBP1|DAAM1|EIF4E|EIF4G1|GNG5|HDAC3|HSP90AA1|JAK2|LFNG|MEF2A|PRDM4|PRKAR2A|PTCH1|RAF1|RHOA|SMARCA4|SNW1|SOCS1|SRC|STUB1|TGIF1|THBS2|TNKS2|TRIO|UBA52|WNT5A
Immune System	31	ADCY9|ANAPC1|ANAPC11|ARPC2|ARPC5|CDK1|CREB1|CTSD|EIF4E|EIF4G1|FADD|FZR1|HSP90AA1|IP6K2|JAK2|MEF2A|NUP50|PLD1|POM121|PRKAR2A|PRKDC|PVR|RAE1|RAF1|RNF19B|SOCS1|SRC|STUB1|TCEB2|UBA52|XRCC5
Metabolism of proteins	25	CCT3|CTSD|DDIT3|DNAJB9|DNAJC3|EEF1A1|EEF1D|EIF2S1|EIF2S2|EIF4E|EIF4G1|FBXW5|GFPT1|GLB1|HSPA9|HSPD1|PFDN1|RPL13A|RPL14|RPL36|RPS13|RPS21|RPS29|THBS2|UBA52
Mitotic M-M/G1 phases	23	ANAPC1|ANAPC11|APITD1|AURKB|CCNB1|CDC7|CDK1|CDT1|CENPN|CLASP2|FBXO5|MCM2|MCM4|MCM6|NUP50|ORC6|POM121|RAE1|SET|SPC24|SPDL1|UBA52|ZWINT
Developmental Biology	21	ARPC2|ARPC5|CDK1|CLASP2|CREB1|CTNNA2|DPYSL2|HDAC3|HSP90AA1|HSPA8|ITGA1|MED20|MEF2A|MYH10|NRTN|RAF1|RHOA|SCN3B|SDCBP|SRC|TRIO
Diethylhexyl Phthalate interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of Genes:**	**Annotated Genes**
Metabolism	21	ACADM|ALAS1|ALDOA|BCAT2|BSG|CYCS|FASN|FDPS|GSR|GSTM3|HSD17B4|HSP90AA1|LDHA|LSS|MMADHC|NDUFA3|ODC1|PAPSS1|PLD1|PYGL|SLC37A4
Metabolic pathways	15	ACADM|ALAS1|ALDOA|BCAT2|DNMT1|FASN|FDPS|HSD17B4|LDHA|LSS|NDUFA3|ODC1|PAPSS1|PLD1|POLE4
Disease	15	AKT2|ALDOA|FASN|HDAC2|HDAC4|HSP90AA1|IRS1|MMADHC|NPM1|PAPSS1|PYGL|RBX1|RPL36|RPS13|SLC37A4
Immune System	12	AKT2|ANAPC11|CDC34|DYNLL1|EIF4G1|HSP90AA1|IRS1|KIF18A|PLD1|RBX1|SEC61G|TUBB4B
Metabolism of proteins	11	CCT3|CCT6A|DNAJB9|EIF4G1|GRPEL2|HSPA9|HSPD1|RPL36|RPS13|SEC61G|TUBB4B
Cell Cycle	9	ANAPC11|CCNB1|CCNE1|DYNLL1|HSP90AA1|KIF18A|NPM1|TUBB4B|ZWINT
Cellular responses to stress	8	ANAPC11|CBX2|CCNE1|CYCS|GSR|HSP90AA1|HSPA8|RBX1

Pathways in cancer	8	AKT2|CCNE1|CYCS|HDAC2|HSP90AA1|MSH2|PLD1|RBX1
Developmental Biology	8	AKT2|DPYSL2|HSP90AA1|HSPA8|ITGA1|SCN3B|SIAH2|TUBB4B
Cell cycle	5	ANAPC11|CCNB1|CCNE1|HDAC2|RBX1
Polychlorinated Biphenyls interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of Genes:**	**Annotated Genes**
Cell Cycle	13	AURKA|AURKB|CDK1|CDT1|CENPN|CKS1B|FBXO5|MCM2|MCM6|PCNA|PLK4|SMC4|ZWINT
Mitotic M-M/G1 phases	9	AURKB|CDK1|CDT1|CENPN|FBXO5|MCM2|MCM6|SMC4|ZWINT
DNA Replication	4	CDT1|MCM2|MCM6|PCNA
Cell cycle	4	CDK1|MCM2|MCM6|PCNA
DNA replication	3	MCM2|MCM6|PCNA
DNA replication and repair	3	CDK1|PCNA|UNG
Pancreatic cancer	3	ARAF|CDC42|RAF1
Cadmium interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of Genes:**	**Annotated Genes**
Metabolism	26	ACADM|ALDOA|AUH|BCAT1|COX5B|COX6C|CYCS|DTYMK|ENO1|FASN|GCLC|GSR|GSS|GSTM3|HSD17B4|HSP90AA1|INPP5K|LDHA|MGST3|OAZ2|PAICS|RAN|SDHA|SGMS1|SLC16A1|SLC37A4
Gene Expression	25	CCNT2|CDKN2B|DNMT1|EEF1A1|EEF1D|EEF1G|EXOSC2|HARS|HNRNPA1|HNRNPH1|HSPA8|LSM2|MARS2|MED20|RAN|RPL10|RPL13A|RPL14|RUNX2|SRRM1|TAF12|TCEB2|THRA|XPO5|YWHAZ
Disease	24	ALDOA|CCNT2|CDC42|CDK1|CDKN2B|CREB1|CTBP1|ENO1|FASN|HSP90AA1|IRS1|OS9|PPIA|RAC1|RAF1|RAN|RPL10|RPL13A|RPL14|SHC1|SLC37A4|TAF12|TCEB2|YWHAZ
Signal Transduction	21	ARHGDIA|CCNT2|CDC42|CDK1|CDKN2B|CREB1|CTBP1|E2F1|FSTL3|GPR37|HSP90AA1|IRS1|OS9|PTK2|RAC1|RAF1|RELA|ROCK1|RPS6KB1|SHC1|YWHAZ
Metabolic pathways	20	ACADM|ALDOA|AUH|BCAT1|COX5B|COX6C|DNMT1|DTYMK|ENO1|FASN|GAA|GCLC|GSS|HSD17B4|INPP5K|LDHA|PAICS|SDHA|SGMS1|SHMT2

Immune System	18	CDC42|CDK1|CREB1|CTSD|HSP90AA1|IRS1|KIF4A|PELI1|PTK2|PVR|RAC1|RAF1|RELA|RNF19B|SHC1|TCEB2|UBE2D4|YWHAZ
Cell Cycle	17	AURKA|BUB1|CCNB1|CCNE1|CDK1|CDKN2B|CKS1B|E2F1|FBXO5|HSP90AA1|MAD2L1|MCM2|MCM4|MCM6|NEK2|OIP5|SMC4
Pathways in cancer	**15**	CCNE1|CDC42|CDKN2B|CKS1B|CTBP1|CYCS|E2F1|HSP90AA1|MSH2|PTK2|RAC1|RAF1|RASSF1|RELA|TCEB2
Developmental Biology	15	CDC42|CDK1|CREB1|HSP90AA1|HSPA8|KIF4A|MED20|MYH10|MYH14|NRTN|PTK2|RAC1|RAF1|ROCK1|SPTAN1
Metabolism of proteins	12	CTSD|DDIT3|DNAJB9|EEF1A1|EEF1D|EEF1G|EIF5A|HSPD1|RPL10|RPL13A|RPL14|SHC1
Arsenic interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of Genes:**	**Annotated Genes**
Metabolism	33	ADCY9|ALDOA|CYCS|ENO1|ERCC2|ETFB|ETFDH|FASN|GCLC|GSR|GSS|GSTM3|HSD17B4|HSP90AA1|INPP5A|IP6K2|LDHA|MMADHC|NUBP1|P4HB|PAICS|PLCG1|PLD1|POM121|PPAT|PRKAR2A|SDHA|SGMS1|SLC44A2|STX1A|SUCLA2|TPMT|UBA52
Immune System	30	ADCY9|ARPC2|CASP2|CDC42|CDK1|CREB1|CTSD|FZR1|HRAS|HSP90AA1|IP6K2|JAK2|KIF4A|MAPK7|PCBP2|PELI1|PLCG1|PLD1|POM121|PRKAR2A|PRKDC|PTK2|PVR|RAF1|SOS1|SRC|TUBB4B|UBA52|UBE2D4|XRCC5
Disease	27	ADCY9|ALDOA|CDC42|CDK1|CDKN2B|CREB1|CTBP1|ENO1|ERCC2|FASN|HDAC4|HRAS|HSP90AA1|MMADHC|NPM1|P4HB|PLCG1|POM121|PRKAR2A|RAF1|RPL36|SMARCA4|SOS1|SRC|STX1A|UBA52|XRCC5
Signal Transduction	24	ADCY9|CASP2|CDC42|CDK1|CDKN2B|CREB1|CTBP1|E2F1|HDAC4|HRAS|HSP90AA1|JAK2|MAPK7|P4HB|PLCG1|PRKAR2A|PTCH1|PTK2|RAF1|ROCK1|SMARCA4|SOS1|SRC|UBA52
Developmental Biology	22	ABLIM2|ARPC2|CDC42|CDK1|CREB1|HRAS|HSP90AA1|HSPA8|KIF4A|MED18|MYH10|MYH14|NRTN|PLCG1|PTK2|RAF1|ROCK1|SCN3B|SIAH2|SOS1|SRC|TUBB4B
Metabolic pathways	20	ALDOA|COX6A2|DNMT1|ENO1|FASN|FUT8|GCLC|GSS|HSD17B4|INPP5A|LAP3|LDHA|PAICS|PLCG1|PLD1|PPAT|SDHA|SGMS1|SUCLA2|SUFU
Cell Cycle	19	ATM|AURKA|CCNB1|CCNE1|CDK1|CDKN2B|CDKN2D|E2F1|FZR1|HSP90AA1|MAD2L1|NPM1|PCNA|POM121|SET|SPDL1|TUBB|TUBB4B|UBA52
Gene Expression	19	CDKN2B|CNOT1|DNMT1|EEF1G|ERCC2|EZH2|HNRNPA1|HSPA8|LSM2|PCBP2|PTBP1|RNPS1|RPL36|RUNX2|SET|UBA52|UPF1|VARS2|ZNF610
Pathways in cancer	17	CCNE1|CDC42|CDKN2B|CTBP1|CYCS|E2F1|HRAS|HSP90AA1|MSH2|PLCG1|PLD1|PTCH1|PTK2|RAF1|RASSF1|SOS1|SUFU
Cellular responses to stress	16	ATM|CCNE1|CDKN2B|CDKN2D|CYCS|E2F1|EHMT1|EZH2|FZR1|GSR|HSP90AA1|HSPA8|MAPK7|P4HB|PRDX5|UBA52

Manganese interacting common E2- and NRF1-target genes		
KEGG Pathway	**Number of Genes:**	**Annotated Genes**
Cellular responses to stress	6	ATM|CYCS|GSR|HSPA8|P4HB|RELA
Developmental Biology	5	CREB1|HSPA8|SCN3B|SPTAN1|SRC
Tuberculosis	4	CREB1|CYCS|RELA|SRC
p53 signaling pathway	3	ATM|CYCS|PPM1D
Small cell lung cancer	3	CKS2|CYCS|RELA
Apoptosis	3	ATM|CYCS|RELA
Cell cycle	3	ATM|BUB1|MCM4

Table 2: Interaction of Estrogenic Endocrine Disrupting Chemicals Modified Genes with Estrogen Signaling and NRF1 network genes in the Individual Neurodegenerative Disease	
Endocrine Disrupting Chemical (EDC)	**Individual EDC responsive modified genes common to both NRF1 and E2 target. * Indicates E2 responsive.**
Alzheimer's Disease (AD)	
17 beta-estradiol	6 genes: *APBB2* | *DPYSL2* | *EIF2S1* | *ENO1* | *MAPT* | *PAXIP1*
Ethinyl Estradiol	6 genes: *APBB2** | *EIF2S1** | *ENO1** | *IDE* | *MAPT** | *PAXIP1**
Bisphenol A	8 genes: *APBB2** | *DPYSL2** | *EIF2S1** | *ENO1** | *IDE* | *MAPT** | *PAXIP1** | *SLC30A4*
Dibutyl Phthalate	4 genes: *DPYSL2** | *EIF2S1** | *ENO1** | *IDE*
Diethylhexyl Phthalate	2 genes: *DPYSL2** | *MAPT**
Cadmium	2 genes: *ENO1** | *SLC30A4*
Arsenic	2 genes: *ENO1 *| MAPT*
Manganese	1 gene: *ENO1**
Parkinson's Disease (PD)	
17 beta-estradiol	8 genes: *HSPA9* | *MAPT* | *RPL14*
Ethinyl Estradiol	3 genes: *HSPA9** | *MAPT** | *PINK1*
Bisphenol A	8 genes: *GAK* | *HSPA9** | *MAPT** | *PARK2* | *PARK7* | *PINK1* | *RPL14** | *VPS35*
Dibutyl Phthalate	4 genes: *HSPA9** | *PARK2* | *PARK7* | *RPL14**
Diethylhexyl Phthalate	3 genes: *HSPA9** |*MAPT** | *PARK2*
Cadmium	3 genes: *PARK2* | *PINK1* | *RPL14**
Arsenic	4 genes: *GAK* | *HSPA9** | *MAPT** | *PARK2*
Manganese	2 genes: *PARK2* | *PARK7*

Huntington's Disease (HD)	
17 beta-estradiol	2 genes: *AIFM1* | *IP6K2*
Ethinyl Estradiol	1 gene: *AIFM1**
Bisphenol A	2 genes: *AIFM1** | *IP6K2**
Dibutyl Phthalate	1 gene: *IP6K2**
Cadmium	1 gene: *AIFM1**
Arsenic	1 gene*: IP6K2**
Amyotrophic Lateral Sclerosis (ALS)	
17 beta-estradiol	1 gene: *GSR* | *CHMP2B*
Ethinyl Estradiol	1 gene: *GSR**
Bisphenol A	2 genes: *GSR** | *CHMP2B** | *UNC13A*
Dibutyl Phthalate	1 gene: *GSR**
Diethylhexyl Phthalate	1 gene: *GSR**
Cadmium	1 gene: *GSR**
Arsenic	1 gene: *GSR**
Manganese	1 gene: *GSR*
Autism Spectrum Disorder (ASD)	
17 beta-estradiol	3 genes: *CIRBP* | *PCDH9* | *GTF2I*
Ethinyl Estradiol	2 genes: *CIRBP** | *GTF2I**
Bisphenol A	3 genes: *CIRBP** | *GTF2I** | *PCDH9**
Polychlorinated Biphenyls	1 gene: *CIRBP**

Cadmium	1 gene: *CIRBP**
Arsenic	1 gene: *PCDH9**
Brain Neoplasms	
17 beta-estradiol	3 genes: *PCNA* | *PTCH1* | *RELA*
Ethinyl Estradiol	2 genes: *PCNA** | *PTCH1**
Bisphenol A	4 genes: *EML4* | *PCNA** | *PTCH1** | *RELA**
Dibutyl Phthalate	2 genes: *PCNA** | *PTCH1**
Polychlorinated Biphenyls	1 gene: *PCNA*
Cadmium	1 gene: *RELA**
Arsenic	2 genes: *PCNA** | *PTCH1**
Manganese	1 gene: *RELA**

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CHAPTER III

HYPOTHESIS AND SPECIFIC AIMS

Hypothesis

Exposure to estrogenic endocrine disrupting chemicals (EEDCs) result in adverse brain health outcomes.

Specific Aims

Specific Aim 1: Assess exposure to phthalates and bisphenol-A (BPA) using urinary biomarkers from the CDC NHANES 2011-2014 datasets to find associations between phthalate and BPA bioburden and adverse brain health using surrogate indicators of brain health.

Specific Aim 2: Assess exposure to the metalloestrogens, cadmium (Cd), arsenic (As), and manganese (Mn) using urinary biomarkers from the CDC NHANES 2011-2014 datasets to find associations between phthalate and BPA bioburden and adverse brain health using surrogate indicators of brain health.

Specific Aim 3: Assess exposure to oral contraceptives (OC) and hormonal replacement therapy (HRT) using urinary biomarkers from the CDC NHANES 2011-2014 datasets to find associations between phthalate and BPA bioburden and adverse brain health using surrogate indicators of brain health.

Specific aim 4: Assess estrogen-responsive genes networks common to the EEDCs, phthalates, BPA, Cd, As, and Mn, NRF1, and neurodegenerative disease using bioinformatics methods.

CHAPTER IV

METHODS

Study Design and Population: NHANES is a continuous cross-sectional data collection utilizing a complex multi-stage sampling design that creates a survey representative of the non-institutionalized population of the United States [1,2]. The survey has been conducted since 1999 and consists of an at-home questionnaires followed by a standardized physical examination and specimen collection conducted in mobile examination centers (MEC) [1,2]. Eligibility is determined using preset selection probabilities for the desired demographic subdomains [2]. A household screener is performed before to determine if any household members are eligible for the interview and examination [2]. The interview collects demographic, health, nutrition, and household information, while the physical examination includes physical measurements, dental examination, and the collection of blood and urine specimens for laboratory testing [2]. Prior to any to interviews and examinations, informed consent was obtained and all procedures were approved by the CDC Institutional Review Board [3].

In our study, we merged the NHANES 2011-2012 and 2013-2014 data cycles. All our analyses were limited to individuals 60 years of age and older who have recorded responses to cognitive test scores and/or memory and taste/smell questions and have EEDC urine measurements.

Inclusion/Exclusion Criteria

Inclusion criteria:

1. Males and females, 60 years of age and older
2. Available EEDC urine measurements (Phthalates, BPA, Mn, As, Cd, OC use, HRT use)
3. Urine creatinine measurements >30 mg/dl and <300 mg/dl.
4. Complete responses to identified outcome variables.

Exclusion criteria:

1. Males and females, 59 years of age and younger
2. Unavailable EEDC urine measurements (Phthalates, BPA, Mn, As, Cd, OC use, HRT use)
3. Urine creatinine measurements <30mg/dl and >300mg/dl
4. Incomplete responses to identified outcome variables.

Phthalate Exposure Assessment and Measurements

Phthalates were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [4,5] . The laboratory utilized high performance liquid chromatography-electrospray ionization-tandem mass spectrometry to analyze urine phthalate levels and was consistently used in both survey cycles [4,5]. Phthalate levels were provided in ng/ml and was used in our analyses. The following phthalates were used in our analyses: Mono (carboxynonyl) Phthalate (CNP); Mono (carboxyoctyl) Phthalate (COP); Mono-(2-ethyl-5-carboxypentyl) Phthalate (ECP); Mono-n-butyl Phthalate (MBP); Mono-(3-carboxypropyl) Phthalate (MC1); Mono-ethyl Phthalate (MEP); Mono

(2-ethyl-5-hydroxy hexyl) Phthalate (MHH); Mono-(2-ethyl-5-oxohexyl) Phthalate (MOH); Mono-benzyl Phthalate (MZP); Mono-isobutyl Phthalate (MIB).

The limit of detection variables indicates if subjects have urine phthalate levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy phthalate level of the LOD divided by the square root of two [6]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [7]. The specific phthalate metabolites were selected as >60% of study subjects had urine phthalate levels above the LOD. A total of 5,175 subjects had available urinary phthalate measurements in the 2011-2012 and 2013-2014 datasets.

BPA Exposure Assessment and Measurements

BPA was measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [8,9] . The laboratory on-line solid phase extraction coupled to high performance liquid chromatography and tandem mass spectrometry to analyze urine BPA levels and was consistently used in both survey cycles [8,9]. BPA levels were provided in ng/ml.

The limit of detection variables indicates if subjects have urine phthalate levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy BPA level of the LOD divided by the square root of two [6]. Some LODs differ between survey cycles and a conservative approach was used to

account for differing LODs per survey cycle [7]. A total of 5,175 subjects had available urinary BPA measurements in the 2011-2012 and 2013-2014 datasets.

Cadmium Exposure Assessment and Measurements

Cadmium were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [10–12] . The laboratory inductively coupled-plasma dynamic reaction cell-mass spectrometry to analyze urine Cadmium levels and was consistently used in both survey cycles [10–12]. Cadmium levels were provided in ug/L and was used in our analyses. Urinary cadmium was used in our analyses and coded as URXUCD, with a limit of detection variable coded as URDUCDLC. The limits of detection were 0.056 ug/L for 2011-2012 and 0.036 ug/L for 2013-2014.

The limit of detection variables indicates if subjects have urine Cadmium levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy Cadmium level of the LOD divided by the square root of two [6]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [7].

Manganese Exposure Assessment and Measurements

Manganese were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [10–12] . The laboratory inductively coupled-plasma dynamic reaction cell-mass spectrometry to analyze urine Manganese levels and was consistently used in both survey cycles [10–12]. Manganese levels were provided in ug/L and was used in

our analyses. The following Manganese metabolites were used in our analyses. Urinary manganese was used in our analyses and coded as URXUMN, with a limit of detection variable coded as URDUMNLC. The limits of detection were 0.08 ug/L for 2011-2012 and 0.013 ug/L for 2013-2014.

The limit of detection variables indicates if subjects have urine Manganese levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy Manganese level of the LOD divided by the square root of two [6]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [7].

Arsenic Exposure Assessment and Measurements

Arsenic were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [10–12] . The laboratory inductively coupled-plasma dynamic reaction cell-mass spectrometry to analyze urine arsenic levels and was consistently used in both survey cycles [10–12]. Arsenic levels were provided in ug/L and was used in our analyses. Total urinary arsenic was used in our analyses and coded as URXUAS, with a limit of detection variable coded as URDUASLC. The limits of detection were 1.25 ug/L for 2011-2012 and 0.26 ug/L for 2013-2014.

Only total arsenic was analyzed in the study. The limit of detection variables indicates if subjects have urine arsenic levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy arsenic

level of the LOD divided by the square root of two [6]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [7]. The specific arsenic metabolites were selected as >60% of study subjects had urine arsenic levels above the LOD.

Oral Contraceptive Use Assessment and Measurements

Oral contraceptive use was recorded by the question yes/no question, "Have you ever taken birth control pills for any reason?". Female participants aged 12 years and older were eligible [13,14]. These questions were administered in the mobile examination center (MEC) by trainer interviewers [13,14]. A total of 1670 female subjects over the age of 60, provided a response, with 952 participants responding "yes" and 718 participants responding "no".

Hormonal Replacement Therapy Use Assessment and Measurements

Oral contraceptive use was recorded by the question yes/no question, "Have you ever used female hormones such as estrogen and progesterone?". Female participants aged 12 years and older were eligible [13,14]. These questions were administered in the mobile examination center (MEC) by trainer interviewers [13,14]. A total of 1662 female subjects over the age of 60, provided a response, with 628 participants responding "yes" and "1034" participants responding "no".

Assessment of Surrogate Brain Health Indicators – Cognitive Scores

CERAD Word Learning Subtest – Immediate Recall and Delayed Recall: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning Subtest assesses both immediate and delayed learning [15,16]. The delayed and immediate recall tests available in NHANES assess the ability to process new verbal information

[15,16]. The tests are part of the neuropsychological assessment for the entire CERAD testing protocol, which was initially created to standardize Alzheimer's disease (AD) assessment and diagnosis [17]. The tests in the neuropsychological assessment itself were chosen because of their ability to assess cognitive functions inherent in AD [17]. The assessments have the ability to differentiate those of adequate cognitive status versus those who have mild cognitive impairment or dementia [17–20]. Although developed for use in the assessment of AD, the CERAD assessments have shown utility in use for Parkinson's disease [20] and frontotemporal lobar degeneration [21].

Immediate Recall: For immediate recall, the subjects are asked to read aloud a sequence of 10 unrelated words as they are presented to them and immediately after, they are asked to recall as many words as possible [15,16]. This is done in three trials with the order of the words differing in each trial. [15,16]. Each trial has a maximum score of 10, with a maximum overall score of 30 [15,16,18].

In our study, we included subjects 60 years of age and older who completed all immediate recall word list trials identified as: CFDCST1, CFDCST2, and CFDCST3 in the 2011-2012 and 2013-2014 NHANES data cycles. Those who did not have three trials completed were not included in the immediate recall analysis. We summed the total of the three trials and created a new variable with cut-off scores named IMMEDIATERECALL. A cut-off score of ≤ 13 and ≥ 14 was used as it is the standard in other assessments [18,22]. A total of 3,149 subjects from the 2011-2012 and 2013-2014 responded with complete immediate recall trials.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as

these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 940 subjects, 146 subjects with cut-off scores ≤ 13 and 794 subjects with cut-off scores ≥ 14. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our immediate recall study population consisted of 940 subjects, 146 subjects ≤ 13 and 794 subjects ≥ 14. We then accounted for those who provided responses to OC and HRT use. After, our OC/immediate recall study population consisted of 1576 subjects, 193 subjects ≤ 13 and 1383 subjects ≥ 14. Our HRT/immediate recall study population consisted 1567 subjects, with 189 subjects ≤ 13 and 1378 subjects ≥ 14.

Delayed Recall: For delayed recall, the subject is asked to repeat the sequence of 10 unrelated words after the other cognitive tests are completed, which is typical 8 to 10 minutes after the start of the word learning trials [15,16]. The maximum score is 10 for delayed recall [15,16].

In our study, we included subjects 60 years of age and older who completed the delayed recall trial, identified as CFDCSR, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with the cut-off scores named DELAYEDRECALL. A cut-off score of ≤ 3 and ≥ 4 was used as it is the standard in other assessments [18,22,24].

A total of 3,126 subjects from the 2011-2012 and 2013-2014 responded with a complete delayed recall trial. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or

concentrated [23]. After, our study population consisted of 930 subjects,157 subjects ≤ 3 and 776 subjects ≥ 4. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our delayed recall study population consisted of 930 subjects,157 subjects ≤ 3 and 776 subjects ≥ 4. We then accounted for those who provided responses to OC and HRT use. After, our OC/delayed recall study population consisted of 1568 subjects, 218 subjects ≤ 3 and 1350 subjects ≥ 4. Our HRT/delayed recall study population consisted of 1560 subjects with 213 subjects ≤ 3 and 1347 subjects ≥ 4.

Animal Fluency: The animal fluency test is used to determine categorical verbal fluency, which is part of executive function and can differentiate between with normal cognition versus those with MCI and more severe cognitive impairment, such as AD [15,16]. Since the test uses animal names, it does not require cultural consideration or formal education experience [15,16]. In the test, subjects are asked to name as many animals in a one minute span, with a maximum range of 40 words in the NHANES 2011-2014 data set. [15,16]. A sample test is given to each subject before the actual test [15,16].

In our study, we included subjects 60 years of age and older who completed the animal fluency trial, identified as CFDAST, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with cut-off scores named VERBALFLUENCY. cut-off score of ≤ 11 and ≥ 12 was used as it is the standard in other assessments [18,22,24,25].

A total of 3,110 subjects from the 2011-2012 and 2013-2014 responded with complete animal fluency scores. We then accounted for subjects who had urinary

phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 931 subjects,187 subjects ≤ 11 and 744 subjects ≥ 12. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 931 subjects,187 subjects ≤ 11 and 744 subjects ≥ 12. We then accounted for those who provided responses to OC and HRT use. After, our OC/Animal Fluency study population consisted of 1565 subjects, 321 subjects ≤ 321 and 1244 subjects ≥ 12. Our HRT/Animal Fluency study population consisted of 1557 subjects with 318 subjects ≤ 11 and 1239 subjects ≥ 12.

Digit Symbol Substitution Test: The Digit Symbol Substitution Test (DSST) is part of the Wechsler Adult Intelligence Scale (WAIS III) [15,16,26]. The test measures processing speed, sustained attention, and working memory [15,16,26]. The subtests have shown utility in the identification of dementia and other neurodegenerative disorders such as AD [27–29]. The test is given in paper form, with a key that has 9 numbers paired to different symbols. The subject has 2 minutes to match each symbol to 133 boxes with a number associated to it, with the score as the total correct matches with a maximum score of 105 in the 2011-2014 NHANES dataset. [15,16]. A sample test is given to each subject before the actual test [15,16].

In our study, we included subjects 60 years of age and older who completed the animal fluency trial, identified as CFDDS, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with cut-off scores named DSST, cut-off

score of ≤ 27 and ≥ 28 was used as it is the standard in other assessments [30–32]. A total of 3,014 subjects from the 2011-2012 and 2013-2014 responded with complete DSST. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 891 subjects,129 subjects ≤ 27 and 762 subjects ≥ 28. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 891 subjects,129 subjects ≤ 27 and 744 subjects ≥ 28. We then accounted for those who provided responses to OC and HRT use. After, our OC/DSST study population consisted of 1511 subjects, 227 subjects ≤ 27 and 1284 subjects ≥ 28. Our HRT/DSST study population consisted of 1505 subjects with 226 subjects ≤ 27 and 1279 subjects ≥ 28. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,074 subjects,188 subjects answered “1” and 783 subjects answered “2”. We then accounted for those who provided responses to OC and HRT use. After, our OC/MCQ084 study population consisted of 1669 subjects, 274 subjects responded “yes” and 1395 subjects responded “no”. Our HRT/MCQ084 study population consisted of 1661 subjects with 272 subjects responded “yes” and 1389 subjects responded “no”.

Assessment of Surrogate Brain Health Indicators – Memory Function

During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the yes/no question, "During the past 12 months, have you experienced confusion or memory loss that is happening more often or is getting worse?" [33]. As memory loss and confusion are early indicators of cognitive decline, dementia, and AD [34]. 3,628 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,025 subjects,181 subjects answered "yes" and 844 subjects answered "no". We then accounted for those who provided responses to OC and HRT use. After, our OC/MCQ084 study population consisted of 1669 subjects, 274 subjects responded "yes" and 1395 subjects responded "no". Our HRT/MCQ084 study population consisted of 1661 subjects with 272 subjects responded "yes" and 1389 subjects responded "no".

During the past 7 days, how often have you had trouble remembering where you put things?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question," During the past 7 days, how often have you had trouble remembering where you put things, like you keys or your wallet?" [33]. 3,448 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

The question is multi-leveled, where 3,448 subjects answered “Never” equaling the value “0”, 809 subjects answered “About once” equaling the value “1”, 544 subjects answered “Two or three times” equaling the value “2”, 175 subjects answered “Nearly every day” equaling the value “3”, and 102 subjects answered “Several times a day” equaling the value “4”. We created a new variable named MCQ380_WK, which combines responses coded as “Never” equaling “0” and “About once” equaling “1” into a variable, “No” equaling “1”, and “Two or Three Times” equaling “2”, “Nearly Every day” equaling “3”, and “Several times a day” equaling “4”, into a new variable, “Yes” equaling “1”.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 971 subjects,188 subjects answered “1” and 783 subjects answered “2”. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,074 subjects,188 subjects answered “1” and 783 subjects answered “2”.

We then accounted for those who provided responses to OC and HRT use. After, our OC/MCQ380_WK study population consisted of 1576 subjects, 335 subjects responded “yes” and 1241 subjects responded “no”. Our HRT/MCQ380_WK study population consisted of 1568 subjects with 332 subjects responded “yes” and 1236 subjects responded “no”.

Are you limited in any way because of difficulty remembering or because you experience periods of confusion?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" [33]. Limitations in physical movement due to difficulty remembering and confusion can indicate the development of cognition issues [35]. 11, 323 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,024 subjects, 165 subjects answered "yes" and 859 subjects answered "no". We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,133 subjects,181 subjects answered yes and 952 subjects answered no. We then accounted for those who provided responses to OC and HRT use. After, our OC/PFQ057 study population consisted of 1670 subjects, 259 subjects responded "yes" and 1411 subjects responded "no". Our HRT/PFQ057 study population consisted of 1662 subjects with 254 subjects responded "yes" and 1408 subjects responded "no".

Assessment of Surrogate Brain Health Indicators – Taste and Smell Function

It has been observed that neurodegenerative disease has been shown to be preceded by smell and taste disorders [36–39]. The causes of these disorders have been

linked to genetic alterations [36], overexpression of key proteins[37], and direct effect of some environmental chemicals on the olfactory mucosa [40], which can have associations with exposure to EEDCs [36,37,39,40]. However, issues with olfaction can also be caused by upper respiratory tract infections, sino-nasal disease, head trauma, idiopathic causes, surgery of the nasal area, and congenital loss of smell [41].

The two most common and prevalent neurodegenerative diseases, AD and PD have been shown to be preceded by smell disorders [42–47]. These disorders manifest themselves when evidence of pathological changes in the olfactory system are evident [47]. These are characterized by the build-up of pathological proteins, which cause the death of olfactory cells [47]. Several human epidemiological studies have also alluded to the utility of using sensory biomarkers as an early detection for neurodegenerative diseases [48–51].

Do you sometimes smell and unpleasant, bad, or burning odor when nothing is there?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question, "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" [33]. 7,399 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,024 subjects, 74 subjects answered "yes" and "950" subjects answered no. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated

[23]. After, our study population consisted of 1,050 subjects, 74 subjects answered yes and 950 subjects answered no. We then accounted for those who provided responses to OC and HRT use. After, our OC/CSQ040 study population consisted of 1664 subjects, 123 subjects responded "yes" and 1541 subjects responded "no". Our HRT/CSQ040 study population consisted of 1655 subjects with 123 subjects responded "yes" and 1532 subjects responded "no".

During the past 12 months have you had a taste or other sensation in your mouth that does not go away?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question," During the past 12 months have you had a taste or other sensation in your mouth that does not go away?"[33]. 7,407 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,024 subjects, 66 subjects answered yes and 958 subjects answered no. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [23]. After, our study population consisted of 1,024 subjects, 66 subjects answered yes and 958 subjects answered no. We then accounted for those who provided responses to OC and HRT use. After, our OC/CSQ110 study population consisted of 1667 subjects, 134 subjects responded "yes" and 1533 subjects responded "no". Our HRT/CSQ110 study population

consisted of 1658 subjects with 134 subjects responded “yes” and 1524 subjects responded “no”.

Covariates and Confounding Variables

In our study we included a number of covariates, based off a review of literature and well-known risk factors for neurodegenerative diseases, if they were available in the NHANES datasets. Confounding variables were controlled for in our logistic regression models.

The demographic variables are as follows: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade) [33].

Modifiable health variables and risk factors are as follows: ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [33].

Statistical Analysis

Statistical analysis was performed using SAS software [52]. The 2011-2012 and 2013-2014 survey cycles were merged and a four-year sampling weight was calculated to account for the complex sampling design in order to calculate correct statistical estimates and standard errors when calculating means, geometric means, and other statistics [53].

For phthalate and BPA variables, a value of “0” indicates above the limit of detection and a value of “1” indicates below the limit of detection. Individuals with a

below the limit of detection were given a dummy phthalate level of the LOD divided by the square root of two [6]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle, where the LOD for that year was used to make a determination if the EEDC was above or below the LOD. [7]. We log-transformed and then adjusted for creatinine all phthalate and BPA variables [54–56] since environmental chemical data is not normally distributed and urine dilution varies from person to person. We used the SAS Survey procedures to account for the complex sampling design of the NHANES data sets [57].

We used PROC SURVEYFREQ was used to obtain descriptive statistics for the different populations we were examining in our study which accounts for the complex survey design of the NHANES data sets [57]. Descriptive statistics were organized based on the following categories per variable: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade), ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [33].

We used PROC SURVEYREG and guidance provided by the SAS institute to directly to determine the geometric mean of the EEDC to test if they were significant between the responses of our outcome variables [57,58]. The standard errors were calculated using the Taylor Series linearization method, which is the default method in the survey procedures to calculate standard error [57]. Geometric means (GM), geometric standard

errors (GSE), and number of subjects were reported for the results of the outcome variables for all subjects that had EEDCs over the LOD. We looked at geometric means between the surrogate of brain health (yes vs. no, low test score vs. high test score), and also performed age-specific, gender-specific, and race/ethnicity-specific geometric means between the responses to the outcome variable. Due to the smaller range of ages in our dataset, 60 years and older, we calculated age-specific rates in lieu of age-standardized rates.

For OC and HRT use, which are both dichotomous variables, we performed a chi-square test of independence using PROC SURVEYREG with the CHISQ command to look for any relationships between OC and HRT use and our surrogate brain health indicators. We used PROC SURVEYLOGISTIC to find the unadjusted and adjusted odds ratios (ORs) and the 95% confidence intervals (CI) to examine the association between the surrogates of brain health and exposures to phthalates and BPA [57]. Analysis was done per EEDC per outcome variable. We presented three logistic regression models which were stratified by gender and examined phthalate and BPA exposures in the following groups, variable < LOD to 50^{th} percentile (reference) and $\geq 50^{th}$ percentile. The three logistic regression models are as follows: unadjusted, adjusted for known risk factors, age, education, race/ethnicity, adjusted for known and suspected risk factors, age, education, race/ethnicity, smoking, blood pressure history, history of coronary heart disease, stroke, heart attack, diabetes status, head trauma, and alcohol use. We did not include income, OC and HRT use in our models as they significantly reduced the size of the population.

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CHAPTER V

MANUSCRIPT II

EXPOSURE TO PHTHALATES AND BISPHENOL-A AND ASSOCIATIONS WITH BRAIN HEALTH: NHANES 2011-2014

ABSTRACT

BACKGROUND: The role of estrogenic endocrine disrupting chemicals (EEDCs) and their role in the development of neurodegenerative disease is of great public health concern, due to increasing exposures to these chemicals and increasingly aging population. Evidence suggests EEDCs exposure plays a role in the development of neurodegenerative disease, although epidemiological evidence is lacking in this area. Phthalates and Bisphenol-A are two of the most widespread EEDCs with demonstrated estrogenic activity, which affects brain health.

OBJECTIVE: The objective of this study is to investigate the relationship between surrogate brain health indicators and exposure to phthalates and BPA among the older individuals of the United States (US) population.

METHODS: In this study, we analyzed participants from the Center for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) in the survey cycles 2011-2012 and 2013-2014. The participants were 60 years of age and older who had phthalates and BPA urine samples taken during the examination portion of the survey. Other data pertaining to covariates and demographics were also obtained. In total, ten phthalate metabolites and Bisphenol-A were selected since >60% of participants had levels over the established limit of detection (LOD). The ten analyzed EEDCs were the following: Mono (carboxynonyl) Phthalate (CNP); Mono (carboxyoctyl) Phthalate

(COP); Mono-(2-ethyl-5-carboxypentyl) Phthalate (ECP); Mono-n-butyl Phthalate (MBP); Mono-(3-carboxypropyl) Phthalate (MC1); Mono-ethyl Phthalate (MEP); Mono (2-ethyl-5-hydroxy hexyl) Phthalate (MHH); Mono-(2-ethyl-5-oxohexyl) Phthalate (MOH); Mono-benzyl Phthalate (MZP); Mono-isobutyl Phthalate (MIB); Bisphenol-A (BPA). These EEDCs were analyzed versus surrogate brain health indicators available in the form of administered cognitive tests and self-reported questions, available in the NHANES datasets. The surrogate brain health indicators were as follows: immediate recall test; delayed recall test; animal fluency test; digit symbol substitution test. The surrogate brain health indicator self-reported questions were as follows: worsening memory over the past 12 months; trouble remembering over the past week; difficulty remembering or because you experience periods of confusion. The following smell and taste questions were also included as surrogate brain health indicators due to their potential as pre-clinical indicators of cognitive impairment: phantom odor (phantosmia) and problems with ability to taste sweet, sour, salty, or bitter foods over the past 12 months. Geometric means were calculated to compare the surrogate brain health indicators versus the EEDC concentrations. Logistic regression was then used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to examine the associations between the surrogate brain health indicators and EEDC concentration. Three logistic regression models were presented in our study, stratified by gender: unadjusted; age, race, education; age, race, education, body mass index (BMI), smoking status, blood pressure, diabetes status, alcohol use, coronary heart disease status, heart attack status, stroke status, head injury status, and physical activity status.

RESULTS: Increased levels of phthalate metabolites were observed in those who had lower cognitive test scores, reported having memory issues, and reported taste and smell deficits compared to those who did not have any observed brain health issues. Females have a greater bioburden of phthalates compared to males. In females, the phthalates ECP, MBP, MOH, MZP, and MIB were observed to have significantly higher bioburdens among two or more of the surrogate brain health indicators. In males, the phthalates ECP, MHH, MOH, and MIB were observed to have significantly higher bioburdens among two or more of the surrogate brain health indicators. BPA did not have any significant results in any of our tests. When controlling for known and suspected covariates of AD in males in our final logistic regression model, COP, ECP, MBP, MC1, MEP, MHH, MOH, and MIB were associated with one or more of the surrogate brain health indicators. When controlling for known and suspected covariates of AD in females in our final logistic regression model, ECP, MBP, MHH, MOH, MZP, and MIB were associated with one or more of the surrogate brain health indicators. BPA did not have any significant results in any of our tests.

CONCLUSION: Our study takes a novel approach to assessing cognitive dysfunction neurodegenerative disease and exposures to phthalate and BPA. It appears there is a link between exposure to phthalates and adverse brain health. Further research is needed with the use of clinical endpoints to further establish the relationship between neurodegenerative disease and phthalate/BPA exposure.

MANUSCRIPT II

EXPOSURE TO PHTHALATES AND BISPHENOL-A AND ASSOCIATIONS WITH BRAIN HEALTH: NHANES 2011-2014

INTRODUCTION

The role of exposure to EEDCs and neurodegenerative disease development is of great public health concern as stated by the World Health Organization (WHO) [1], due to an increasingly aging population [2]. Exposures to EEDCs have been linked to neurodegenerative diseases and other adverse brain health conditions, such as Alzheimer's disease (AD). In this study, we examine the associations of two of the mostly widely present phthalate and phenol compounds, phthalates and BPA, and their associations with brain health in an older US population.

Phthalates are class of estrogenic endocrine disrupting chemicals that have a role in the development of neurodegenerative disease. Phthalates, also known as plasticizers, are chemicals used in plastics to make them flexible and resilient [3–5]. Exposure to phthalates comes through ingestion, inhalation, and to a lesser extent, dermal contact with phthalate-containing products [6]. Phthalates are found in most consumer products. These include the following: wall coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, baby products, toys, shoes, packing materials, medical devices, paints, glue, nail polish, hair spray, insect repellents, food packaging materials, cosmetics, insecticides, and drug products [3–5]. Phthalates have short biological half-lives and do not accumulate, with urine as the primary route of excretion [7]. Specific phthalates are also found in high levels among the US population. One study, found the body burden of the phthalates mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MBP) and and

mono-benzyl phthalate (MBzp) in 97% of samples tested from the CDC NHANES 1999-2000 datasets [8]. As such, most of the US population has some measurable levels of phthalates in their bodies [7].

Phthalates have also been demonstrated to have estrogenic activity and affinity for estrogen receptors [9,10] and have been shown to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [11].

There is limited information regarding human epidemiological studies with neurodegenerative disease and phthalate bioburden. Animal studies are numerous and have shown phthalates to adversely affect brain function. These adverse effects include negatively affecting learning [12,13], negatively affecting memory [13,14], interfering with locomotion [14], negative affecting social behavior [12], and producing cellular effects such as cell death, synaptic loss, and synaptic dysfunction [15]. Some animal studies have reported an improvement in memory [16], and possible dose-dependent effects, where memory improves one dose, but degrades it in another dose [17].

Human epidemiological studies have focused on pre-natal and early life exposure with regards to behavior, IQ, reproductive, and cognitive development with few focusing on older populations. Studies have indicated phthalate exposure to be associated with social deficits [18], decreased visual recognition memory [19] and decreased IQ [20]. However, there is evidence to suggest inconsistent cognitive and behavioral effects in children with regards to phthalate type and gender [21,22]. Only one study, using the NHANES 2011-2012 datasets found higher bioburdens of phthalates in individuals with memory issues [23].

BPA is a synthetic chemical that is widely used to make polycarbonate plastics and resins [24]. BPA is found in many consumer products and plastics. These products

include the following: baby bottles, compact discs, impact-resistant safety equipment, medical devices, food cans and tops, water supply pipes, ATM receipts and dental sealants and composites [24]. Food containers made with BPA can cause BPA to leech into foods by the use of high heat [24]. It is of note that during the 2003-2004 NHANES data cycle, BPA was detected in 93% of urine samples collected from subjects 6 years of age and older [25].

BPA has been shown to be weakly estrogenic and have a low affinity for binding to ER receptors, but is speculated to exert its effects through other non-classical pathways [26]. BPA has also been shown to interact with estrogen-responsive genes that are implicated in neurodegenerative disease pathways [11].

Animal studies are numerous and have demonstrated BPA's negative effects on brain health and function. In animal studies BPA has been shown to negatively affect memory [27–41], negatively affect neurogenesis [33,42], negatively affect the structure of dendritic spines and synaptogenesis [27,29,32,38,40,43], and negatively affect cellular processes, protein expression and expression [31,36,39,41]. There are also animal studies that shows BPA exerts no negative effects on spatial and working memory [44–46].

The few human epidemiological studies have concentrated on pre-natal BPA exposure and exposure in children which have been associated with significant behavioral issues in children [35,47–50].

OBJECTIVE

There is limited information regarding exposures to phthalates and BPA the development of cognitive dysfunction and neurodegenerative disease in older populations. In this study we examine the relationship between 10 different phthalate metabolites and BPA with surrogate brain health indicators, from the CDC's NHANES 2011-2012 and 2013-2014 data cycles. The objectives of the study are as follows: 1) to assess the mean phthalate and BPA levels in older adults in the US, 60 years of age and above with the surrogates of brain health indicators in the US population, 2) assess the association between phthalate and BPA levels and surrogate brain health indicators in older adults in the US, to find the risk of poor cognitive function and development of mild cognitive impairment, dementia, and AD.

METHODS

Study Design and Population: NHANES is a continuous cross-sectional data collection utilizing a complex multi-stage sampling design that creates a survey representative of the non-institutionalized population of the United States [51,52]. The survey has been conducted since 1999 and consists of an at-home questionnaires followed by a standardized physical examination and specimen collection conducted in mobile examination centers (MEC) [51,52]. Eligibility is determined using preset selection probabilities for the desired demographic subdomains [52]. A household screener is performed before to determine if any household members are eligible for the interview and examination [52]. The interview collects demographic, health, nutrition, and household information, while the physical examination includes physical measurements, dental examination, and the collection of blood and urine specimens for laboratory testing [52].

Prior to any to interviews and examinations, informed consent was obtained and all procedures were approved by the CDC Institutional Review Board [53].

In our study, we merged the NHANES 2011-2012 and 2013-2014 data cycles. All our analyses were limited to individuals 60 years of age and older who have recorded responses to cognitive test scores and/or memory and taste/smell questions and have EEDC urine measurements.

Inclusion/Exclusion Criteria

Inclusion criteria:

5. Males and females, 60 years of age and older
6. Available EEDC urine measurements (Phthalates, BPA)
7. Urine creatinine measurements >30 mg/dl and <300 mg/dl.
8. Complete responses to identified outcome variables.

Exclusion criteria:

5. Males and females, 59 years of age and younger
6. Unavailable EEDC urine measurements (Phthalates, BPA)
7. Urine creatinine measurements <30mg/dl and >300mg/dl
8. Incomplete responses to identified outcome variables.

Phthalate Exposure Assessment and Measurements

Phthalates were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [54,55] . The laboratory utilized high performance liquid chromatography-electrospray ionization-tandem mass spectrometry to analyze urine phthalate levels and was consistently used in both survey cycles [54,55]. Phthalate levels

were provided in ng/ml and was used in our analyses. The following phthalates were used in our analyses: Mono (carboxynonyl) Phthalate (CNP); Mono (carboxyoctyl) Phthalate (COP); Mono-(2-ethyl-5-carboxypentyl) Phthalate (ECP); Mono-n-butyl Phthalate (MBP); Mono-(3-carboxypropyl) Phthalate (MC1); Mono-ethyl Phthalate (MEP); Mono (2-ethyl-5-hydroxy hexyl) Phthalate (MHH); Mono-(2-ethyl-5-oxohexyl) Phthalate (MOH); Mono-benzyl Phthalate (MZP); Mono-isobutyl Phthalate (MIB).

The limit of detection variables indicates if subjects have urine phthalate levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy phthalate level of the LOD divided by the square root of two [56]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [57]. The specific phthalate metabolites were selected as >60% of study subjects had urine phthalate levels above the LOD. A total of 5,175 subjects had available urinary phthalate measurements in the 2011-2012 and 2013-2014 datasets.

BPA Exposure Assessment and Measurements

BPA was measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [58,59] . The laboratory on-line solid phase extraction coupled to high performance liquid chromatography and tandem mass spectrometry to analyze urine BPA levels and was consistently used in both survey cycles [58,59]. BPA levels were provided in ng/ml.

The limit of detection variables indicates if subjects have urine phthalate levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy BPA level of the LOD divided by the square root of two [56]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [57]. A total of 5,175 subjects had available urinary BPA measurements in the 2011-2012 and 2013-2014 datasets.

Assessment of Surrogate Brain Health Indicators – Cognitive Scores

CERAD Word Learning Subtest – Immediate Recall and Delayed Recall: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning Subtest assesses both immediate and delayed learning [60,61]. The delayed and immediate recall tests available in NHANES assess the ability to process new verbal information [60,61]. The tests are part of the neuropsychological assessment for the entire CERAD testing protocol, which was initially created to standardize Alzheimer's disease (AD) assessment and diagnosis [62]. The tests in the neuropsychological assessment itself were chosen because of their ability to assess cognitive functions inherent in AD [62]. The assessments have the ability to differentiate those of adequate cognitive status versus those who have mild cognitive impairment or dementia [62–65]. Although developed for use in the assessment of AD, the CERAD assessments have shown utility in use for Parkinson's disease [65] and frontotemporal lobar degeneration [66].

Immediate Recall: For immediate recall, the subjects are asked to read aloud a sequence of 10 unrelated words as they are presented to them and immediately after, they are asked to recall as many words as possible [60,61]. This is done in three trials with the order of the

words differing in each trial. [60,61]. Each trial has a maximum score of 10, with a maximum overall score of 30 [60,61,63].

In our study, we included individuals 60 years of age and older who completed all immediate recall word list trials identified as: CFDCST1, CFDCST2, and CFDCST3 in the 2011-2012 and 2013-2014 NHANES data cycles. Those who did not have three trials completed were not included in the immediate recall analysis. We summed the total of the three trials and created a new variable with cut-off scores named IMMEDIATERECALL. A cut-off score of ≤ 13 and ≥ 14 was used as it is the standard in other assessments [63,67]. A total of 3,149 subjects from the 2011-2012 and 2013-2014 responded with complete immediate recall trials. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our study population consisted of 940 subjects, 146 subjects with cut-off scores ≤ 13 and 794 subjects with cut-off scores ≥ 14.

Delayed Recall: For delayed recall, the subject is asked to repeat the sequence of 10 unrelated words after the other cognitive tests are completed, which is typical 8 to 10 minutes after the start of the word learning trials [60,61]. The maximum score is 10 for delayed recall [60,61].

In our study, we included subjects 60 years of age and older who completed the delayed recall trial, identified as CFDCSR, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with the cut-off scores named DELAYEDRECALL. A cut-off score of ≤ 3 and ≥ 4 was used as it is the standard in other assessments [63,67,69]. A total of 3,126 subjects from the 2011-2012 and 2013-2014

responded with a complete delayed recall trial. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our study population consisted of 930 subjects,157 subjects ≤ 3 and 776 subjects ≥ 4.

Animal Fluency: The animal fluency test is used to determine categorical verbal fluency, which is part of executive function and can differentiate between with normal cognition versus those with MCI and more severe cognitive impairment, such as AD [60,61]. Since the test uses animal names, it does not require cultural consideration or formal education experience [60,61]. In the test, subjects are asked to name as many animals in a one minute span, with a maximum range of 40 words in the NHANES 2011-2014 data set. [60,61]. A sample test is given to each subject before the actual test [60,61].

In our study, we included subjects 60 years of age and older who completed the animal fluency trial, identified as CFDAST, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with cut-off scores named VERBALFLUENCY. cut-off score of ≤ 11 and ≥ 12 was used as it is the standard in other assessments [63,67,69,70]. A total of 3,110 subjects from the 2011-2012 and 2013-2014 responded with complete animal fluency scores. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our study population consisted of 931 subjects, 187 subjects ≤ 11 and 744 subjects ≥ 12.

Digit Symbol Substitution Test: The Digit Symbol Substitution Test (DSST) is part of the Wechsler Adult Intelligence Scale (WAIS III) [60,61,71]. The test measures processing speed, sustained attention, and working memory [60,61,71]. The subtests have shown utility in the identification of dementia and other neurodegenerative disorders such as AD [72–74]. The test is given in paper form, with a key that has 9 numbers paired to different symbols. The subject has 2 minutes to match each symbol to 133 boxes with a number associated to it, with the score as the total correct matches with a maximum score of 105 in the 2011-2014 NHANES dataset. [60,61]. A sample test is given to each subject before the actual test [60,61].

In our study, we included subjects 60 years of age and older who completed the animal fluency trial, identified as CFDDS, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with cut-off scores named DSST, cut-off score of ≤ 27 and ≥ 28 was used as it is the standard in other assessments [75–77]. A total of 3,014 subjects from the 2011-2012 and 2013-2014 responded with complete DSST. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our study population consisted of 891 subjects,129 subjects ≤ 27 and 762 subjects ≥ 28.

Assessment of Surrogate Brain Health Indicators – Memory Function

During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the yes/no question, "During the past 12 months, have you experienced confusion or memory loss

that is happening more often or is getting worse?" [78]. As memory loss and confusion are early indicators of cognitive decline, dementia, and AD [2]. 3,628 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle. We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our study population consisted of 1,025 subjects,181 subjects answered "yes" and 844 subjects answered "no".

During the past 7 days, how often have you had trouble remembering where you put things?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question," During the past 7 days, how often have you had trouble remembering where you put things, like you keys or your wallet?" [78]. 3,448 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

The question is multi-leveled, where 3,448 subjects answered "Never" equaling the value "0", 809 subjects answered "About once" equaling the value "1", 544 subjects answered "Two or three times" equaling the value "2", 175 subjects answered "Nearly every day" equaling the value "3", and 102 subjects answered "Several times a day" equaling the value "4". We created a new variable named MCQ380_WK, which combines responses coded as "Never" equaling "0" and "About once" equaling "1" into a variable, "No" equaling "1", and "Two or Three Times" equaling "2", "Nearly Every day" equaling "3", and "Several times a day" equaling "4", into a new variable, "Yes" equaling "1".

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our study population consisted of 971 subjects,188 subjects answered "1" and 783 subjects answered "2".

Are you limited in any way because of difficulty remembering or because you experience periods of confusion?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" [78]. Limitations in physical movement due to difficulty remembering and confusion can indicate the development of cognition issues [79]. 11, 323 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our study population consisted of 1,024 subjects, 165 subjects answered "yes" and 859 subjects answered "no".

Assessment of Surrogate Brain Health Indicators – Taste and Smell Function

It has been observed that neurodegenerative disease has been shown to be preceded by smell and taste disorders [80–83]. The causes of these disorders have been linked to genetic alterations [80], overexpression of key proteins[81], and direct effect of some environmental chemicals on the olfactory mucosa [84], which can have associations with exposure to EEDCs [80,81,83,84]. However, issues with olfaction can also be caused by upper

respiratory tract infections, sino-nasal disease, head trauma, idiopathic causes, surgery of the nasal area, and congenital loss of smell [85].

The two most common and prevalent neurodegenerative diseases, AD and PD have been shown to be preceded by smell disorders [86–91]. These disorders manifest themselves when evidence of pathological changes in the olfactory system are evident [91]. These are characterized by the build-up of pathological proteins, which cause the death of olfactory cells [91]. Several human epidemiological studies have also alluded to the utility of using sensory biomarkers as an early detection for neurodegenerative diseases [92–95].

Do you sometimes smell and unpleasant, bad, or burning odor when nothing is there?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question, "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" [78]. 7,399 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our delayed recall study population consisted of 1,024 subjects, 74 subjects answered "yes" and "950" subjects answered no.

During the past 12 months have you had a taste or other sensation in your mouth that does not go away?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question," During the past 12 months have you had a taste or other sensation in your mouth that does not go away?"[78]. 7,407 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for subjects who had urinary phthalates and BPA samples taken and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [68]. After, our delayed recall study population consisted of 1,024 subjects, 66 subjects answered yes and 958 subjects answered no.

Covariates

In our study we included a number of covariates, based off a review of literature and well-known risk factors for neurodegenerative diseases, if they were available in the NHANES datasets.

The demographic variables are as follows: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade) [78].

Modifiable health variables and risk factors are as follows: ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [78].

Statistical Analysis

Statistical analysis was performed using SAS software [96]. The 2011-2012 and 2013-2014 survey cycles were merged and a four-year sampling weight was calculated to account for the complex sampling design in order to calculate correct statistical estimates and standard errors when calculating means, geometric means, and other statistics [97].

For phthalate and BPA variables, a value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy phthalate level of the LOD divided by the square root of two [56]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle, where the LOD for that year was used to make a determination if the EEDC was above or below the LOD. [57]. We log-transformed and then adjusted for creatinine all phthalate and BPA variables [98–100] since environmental chemical data is not normally distributed and urine dilution varies from person to person.

We used the SAS Survey procedures to account for the complex sampling design of the NHANES data sets [101].

We used PROC SURVEYFREQ was used to obtain descriptive statistics for the different populations we were examining in our study which accounts for the complex survey design of the NHANES data sets [101]. Descriptive statistics were organized based on the following categories per variable: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade), ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [78].

We used PROC SURVEYREG and guidance provided by the SAS institute to directly to determine the geometric mean of the EEDC to test if they were significant

between the responses of our outcome variables [101,102]. The standard errors were calculated using the Taylor Series linearization method, which is the default method in the survey procedures to calculate standard error [101]. Geometric means (GM), geometric standard errors (GSE), and number of subjects were reported for the results of the outcome variables for all subjects that had EEDCs over the LOD. We looked at geometric means between the surrogate of brain health (yes vs. no, low test score vs. high test score), and also performed age-specific, gender-specific, and race/ethnicity-specific geometric means between the responses to the outcome variable. Due to the smaller range of ages in our dataset, 60 years and older, we calculated age-specific rates in lieu of age-standardized rates.

We used PROC SURVEYLOGISTIC to find the unadjusted and adjusted odds ratios (ORs) and the 95% confidence intervals (CI) to examine the association between the surrogates of brain health and exposures to phthalates and BPA [101]. Analysis was done per EEDC per outcome variable. We presented three logistic regression models which were stratified by gender and examined phthalate and BPA exposures in the following groups, variable < LOD to 50^{th} percentile (reference) and $\geq 50^{th}$ percentile. The three logistic regression models are as follows: unadjusted, adjusted for known risk factors, age, education, race/ethnicity, adjusted for known and suspected risk factors, age, education, race/ethnicity, smoking, blood pressure history, history of coronary heart disease, stroke, heart attack, diabetes status, head trauma, and alcohol use. We did not include income, OC and HRT use in our models as they significantly reduced the size of the population.

RESULTS

Descriptive statistics of Surrogates of Brain Health Indicators and Covariates:

Descriptive statistics of the study populations are described in table 1.1 for each of our 9 outcomes with their respective covariates. Urinary phthalate and BPA levels were available for 5,175 subjects in the 2011-2012 and 2013-2014 NHANES data cycles. Immediate Recall test scores were available for 940 subjects with 146 (12.43%) having lower immediate recall test scores. Delayed recall scores were available for 930 subjects with 157 (13.14%) having lower delayed recall scores. Animal Fluency scores were available for 931 subjects with 187 (12.85%) having lower animal fluency scores. DSST scores were available for 891 subjects with 129 (7.10%) having lower DSST scores. 1,025 subjects had yes/no responses to "Past 12 months, memory getting worse" with 181 (15.50%) responding "yes" to having worsening memory over the past 12 months. 971 subjects had yes/no responses to "Past 7 days, trouble remembering?" with 188 (18.16%) responding "yes" to having memory issues in the past 7 days. 1,024 subjects had yes/no responses to, "Limited due to difficulty remembering or confusion", with 165 (3.14%) responding "yes". 1,024 subjects had yes/no responses to experiencing phantom odor, with 74 (2.42%) responding "yes". 1,024 subjects had yes/no responses to experiencing sensation in their mouths that does not go away, with 66 (2.11%) answering "yes".

Among all the outcome variables and covariates, gender was fairly distributed between males and females. (Table 1.1). A majority of subjects fell with the 60-69-year age group (>50%), were predominantly non-Hispanic White (>70%), have completed >12th grade education (>55%), fall mostly in the overweight or obese range of BMI (>70%), have reported using alcohol (>70%), are fairly distributed by smoking status,

and are more physically inactive (>55%) (Table 1.1). Most subjects reported not having diabetes (>70%), having normal blood pressure (>65%), have not had a stroke (>90%), have not been diagnosed with coronary heart disease (>80%), and have not experienced significant head trauma (>85%). Among females, a majority reported using female hormones (>65%) and were fairly distributed in regards to birth control use.

Table 1.1 - Descriptive Statistics -- Surrogate brain health indicators and covariates for Pthalates and BPA	Immediate Recall Score (n=940)				Delayed Recall Score (n=930)				Animal Fluency Score (n=931)				Digit Symbol Substitution Test Score (n=891)				Past 12 months, memory getting worse? (1,025)				Past 7 days, trouble remembering? (n=971)				Limited due to difficulty remembering or confusion? (n=1,024)				Phantom Odor? (n=1,024)				Sensation in mouth that does not go away? (n=1024)			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total Population	≤ 13		≥ 14		≤ 3		≥ 4		≤ 11		≥ 12		≤ 27		≥ 28		Yes		No		Yes		No		Yes		No		Yes		No		Yes		No	
	146	12.43	794	87.57	157	13.14	776	86.86	187	12.85	744	87.15	129	7.10	762	92.90	181	15.50	844	84.50	188	18.16	783	81.84	165	3.14	859	23.09	74	2.42	950	39.04	66	2.11	958	39.35
Gender (n, %)																																				
Male	80	7.01	394	41.97	89	7.60	381	41.48	85	5.49	382	43.23	69	3.11	387	46.16	80	5.68	438	43.08	71	5.81	426	42.96	72	4.85	445	43.87	31	2.61	486	46.13	25	1.91	493	46.87
Female	66	5.42	400	45.61	68	5.54	395	45.38	102	7.35	362	43.92	60	3.99	375	46.75	101	9.82	406	41.42	117	12.35	357	38.88	93	7.12	414	44.16	43	3.23	464	48.03	41	3.18	465	48.05
Age (years) (n, %)																																				
60-69	56	3.46	439	48.68	61	4.10	430	48.18	84	4.06	408	48.38	53	2.16	429	51.13	69	5.11	464	46.69	89	7.85	419	44.66	75	4.69	458	47.15	50	4.06	482	47.72	40	3.06	492	48.73
70-79	37	4.39	242	27.57	43	4.57	235	27.45	56	5.04	218	26.56	40	2.08	230	30.08	52	5.37	250	26.15	59	6.26	229	24.85	36	2.98	266	28.57	17	1.25	285	30.28	13	1.01	289	30.52
80 +	53	4.58	113	11.33	53	4.47	111	11.23	47	3.75	118	12.22	36	2.85	103	11.69	60	5.02	130	11.66	40	4.06	135	12.33	54	4.30	135	12.31	7	0.53	183	16.16	13	1.01	177	15.67
Race/Ethnicity (n, %)																																				
Hispanic	37	1.69	158	6.27	42	1.93	152	6.04	43	1.83	151	6.15	49	2.20	129	5.23	38	1.51	177	6.79	42	1.71	150	5.96	50	1.99	165	6.32	21	0.89	194	7.42	26	0.93	189	7.38
Non-Hispanic White	56	8.45	360	69.72	53	8.86	360	69.32	47	6.79	364	71.25	23	2.49	377	76.45	86	11.58	356	65.36	89	13.65	333	63.64	58	7.44	383	69.48	25	3.88	417	73.09	25	3.57	417	73.39
Non-Hispanic Black	35	1.31	209	7.88	48	1.71	195	7.49	75	2.96	169	6.41	48	1.90	182	7.04	31	1.12	231	8.25	39	1.52	216	8.11	35	1.39	227	7.99	21	0.75	241	8.63	8	0.26	254	9.11
Non-Hispanic Asian/Other	18	0.98	67	3.69	14	0.63	83	4.65	22	1.27	60	3.35	9	0.50	74	4.18	26	1.27	80	4.11	18	1.29	84	4.13	22	1.14	84	4.25	7	0.33	98	5.02	7	0.31	98	5.04
Education (n, %)																																				
<12th Grade	80	4.71	218	16.99	79	4.71	216	16.90	102	6.08	192	15.44	93	4.52	171	16.17	74	5.63	271	18.05	71	4.91	252	18.27	77	5.34	268	18.37	35	2.04	310	21.66	35	2.19	309	21.47
Completed High School	29	3.28	177	18.10	31	3.29	173	18.11	43	3.32	161	18.14	15	1.16	184	20.27	38	2.73	182	18.05	45	4.22	164	16.20	38	2.82	181	17.90	19	1.42	201	19.37	11	0.72	209	20.07
>12 Grade	37	4.45	397	52.48	47	5.14	385	51.84	41	3.43	390	53.59	20	1.40	406	56.49	68	7.02	389	48.51	71	8.92	365	47.47	49	3.69	408	51.88	20	2.40	436	53.12	20	2.18	437	53.37
BMI (kg/m2) (n, %)																																				
Underweight (<18.5)	9	1.25	25	2.88	8	0.93	26	3.21	13	1.11	21	3.04	9	0.74	19	3.06	8	0.55	33	3.59	7	0.74	28	2.93	10	0.71	31	3.43	2	0.12	39	4.01	3	0.26	38	3.88
Normal Weight (18.5 to 24.9)	45	3.73	191	20.90	41	3.43	192	20.95	52	4.12	182	20.53	31	1.94	192	22.73	53	4.95	210	19.96	45	5.07	204	19.40	47	4.13	215	20.72	17	0.82	245	24.06	18	1.20	244	23.69
Overweight (25.0 to 29.9)	56	4.45	283	32.16	62	5.09	274	31.61	62	3.87	272	32.54	43	2.06	281	34.56	57	4.46	308	31.91	66	6.26	281	30.56	49	3.12	316	33.28	21	2.38	344	34.01	19	1.04	346	35.34
Obese (30.0+)	36	3.00	295	31.64	46	3.68	284	31.08	60	3.75	269	31.03	46	2.36	270	32.55	63	5.53	293	29.05	70	6.10	270	28.95	59	4.01	297	30.60	34	2.52	322	32.07	26	2.58	330	32.01
Alcohol Use (n, %)																																				
Yes	79	7.28	535	65.32	89	7.81	523	64.93	109	8.04	502	64.85	71	3.85	528	69.82	105	9.97	527	61.64	114	11.74	489	59.74	89	7.07	542	64.51	43	4.30	588	67.30	40	3.89	591	67.71
No	61	5.13	241	22.27	62	5.21	235	22.05	70	4.57	226	22.55	52	3.04	221	23.29	56	4.59	273	23.80	62	6.25	247	22.27	61	4.29	268	24.12	23	1.44	306	26.96	21	1.11	308	27.29
Ever Smoked (n, %)																																				
Yes	67	6.06	432	46.55	78	7.29	417	45.45	91	6.67	401	45.72	63	3.10	413	49.45	95	8.13	441	44.02	83	7.90	422	43.76	90	6.55	446	45.65	45	3.31	490	48.82	34	3.13	502	49.04
No	79	6.38	360	41.00	78	5.83	358	41.43	96	6.19	341	41.42	66	4.00	348	43.45	86	7.38	401	40.47	105	10.29	359	38.06	75	5.44	411	42.37	29	2.54	458	45.33	32	1.96	454	45.88
Physically Active? (n, %)																																				
Yes	49	4.22	310	37.22	52	5.10	305	36.50	55	3.50	302	38.03	36	1.69	309	40.29	48	4.06	332	36.14	59	6.05	302	33.66	44	3.00	335	37.15	25	2.17	355	38.04	17	1.14	362	39.04
No	97	8.20	484	50.35	105	8.04	471	50.36	132	9.35	442	49.12	93	5.41	453	52.61	133	11.43	512	48.37	129	12.11	481	48.17	121	8.97	524	50.88	49	3.67	595	56.11	49	3.95	596	55.88
Diabetes (n, %)																																				
Yes	42	2.64	200	18.09	42	2.37	200	18.47	63	3.72	179	17.16	49	2.67	177	18.00	50	3.77	213	16.70	48	3.84	200	16.95	51	3.07	212	17.41	28	2.36	235	18.11	21	1.35	241	19.09
No	93	9.07	558	68.73	105	9.93	540	64.77	114	8.55	528	66.07	75	4.13	546	70.90	120	11.24	592	63.96	131	13.60	543	61.08	105	8.31	606	66.87	43	3.29	668	71.90	42	3.58	670	71.65
Borderline	11	0.72	36	3.75	10	0.83	36	3.63	10	0.58	37	3.92	5	0.29	39	4.01	11	0.49	39	3.85	9	0.72	40	3.81	9	0.59	41	3.75	3	0.19	47	4.15	3	0.15	47	4.18
Blood Pressure (n, %)																																				
Normal	91	7.47	548	62.58	92	7.60	542	62.54	107	7.83	525	62.22	65	3.22	544	66.83	118	10.43	574	59.23	130	12.56	528	57.12	97	7.17	595	62.55	49	4.42	643	65.27	38	3.56	654	66.13
High	55	4.96	246	25.00	65	5.54	234	24.32	80	5.02	219	24.94	64	3.88	218	26.08	63	5.06	270	25.28	58	5.60	255	24.72	68	4.80	264	25.48	25	1.42	307	28.89	28	1.52	304	28.79
Myocardial Infarction (n, %)																																				
Yes	18	2.15	68	8.42	15	2.14	70	8.46	21	1.99	63	8.57	14	1.02	65	9.43	23	1.98	70	8.29	15	1.62	68	7.70	22	1.93	71	8.35	12	1.41	81	8.87	5	0.51	88	9.76
No	128	10.28	725	79.15	142	11.01	705	78.40	166	10.87	680	78.58	115	6.08	696	83.47	158	13.53	773	76.20	173	16.55	714	74.12	143	10.05	787	79.67	62	0.87	868	85.28	61	4.57	869	85.15
Stroke (n, %)																																				
Yes	16	0.82	53	4.77	16	0.93	53	4.69	30	1.59	38	4.01	16	0.87	41	4.11	23	1.45	63	4.91	20	1.73	60	4.61	26	1.68	60	4.68	8	0.49	77	5.83	2	0.15	84	6.21
No	130	11.65	738	82.77	141	12.15	720	82.13	156	11.08	704	83.32	113	6.25	718	88.77	157	14.06	779	79.59	168	16.49	720	77.17	139	10.32	796	83.31	66	5.37	870	88.31	64	4.95	871	88.69
Coronary Heart Disease (n, %)																																				
Yes	15	1.75	64	8.94	16	2.04	63	8.70	17	1.38	61	9.31	10	0.69	60	9.66	24	2.22	66	8.47	20	2.17	62	8.03	22	1.50	68	9.20	13	1.55	77	9.15	6	0.51	84	10.19
No	131	10.73	724	78.59	141	11.15	707	78.11	170	11.52	677	77.78	117	6.23	699	83.42	157	13.34	771	75.97	167	15.98	715	73.83	142	10.49	785	78.80	61	4.32	866	84.98	60	4.60	867	84.71
Head Trauma (n, %)																																				
Yes	20	2.14	98	11.74	15	1.70	102	12.14	17	1.42	97	12.35	8	0.56	103	13.17	35	2.65	85	10.52	31	2.81	78	10.25	32	2.12	87	10.98	13	0.85	107	12.33	9	0.92	111	12.26
No	126	10.33	695	75.78	142	11.48	673	74.68	170	11.48	646	74.76	121	6.56	658	79.71	146	12.90	757	73.93	156	15.40	704	71.54	133	9.89	770	77.01	61	5.02	841	81.81	57	4.18	845	82.64
Used Female Hormones (n, %)																																				
Yes	21	4.01	239	62.69	24	3.80	235	62.97	44	6.71	217	60.40	17	1.89	238	66.50	39	10.11	227	55.31	60	15.63	192	51.18	36	6.24	230	59.18	21	4.29	245	61.13	27	4.64	238	60.76
No	40	6.48	149	26.81	41	6.96	146	26.28	54	7.58	132	25.31	38	5.65	129	25.96	48	7.90	156	26.68	46	8.11	142	25.07	48	6.97	156	27.61	18	1.97	186	32.61	11	1.44	193	33.16
Used Birth Control (n, %)																																				
Yes	11	2.47	159	46.00	8	1.46	161	46.81	22	4.03	148	44.43	6	0.68	159	48.32	30	7.41	141	36.69	36	10.44	127	36.99	14	2.54	157	44.57	10	2.04	161	45.07	14	2.17	157	44.97
No	48	7.77	226	43.76	54	9.07	219	42.66	75	10.13	198	41.41	49	6.77	206	44.22	57	10.60	237	42.30	68	13.04	204	39.53	67	10.29	227	42.61	29	4.28	265	48.62	24	3.96	269	48.91

Associations Between Exposures to Phthalate and BPA and Cognitive Test Scores

Exposures to the 12 phthalate metabolites and BPA and four cognitive scores (immediate and delayed recall, animal fluency, and DSST score) are summarized in tables 1.2 to 1.21. The cognitive test scores have been used as a surrogate indicator of brain health to assess cognitive decline and the possible development of mild cognitive impairment, dementia, and/or AD elderly patients as part of neuropsychological testing.

Immediate Recall Scores and Exposure to BPA and Phthalates: Tables 1.2 to 1.5 present the GMs and GSEs of urinary phthalates and BPA levels among subjects with immediate recall scores. Table 1.2 presents GMs and GSEs of subjects who have measurable phthalate and BPA levels over the LOD by immediate recall cut-off scores. The phthalate metabolite, ECP, was significantly higher in subjects with immediate recall scores ≤ 13 compared to subjects who scored ≥ 14 ($p < 0.05$). Table 1.3 presents the age-specific GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by immediate recall cut-off score. In the 60-69 age group, the phthalate metabolite MEP was significantly higher in subjects who scored ≥ 14 than subjects who scored ≤ 13 ($p<0.05$). In the 70-79 age group, the GM mean of the phthalate metabolite MBP to be higher in subjects who scored ≤ 13 than in subjects who scored ≥ 14. ($p<0.05$). Table 1.4 presents the gender-specific GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by immediate recall cut-off score. Several phthalates were significantly higher in females with immediate recall scores ≤ 13 than in females who scored ≥ 14. ECP and MOH were found to be significantly higher in females with immediate recall scores ≤ 13 than in the ≥ 14 group ($p<0.05$), while MBP was found to be very significant in females who scored ≤ 13 than those who scored ≥ 14 group

($p<0.001$). Table 1.5 presents race-specific geometric GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by immediate recall cut-off score. Only one significant result was found with phthalate metabolite MIB being significantly higher in subjects who scored ≥ 14 score compared to subjects who scored ≤ 13 ($p<0.05$), among Asian/Others racial group. Table 1.6 presents the estimated ORs of phthalate and BPA levels by immediate recall scores. For ECP in the ≥ 50th percentile among females compared to the reference group, ECP was significantly associated with lower immediate recall scores in the unadjusted model (OR=2.591, 95% CI: 1.240-5.412), in adjusted model #1 (OR=2.361, 95% CI=1.0998-5.078), and adjusted model #2 (OR=2.402, 95% CI: 1.036-5.566). In the ≥ 50th percentile among females compared to the reference group, MBP was found to be significantly associated with lower immediate test scores in the unadjusted (OR=2.669, 95% CI: 1.394-5.111) and adjusted model #1 (OR=2.157, 95% CI: 1.086-4.283).

Table 1.2 Geometric Mean Urinary Phthalate and BPA Levels by Immediate Recall Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD						
EEDC	Geometric Mean (ng/ml) (GSE, N)					
	Immediate Recall Score ≤ 13			**Immediate Recall Score ≥ 14**		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	2.57	0.2472,	141	2.65	0.25	792
Mono (carboxyoctyl) Phthalate - COP	17.25	2.14	143	19.03	1.58	793
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**14.65**	**1.21**	**142 ***	11.72	0.61	793
Mono-n-butyl Phthalate - MBP	11.27	1.10	140	9.71	0.53	783
Mono-(3-carboxypropyl) Phthalate - MC1	2.91	0.37	138	2.68	0.18	755
Mono-ethyl Phthalate -MEP	45.78	7.12	143	57.46	5.22	794
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.44	0.77	143	7.12	0.35	793
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.75	0.53	142	4.80	0.25	793
Mono-benzyl Phthalate - MZP	4.80	0.54	140	4.10	0.21	784
Mono-isobutyl Phthalate - MIB	5.84	0.67	142	6.28	0.28	785
Bisphenol A - BPA	1.41	0.15	130	1.55	0.08	755

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.3 Age-Specific Geometric Mean Urinary Phthalate and BPA Levels by Immediate Recall Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD																		
EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Immediate Recall Score ≤ 13			**Immediate Recall Score ≥ 14**			**Immediate Recall Score ≤ 13**			**Immediate Recall Score ≥ 14**			**Immediate Recall Score ≤ 13**			**Immediate Recall Score ≥ 14**		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	2.38	0.27	53	2.54	0.18	439	3.34	0.74	36	2.85	0.25	240	2.12	0.21	52	2.66	0.24	113
Mono (carboxyoctyl) Phthalate - COP	17.15	3.06	55	18.12	2.07	438	20.93	5.40	36	21.85	2.02	242	14.33	2.12	52	16.81	2.04	113
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.99	1.92	54	10.70	0.79	438	15.40	2.41	36	13.30	0.76	242	15.31	1.99	52	12.68	0.76	113
Mono-n-butyl Phthalate - MBP	8.23	1.49	54	9.31	0.65	432	**12.66**	**1.25**	**36 ***	9.81	0.83	239	12.93	1.92	50	11.30	1.27	112
Mono-(3-carboxypropyl) Phthalate - MC1	2.55	0.25	50	2.50	0.22	418	4.04	1.30	36	2.91	0.29	229	2.32	0.26	52	2.93	0.31	108
Mono-ethyl Phthalate -MEP	41.12	6.06	55	**60.05**	**7.05**	**439 ***	64.48	14.11	36	58.66	7.45	242	35.60	8.22	52	45.23	5.30	113
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.03	1.08	55	6.59	0.48	438	9.51	1.81	36	8.04	0.44	242	7.81	0.96	52	7.35	0.61	113
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	4.80	0.81	54	4.33	0.31	439	6.53	1.08	36	5.48	0.28	242	5.84	0.72	52	5.43	0.44	112
Mono-benzyl Phthalate - MZP	3.84	1.06	54	4.05	0.32	434	4.12	0.83	36	3.82	0.30	239	5.02	0.89	50	5.13	0.54	111
Mono-isobutyl Phthalate - MIB	5.31	1.10	54	6.53	0.37	436	7.37	0.93	36	6.05	0.36	238	5.01	0.61	52	5.83	0.54	111
Bisphenol A - BPA	1.52	0.20	50	1.50	0.10	421	1.68	0.38	31	1.66	0.11	227	1.14	0.18	49	1.51	0.15	107

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.5 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by Immediate Recall Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic		Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White	
	Immediate Recall Score ≤ 13	**Immediate Recall Score ≥ 14**	**Immediate Recall Score ≤ 13**	**Immediate Recall Score ≥ 14**
Mono (carboxynonyl) Phthalate - CNP	2.2965 (0.1286, 37)	2.2965 (0.1286, 158)	2.4676 (0.2737, 54)	2.8334 (0.1894, 360)
Mono (carboxyoctyl) Phthalate - COP	23.8754 (3.4422, 37)	19.3870 (1.7161, 158)	17.3626 (3.1119, 54)	19.9950 (2.0021, 360)
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	21.0143 (2.3875, 37)	17.0325 (1.2343, 158)	13.9929 (1.6572, 54)	11.4191 (0.6811, 359)
Mono-n-butyl Phthalate - MBP	15.0088 (1.3451, 37)	13.4964 (1.0022, 156)	10.2638 (1.2350, 53)	9.1497 (0.6380, 354)
Mono-(3-carboxypropyl) Phthalate - MC1	2.9123 (0.5823, 36)	2.7870 (0.2652, 149)	2.8808 (0.5064, 53)	2.7439 (0.2397, 344)
Mono-ethyl Phthalate -MEP	96.4011 (37.1953, 37)	103.54 (10.1955, 158)	37.1518 (7.5889, 54)	52.6929 (5.5850, 360)
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	12.1871 (1.5294, 37)	9.8256 (0.8115, 158)	7.9610 (1.0074, 54)	6.9275 (0.3958, 359)
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	7.8263 (0.8892, 37)	6.3021 (0.5447, 158)	5.6054 (0.7171, 53)	4.6890 (0.2825, 359)
Mono-benzyl Phthalate - MZP	4.5260 (1.0839, 37)	3.7164 (0.2857, 158)	4.4628 (0.7253, 53)	4.0416 (0.2188, 354)
Mono-isobutyl Phthalate - MIB	8.9347 (0.6799, 37)	9.2662 (0.5774, 158)	5.0993 (0.7162, 54)	5.7985 (0.2729, 356)
Bisphenol A - BPA	1.7034 (0.3919, 32)	1.5965 (0.1383, 153)	1.2953 (0.1527, 52)	1.5743 (0.1014, 343)
EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black		Geometric Mean (ng/ml) (GSE, N), Asian/Other	
	Immediate Recall Score ≤ 13	**Immediate Recall Score ≥ 14**	**Immediate Recall Score ≤ 13**	**Immediate Recall Score ≥ 14**
Mono (carboxynonyl) Phthalate - CNP	2.2298 (0.1864, 35)	1.9424 (0.1190, 209)	4.9033 (2.8533, 15)	1.8193 (0.1971, 65)
Mono (carboxyoctyl) Phthalate - COP	16.7325 (2.3525, 35)	14.3818 (1.2288, 208)	9.5483 (2.7300, 17)	13.2066 (2.7433, 67)
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.4860 (2.8316, 34)	10.7172 (0.7589, 209)	14.0561 (1.7512, 17)	12.1370 (0.8803, 67)
Mono-n-butyl Phthalate - MBP	10.3880(1.6886, 35)	10.7279 (0.5481, 206)	17.1321 (1.9694, 15)	13.5408 (2.8390, 67)
Mono-(3-carboxypropyl) Phthalate - MC2	2.7616 (0.3375, 32)	2.1801 (0.1632, 204)	3.3319 (0.7287, 17)	2.4152 (0.4367, 58)
Mono-ethyl Phthalate -MEP	59.8544 (12.6913, 35)	83.9700 (8.4832, 209)	49.8820 (13.4898, 17)	48.2367 (15.6196, 67)
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.9757 (1.6401, 35)	7.1347 (0.4916, 209)	6.6561 (0.8808, 17)	6.8298 (0.8575, 67)
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.4584 (1.1728, 35)	4.8532 (0.3093, 209)	4.4377 (0.4585, 17)	4.5599 (0.5473, 67)
Mono-benzyl Phthalate - MZP	4.2698 (1.3594, 34)	4.6965 (0.3901, 207)	3.1107 (0.9491, 16)	4.7131 (1.8994, 65)
Mono-isobutyl Phthalate - MIB	7.6339 (0.6272, 34)	7.5526 (0.4351, 205)	6.1213 (1.2606, 17)	**9.8494 (1.8704, 66) ***
Bisphenol A - BPA	1.4074 (0.2446, 35)	1.4106 (0.06072, 201)	2.3009 (0.8958, 11)	1.2806 (0.1923, 58)

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.4 Gender-specific Geometric Mean Urinary Phthalate and BPA Levels by Immediate Recall Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						**Female**					
	Immediate Recall Score ≤ 13			**Immediate Recall Score ≥ 14**			**Immediate Recall Score ≤ 13**			**Immediate Recall Score ≥ 14**		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	2.50	0.35	78	2.34	0.15	392	2.69	0.37	63	2.97	0.25	400
Mono (carboxyoctyl) Phthalate - COP	14.97	1.82	79	16.83	1.27	393	20.97	4.18	64	21.32	2.72	400
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.68	1.27	79	10.56	0.60	394	**17.87**	**2.05**	**63 ***	12.90	0.84	399
Mono-n-butyl Phthalate - MBP	9.11	1.20	77	9.33	0.74	387	**15.01**	**1.25**	**63 *****	10.07	0.54	396
Mono-(3-carboxypropyl) Phthalate - MC1	2.72	0.47	77	2.49	0.20	376	3.19	0.53	61	2.87	0.26	379
Mono-ethyl Phthalate -MEP	41.95	8.92	79	54.22	6.17	394	51.64	9.54	64	60.62	6.80	400
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.64	0.84	79	6.69	0.41	394	9.69	1.20	64	7.53	0.43	399
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.12	0.60	78	4.52	0.29	393	**6.73**	**0.82**	**64 ***	5.07	0.30	400
Mono-benzyl Phthalate - MZP	3.46	0.43	77	3.63	0.28	389	5.83	1.11	63	4.58	0.25	395
Mono-isobutyl Phthalate - MIB	4.99	0.64	79	5.87	0.32	390	7.27	0.87	63	6.69	0.34	395
Bisphenol A - BPA	1.34	0.20	69	1.39	0.08	379	1.50	0.21	61	1.71	0.11	376

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.6 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by Immediate Recall Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	≤13 / ≥14	Unadjusted Odds Ratio [1]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #1 [2]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	38/199	1.00		38/198	1.00		38/190	1.00	
≥ 50th percentile	41/195	1.403	0.665-2.962	41/195	1.401	0.643-3.053	40/189	1.261	0.475-3.345
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	30/202	1.00		30/201	1.0		27/195	1.00	
≥ 50th percentile	34/198	0.816	0.461-1.442	34/198	1.045	0.585-1.864	32/190	1.235	0.704-2.167
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	39/197	1.00		39/197	1.00		38/190	1.00	
≥ 50th percentile	40/197	0.959	0.485-1.898	40/196	1.188	0.604-2.335	40/189	1.079	0.499-2.331
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	33/199	1.00		33/198	1.00		29/193	1.00	
≥ 50th percentile	31/201	0.770	0.388-1.526	31/201	0.795	0.422-1.498	30/192	1.044	0.531-2.051
ECP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	30/206	1.00		30/206	1.00		30/198	1.00	
≥ 50th percentile	49/188	1.772	0.764-4.110	49/187	1.421	0.612-3.298	48/181	1.195	0.614-2.328
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	24/208	1.00		24/207	1.00		22/200	1.00	
≥ 50th percentile	40/192	**2.591 ***	**1.240-5.412**	40/192	**2.361 ***	**1.098-5.078**	37/185	**2.402 ***	**1.036-5.566**
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	39/197	1.00		40/196	1.00		38/190	1.00	
≥ 50th percentile	40/197	1.012	0.459-2.232	39/197	0.638	0.320-1.272	40/189	0.748	0.375-1.494
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	23/209	1.00		23/208	1.00		21/201	1.00	
≥ 50th percentile	41/191	**2.669 ****	**1.394-5.111**	41/191	**2.157 ***	**1.086-4.283**	38/184	2.141	0.904-5.072
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	34/202	1.00		34/202	1.00		33/195	1.00	
≥ 50th percentile	45/192	1.223	0.563-2.654	45/191	1.227	0.550-2.739	45/184	1.063	0.424-2.666
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	33/199	1.00		33/198	1.00		29/193	1.00	
≥ 50th percentile	31/201	0.772	0.419-1.424	31/201	0.793	0.422-1.490	30/192	0.791	0.429-1.456
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	45/191	1.00		45/191	1.00		44/184	1.00	
≥ 50th percentile	34/203	1.102	0.445-2.726	34/202	1.265	0.529-3.021	34/195	1.235	0.608-2.506
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	33/199	1.00		33/198	1.00		29/193	1.00	
≥ 50th percentile	31/201	0.806	0.414-1.570	31/201	0.708	0.358-1.401	30/192	1.026	0.479-2.196
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	33/203	1.00		33/203	1.00		33/195	1.00	
≥ 50th percentile	46/191	1.485	0.681-3.239	46/190	1.369	0.631-2.972	45/184	1.370	0.728-2.578
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	28/204	1.00		28/203	1.00		27/195	1.00	
≥ 50th percentile	36/196	1.829	0.899-3.722	36/196	1.549	0.747-3.212	32/190	1.347	0.574-3.158
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	30/206	1.00		30/206	1.00		30/198	1.00	
≥ 50th percentile	49/188	1.756	0.792-3.896	49/187	1.439	0.663-3.124	48/181	1.416	0.652-3.072
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	29/203	1.00		29/202	1.00		26/196	1.00	
≥ 50th percentile	35/197	1.677	0.797-3.528	35/197	1.338	0.631-2.835	33/189	1.175	0.508-2.719
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	40/196	1.00		40/196	1.00		39/189	1.00	
≥ 50th percentile	39/198	0.959	0.560-1.644	39/197	1.011	0.600-1.704	39/190	1.168	0.652-2.090
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	31/201	1.00		31/200	1.00		29/193	1.00	
≥ 50th percentile	33/199	1.349	0.776-2.344	33/199	1.023	0.554-1.888	30/192	0.709	0.416-1.208
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	40/196	1.00		40/196	1.00		40/188	1.00	
≥ 50th percentile	39/198	0.953	0.403-2.252	39/197	0.846	0.322-2.221	38/191	0.720	0.285-1.823
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	28/204	1.00		28/203	1.00		26/196	1.00	
≥ 50th percentile	36/196	1.504	0.723-3.130	36/196	1.190	0.523-2.709	33/189	1.224	0.484-3.099
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	43/193	1.00		43/193	1.00		42/186	1.00	
≥ 50th percentile	36/201	0.736	0.367-1.474	36/200	0.718	0.378-1.366	36/193	0.663	0.350-1.257
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	37/196	1.00		37/195	1.00		36/185	1.00	
≥ 50th percentile	27/204	0.659	0.379-1.147	27/204	0.702	0.408-1.208	23/200	0.495	0.244-1.004

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Delayed Recall Scores and Exposure to BPA and Phthalates: Tables 1.7 to 1.11 present the GMs and GSEs of urinary phthalates and BPA levels among subjects with delayed recall scores. Table 1.7 presents GMs and GSEs of subjects who have measurable phthalate and BPA levels over the LOD by delayed recall cut-off scores. The crude GM levels of 6 of the 10 phthalate metabolites, ECP, MBP, MEP, MHH, MOH, and MZP, are higher in subjects that scored ≤ 3. No significant differences were found. Table 1.8 presents the age-specific GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by delayed recall cut-off score. No significant differences were found in any of the age groups. Table 1.9 presents the gender-specific GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by delayed recall cut-off score. There were several significant findings amongst females, with GM mean levels of ECP ($p<0.05$), MBP ($p<0.001$), MOH ($p<0.05$), and MZP ($p<0.05$) being higher in the subjects with a delayed recall score ≤ 3 compared to subjects with a delayed recall score ≥ 4. Table 1.10 presents race-specific geometric GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by delayed recall cut-off score. Significant findings were found, with the GM for MIB among Asian/other being significantly higher in subjects who scored ≥ 14 compared to those who scored ≤ 13 ($p<0.05$). The GMs for MHH, MOH, and MZP among Hispanics were significantly higher ($p<0.05$) in those who scored ≤ 3 compared to those who scored ≥ 4.

Table 1.11 presents estimated ORs of phthalate and BPA levels by delayed recall cut-off scores. For the phthalate ECP in the ≥ 50th percentile among females compared to the reference group, ECP was significantly associated with lower delayed recall scores in the unadjusted model (OR=2.218, 95% CI: 1.084-4.538), but not in the adjusted

models. For the phthalate MBP in the ≥ 50th percentile among females compared to the reference group, MBP was significantly associated with lower delayed recall scores (OR=2.174, 95% CI: 1.026-4.6605) in the unadjusted model. MBP was not found to be significantly associated with lower test scores in the adjusted models. For the phthalate MEP among females in the ≥ 50th percentile compared to the reference group, MEP concentrations were found to be significantly associated with lower delayed recall scores in the unadjusted model (OR=2.019, 95% CI: 1.027-3.969), adjusted model #1 (OR=2.409, 95% CI: 1.214-4.778), and adjusted model #2 (OR=2.443, 95% CI: 1.358-4.393). For the phthalate MOH among females in the ≥ 50th percentile compared to the reference group, MOH concentrations were found to be significantly associated with lower delayed recall scores in the unadjusted model (OR=2.386, 95% CI: 1.134-5.021). No significant associations were found in the adjusted models. For the phthalate MZP in females in the ≥ 50th percentile compared to the reference group, MZP concentrations were found to be significantly associated with lower delayed recall scores in the unadjusted model (OR=1.798, 95% CI: 1.068-3.026). No significant associations were found in the adjusted models. For the phthalate MIB among females in the ≥ 50th percentile, MIB concentrations were found to be significantly associated with lower delayed recall scores (OR=1.844, 95% CI: 1.045-3.252) when compared to the reference group in the unadjusted model. No significant associations were found in the adjusted models.

Table 1.7 Geometric Mean Urinary Phthalate and BPA Levels by Delayed Recall Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)	
	Delayed Recall Score ≤ 3	**Delayed Recall Score ≥ 4**
Mono (carboxynonyl) Phthalate - CNP	2.3874 (0.2028, 156)	2.6792 (0.1433, 773)
Mono (carboxyoctyl) Phthalate - COP	16.3583 (2.4210, 157)	19.1739 (1.5721, 775)
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	13.9383 (1.1101, 156)	11.7602 (0.5800, 775)
Mono-n-butyl Phthalate - MBP	11.7959 (1.1573, 154)	9.6276 (0.5050, 765)
Mono-(3-carboxypropyl) Phthalate - MC1	2.6840 (0.2796, 152)	2.7018 (0.1851, 737)
Mono-ethyl Phthalate -MEP	61.6129 (8.4627, 157)	55.1030 (4.6833, 776)
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.2016 (0.7581, 157)	7.1290 (0.3341, 775)
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.7034 (0.4356, 157)	4.7910 (0.2419, 774)
Mono-benzyl Phthalate - MZP	4.7526 (0.6688, 153)	4.0388 (0.1976, 767)
Mono-isobutyl Phthalate - MIB	5.8055 (0.6299, 156)	6.2925 (0.2863, 767)
Bisphenol A - BPH	1.4799 (0.1033, 150)	1.5383 (0.07611, 732)

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.8 Age-Specific Geometric Mean Urinary Phthalate and BPA Levels by Delayed Recall Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Delayed Recall Score ≤ 3			**Delayed Recall Score ≥ 4**			**Delayed Recall Score ≤ 3**			**Delayed Recall Score ≥ 4**			**Delayed Recall Score ≤ 3**			**Delayed Recall Score ≥ 4**		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	2.24	0.39	60	2.55	0.16	429	2.40	0.45	43	3.01	0.28	233	2.52	0.29	53	2.50	0.22	111
Mono (carboxyoctyl) Phthalate - COP	16.69	4.73	61	18.12	2.04	429	15.60	4.41	43	22.95	2.25	235	16.86	2.28	53	15.73	2.12	111
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.81	1.83	60	10.68	0.75	429	13.88	2.04	43	13.51	0.73	235	15.12	1.66	53	12.65	0.72	111
Mono-n-butyl Phthalate - MBP	12.42	3.42	60	9.01	0.59	423	11.18	1.00	43	9.99	0.87	232	11.90	1.47	51	11.66	1.34	110
Mono-(3-carboxypropyl) Phthalate - MC1	2.53	0.21	58	2.50	0.21	407	2.85	0.81	43	3.09	0.30	222	2.66	0.36	51	2.75	0.28	108
Mono-ethyl Phthalate -MEP	100.17	31.88	61	56.05	5.83	430	64.46	11.90	43	58.60	8.01	235	37.64	9.16	53	44.05	5.32	111
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.09	1.02	61	6.57	0.46	429	8.69	1.60	43	8.15	0.42	235	7.83	0.97	53	7.30	0.54	111
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.12	0.63	61	4.30	0.30	429	6.03	0.91	43	5.54	0.26	235	5.95	0.64	53	5.36	0.44	110
Mono-benzyl Phthalate - MZP	4.83	1.49	60	3.98	0.31	425	4.09	0.90	42	3.83	0.31	233	5.50	0.88	51	4.93	0.53	109
Mono-isobutyl Phthalate - MIB	5.14	1.30	60	6.56	0.35	427	7.17	0.80	43	6.06	0.37	231	5.22	0.73	53	5.73	0.65	109
Bisphenol A - BPA	1.57	0.22	61	1.49	0.09	408	1.54	0.23	39	1.68	0.12	219	1.35	0.18	50	1.41	0.18	105

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.9 Gender-specific Geometric Mean Urinary Phthalate and BPA Levels by Delayed Recall Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4			Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.06	0.17	89	2.43	0.16	378	2.94	0.40	67	2.93	0.27	395
Mono (carboxyoctyl) Phthalate - COP	13.30	2.07	89	17.19	1.37	380	21.74	4.04	68	21.18	2.71	395
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	11.68	1.18	89	10.67	0.61	381	**17.79**	**2.05**	**67 ***	12.86	0.83	394
Mono-n-butyl Phthalate - MBP	10.33	1.54	87	9.12	0.69	374	**14.09**	**1.51**	**67 *****	10.11	0.53	391
Mono-(3-carboxypropyl) Phthalate - MC1	2.49	0.25	88	2.52	0.22	362	2.99	0.57	64	2.88	0.25	375
Mono-ethyl Phthalate -MEP	64.55	13.13	89	50.28	4.94	381	57.80	11.19	68	59.91	6.77	395
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.22	0.81	88	6.74	0.40	381	9.77	1.28	68	7.51	0.42	394
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	4.87	0.49	89	4.55	0.29	379	**7.08**	**0.79**	**68 ***	5.02	0.30	395
Mono-benzyl Phthalate - MZP	3.72	0.54	86	3.58	0.28	377	**6.59**	**1.23**	**67 ***	4.51	0.23	390
Mono-isobutyl Phthalate - MIB	4.88	0.64	89	5.91	0.34	377	7.40	0.75	67	6.67	0.32	390
Bisphenol A - BPA	1.36	0.12	85	1.39	0.08	361	1.65	0.21	65	1.69	0.11	371

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.10 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by Delayed Recall Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4			Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.49	0.31	42	2.29	0.11	152	2.47	0.28	53	2.84	0.18	360
Mono (carboxyoctyl) Phthalate - COP	20.00	2.90	42	20.20	1.66	152	16.36	3.32	53	20.17	2.02	360
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	21.78	2.08	42	16.78	1.22	152	12.95	1.29	53	11.50	0.65	359
Mono-n-butyl Phthalate - MBP	14.98	1.23	42	13.51	1.07	150	11.53	1.60	52	9.00	0.60	354
Mono-(3-carboxypropyl) Phthalate - MC1	2.69	0.52	40	2.85	0.24	144	2.73	0.36	52	2.76	0.24	344
Mono-ethyl Phthalate -MEP	132.82	49.20	42	94.33	10.34	152	54.81	10.04	53	50.27	4.92	360
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**13.09**	**1.18**	**42 ***	9.55	0.76	152	7.53	0.90	53	6.96	0.37	359
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**8.30**	**0.76**	**42 ***	6.15	0.53	152	5.41	0.53	53	4.70	0.27	358
Mono-benzyl Phthalate - MZP	**5.38**	**1.13**	**42 ***	3.51	0.30	152	5.10	0.97	52	3.97	0.20	354
Mono-isobutyl Phthalate - MIB	8.95	0.72	42	9.32	0.56	152	5.16	0.76	53	5.80	0.27	356
Bisphenol A - BPA	1.75	0.27	39	1.58	0.15	145	1.44	0.14	52	1.56	0.10	342
EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4			Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.87	0.18	48	1.98	0.11	195	2.50	0.89	13	2.19	0.39	66
Mono (carboxyoctyl) Phthalate - COP	15.71	2.54	48	14.25	1.10	194	9.92	3.30	14	12.83	2.65	69
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.48	2.26	47	10.58	0.78	195	13.48	1.61	14	12.35	0.77	69
Mono-n-butyl Phthalate - MBP	9.15	1.61	48	11.08	0.64	192	16.09	3.54	12	13.99	2.70	69
Mono-(3-carboxypropyl) Phthalate - MC2	2.37	0.28	46	2.20	0.15	189	2.90	0.97	14	2.56	0.43	60
Mono-ethyl Phthalate -MEP	59.65	10.61	48	85.98	8.94	195	33.44	11.36	14	52.11	15.46	69
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.05	1.40	48	7.23	0.55	195	6.90	1.09	14	6.75	0.76	69
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.21	0.95	48	4.88	0.33	195	4.82	0.78	14	4.48	0.50	69
Mono-benzyl Phthalate - MZP	3.48	0.89	46	4.94	0.44	194	2.66	0.41	13	4.74	1.73	67
Mono-isobutyl Phthalate - MIB	7.03	0.88	47	7.70	0.51	191	4.94	1.67	14	**9.85**	**1.69**	**68 ***
Bisphenol A - BPA	1.36	0.14	47	1.42	0.07	188	1.69	0.53	12	1.40	0.23	57

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.11 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by Delayed Recall Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	≤3 / ≥4	Unadjusted Odds Ratio [1]	95% CI	≤3 / ≥4	Adjusted Odds Ratio #1 [2]	95% CI	≤3 / ≥4	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	46/189	1.00		46/188	1.00		43/183	1.00	
≥ 50th percentile	43/192	0.783	0.407 -1.505	43/192	0.738	0.358-1.522	41/187	0.662	0.307-1.426
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	38/193	1.00		38/193	1.00		35/186	1.00	
≥ 50th percentile	30/202	0.744	0.408 -.356	30/201	0.951	0.511-1.769	31/191	1.059	0.579-1.936
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	41/194	1.00		41/193	1.00		38/189	1.00	
≥ 50th percentile	48/187	0.694	0.297-1.619	48/187	0.747	0.315-1.774	46/181	0.754	0.389-1.462
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	35/196	1.00		35/196	1.00		33/189	1.00	
≥ 50th percentile	33/199	0.903	0.483-1.688	33/198	0.950	0.494-1.827	33/188	1.090	0.509-2.332
ECP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	35/200	1.00		35/199	1.00		32/195	1.00	
≥ 50th percentile	54/181	1.443	0.639-3.258	54/181	1.227	0.495-3.045	52/175	1.136	0.503-2.566
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	26/205	1.00		26/205	1.00		25/196	1.00	
≥ 50th percentile	42/190	**2.218 ***	**1.084-4.538**	42/189	1.950	0.941-4.043	41/181	1.983	0.858-4.582
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	40/195	1.00		40/194	1.00		37/190	1.00	
≥ 50th percentile	49/186	1.336	0.651-2.740	49/186	1.143	0.531-2.460	47/180	1.112	0.524-2.361
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	29/202	1.00		29/202	1.00		28/193	1.00	
≥ 50th percentile	39/193	**2.174 ***	**1.026-4.605**	39/192	1.698	0.749-3.852	38/184	1.742	0.698-4.347
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	37/198	1.00		37/197	1.00		34/193	1.00	
≥ 50th percentile	52/183	0.979	0.459-2.087	52/183	0.952	0.418-2.172	50/177	0.971	0.412-2.287
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	38/193	1.00		38/193	1.00		36/185	1.00	
≥ 50th percentile	30/202	0.584	0.314-1.084	30/201	0.570	0.298-1.092	30/192	0.539	0.275-1.058
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	40/195	1.00		40/194	1.00		37/190	1.00	
≥ 50th percentile	49/186	**2.019 ***	**1.027-3.969**	49/186	**2.409 ***	**1.214- 4.778**	47/180	**2.443 ****	**1.358-4.393**
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	31/200	1.00		32/199	1.00		29/192	1.00	
≥ 50th percentile	37/195	0.952	0.528-1.716	36/195	0.836	0.443-1.579	37/185	1.215	0.596-2.476
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	39/196	1.00		39/195	1.00		36/191	1.00	
≥ 50th percentile	50/185	1.141	0.412-3.156	50/185	1.067	0.351-3.243	48/179	1.232	0.463-3.281
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	26/205	1.00		26/205	1.00		25/196	1.00	
≥ 50th percentile	42/190	**2.411 ***	**1.146 5.072**	42/189	**2.120 ****	**1.013-4.436**	41/181	2.245	0.944-5.342
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	36/199	1.00		36/198	1.00		33/194	1.00	
≥ 50th percentile	53/182	1.315	0.538-3.215	53/182	1.131	0.438-2.920	51/176	1.194	0.498-2.863
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	25/206	1.00		25/205	1.00		24/197	1.00	
≥ 50th percentile	43/189	**2.386 ***	**1.134-5.021**	43/189	1.979	0.974-4.023	42/180	1.996	0.888-4.487
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	44/191	1.00		44/190	1.00		41/186	1.00	
≥ 50th percentile	45/190	1.214	0.613-2.405	45/190	1.213	0.628-2.343	43/184	1.307	0.698-2.447
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	29/202	1.00		29/202	1.00		29/192	1.00	
≥ 50th percentile	39/193	**1.798 ***	**1.068 3.026**	39/192	1.447	0.773-2.709	37/185	1.291	0.607-2.743
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	45/190	1.00		45/189	1.00		42/185	1.00	
≥ 50th percentile	44/191	0.671	0.278-1.620	44/191	0.620	0.250-1.534	42/185	0.539	0.217-1.336
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	29/202	1.00		29/202	1.00		28/193	1.00	
≥ 50th percentile	39/193	**1.844 ***	**1.045 3.252**	39/192	1.451	0.738-2.853	38/184	1.660	0.734-3.755
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	47/188	1.00		47/188	1.00		44/183	1.00	
≥ 50th percentile	42/193	0.705	0.440-1.130	42/192	0.691	0.421-1.133	40/187	0.612	0.328-1.140
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	36/194	1.00		36/196	1.00		35/186	1.00	
≥ 50th percentile	32/201	0.790	0.418-1.493	32/198	0.896	0.430-1.867	31/191	0.629	0.376-1.055

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Animal Fluency Scores and Exposure to BPA and Phthalates: Tables 1.12 to 1.16 present the GMs and GSEs of urinary phthalates and BPA levels among subjects with animal fluency scores. Table 1.12 presents GMs and GSEs of subjects who have measurable phthalate and BPA levels over the LOD by animal fluency cut-off scores. The crude GM mean of 7 of the 10 phthalates (ECP, MBP, MC1, MHH, MOH, MZP, MIB) and BPA are higher in subjects with a score of ≤ 11 compared to those with a score ≥ 12. 4 of the 10 phthalates GM means were found to be significant higher in subjects with an animal fluency score ≤ 11: ECP ($p<0.05$), MBP ($p<0.05$), MZP ($p<0.05$), and MIB ($p<0.05$). Table 1.13 presents the age-specific GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by animal fluency cut-off score. In the 60-69-year age group, 3 phthalates had significantly higher GMs in subjects with a animal fluency score ≤ 11 compared to subjects with a score of ≥ 12: ECP ($p<0.05$), MBP ($p<0.01$), and MIB ($p<0.05$). The phthalate COP has a significantly higher GM in the in subjects with an animal fluency score ≥ 12 ($p<0.05$). In the 70-79-year age group, MIB had a significantly higher GM in subjects with a score of ≤ 11 ($p<0.05$). In the 80+ years age group, 5 phthalates were found to have significantly higher GM mean levels in the Animal fluency Score ≤ 11 group: COP ($p<0.05$), ECP ($p<0.01$), MBP ($p<0.05$), MHH ($p<0.01$), MOH ($p<0.05$). Table 1.14 presents gender-specific geometric GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD by animal fluency cut-off score. In females, 5 of the phthalates had significantly higher GM means in subjects with an animal fluency score ≤ 11: ECP ($p<0.01$), MBP ($p<0.001$), MOH ($p<0.05$), MZP ($p<0.01$), and MIB ($p<0.05$). Table 1.15 presents race-specific geometric GMs and GSEs for subjects who have measurable phthalate and BPA levels over the

LOD by animal fluency cut-off score. In Hispanics, the GM level of MZP was significantly higher in the Animal fluency Score ≤ 11 group ($p<0.001$).

Table 1.16 presents the estimated ORs and 95% CIs of phthalate and BPA levels by animal fluency scores. For the phthalate MBP, with females in the ≥ 50th percentile group compared to the reference group, MBP concentration is associated with lower animal fluency scores in the unadjusted model (OR=2.369, 95% CI: 1.392-4.031), adjusted model #1 (OR=2.080, 95% CI: 1.151-3.757), and adjusted model #2 (OR=2.437, 95% CI: 1.190-4.989). For the phthalate MHH with females in the ≥ 50th percentile group, the MHH concentration is associated with lower animal fluency scores compared to the reference group in the unadjusted model (1.861, 95% CI: 1.078-3.212). The adjusted models were not significant (Table 1.16). For the phthalate MZP, with females in the ≥ 50th percentile, MZP concentration is significantly associated with lower animal fluency scores in the unadjusted model (OR=2.610, 95% CI: 1.573-4.332) and adjusted model #1 (OR=2.175, 95% CI: 1.281-3.692) compared to the reference group (Table 1.16). For the phthalate MIB, for females in the ≥ 50th percentile, MIB concentration is associated with lower animal fluency scores in the adjusted model (OR=2.205, 95% CI: 1.323-3.675) and adjusted model #1 (2.051, 95% CI: 1.111-3.786), compared to the reference group (Table 1.16).

Table 1.12 Geometric Mean Urinary Phthalate and BPA Levels by Animal Fluency Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)					
	Animal Fluency Score ≤ 11			**Animal Fluency Score ≥ 12**		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	2.51	0.18	185	2.68	0.16	742
Mono (carboxyoctyl) Phthalate - COP	17.14	2.05	186	19.24	1.71	744
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**14.26**	**0.97**	**187 ***	11.73	0.61	742
Mono-n-butyl Phthalate - MBP	**11.58**	**0.80**	**186 ***	9.67	0.54	730
Mono-(3-carboxypropyl) Phthalate - MC1	2.75	0.43	177	2.71	0.21	711
Mono-ethyl Phthalate -MEP	54.00	6.58	187	56.91	28.20	744
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.15	0.50	187	7.14	0.35	743
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.67	0.36	187	4.79	0.25	742
Mono-benzyl Phthalate - MZP	**5.51**	**0.66**	**185 ***	3.94	0.21	733
Mono-isobutyl Phthalate - MIB	**7.45**	**0.37**	**184 ***	6.08	0.30	737
Bisphenol A - BPA	1.55	0.12	174	1.53	0.08	705

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.13 Age-Specific Geometric Mean Urinary Phthalate and BPA Levels by Animal Fluency Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Animal Fluency Score ≤ 11			**Animal Fluency Score ≥ 12**			**Animal Fluency Score ≤ 11**			**Animal Fluency Score ≥ 12**			**Animal Fluency Score ≤ 11**			**Animal Fluency Score ≥ 12**		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	2.26	0.20	82	2.55	0.18	408	2.39	0.53	56	3.07	0.31	216	2.99	0.58	47	2.42	0.17	118
Mono (carboxyoctyl) Phthalate - COP	12.59	1.73	83	**18.60**	**2.20**	**408 ***	17.55	4.16	56	22.95	2.61	218	**23.14**	**3.57**	**47 ***	15.01	1.87	118
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**14.39**	**1.57**	**84 ***	10.57	0.78	406	12.55	1.51	56	13.70	0.81	218	**16.75**	**1.35**	**47 ****	12.59	0.85	118
Mono-n-butyl Phthalate - MBP	**12.31**	**1.02**	**83 ****	9.01	0.61	400	8.88	0.96	56	10.40	0.95	215	**15.52**	**2.33**	**47 ***	10.87	1.11	115
Mono-(3-carboxypropyl) Phthalate - MC1	2.24	0.34	79	2.52	0.23	387	2.70	0.88	52	3.13	0.36	210	3.54	0.49	46	2.62	0.29	114
Mono-ethyl Phthalate -MEP	46.72	9.39	84	59.47	6.99	408	54.94	9.76	56	61.26	8.77	218	61.72	13.91	47	37.56	4.22	118
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.11	0.89	84	6.56	0.48	407	7.42	0.79	56	8.36	0.54	218	**9.31**	**0.75**	**47 ****	7.08	0.52	118
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.55	0.64	84	4.26	0.30	407	5.04	0.59	56	5.69	0.35	218	**6.81**	**0.37**	**47 ***	5.25	0.43	117
Mono-benzyl Phthalate - MZP	5.56	1.09	83	3.93	0.31	403	5.06	0.80	55	3.65	0.32	216	6.11	0.97	47	4.77	0.44	114
Mono-isobutyl Phthalate - MIB	**8.11**	**0.78**	**83 ***	6.30	0.37	405	**7.38**	**0.55**	**54 ***	6.03	0.37	216	6.87	0.83	47	5.34	0.54	116
Bisphenol A - BPA	1.69	0.14	79	1.48	0.10	390	1.55	0.26	49	1.69	0.12	205	1.40	0.19	46	1.41	0.16	110

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.14 Gender-specific Geometric Mean Urinary Phthalate and BPA Levels by Animal Fluency Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.69	0.35	84	2.34	0.15	380	2.38	0.31	101	3.06	0.28	362
Mono (carboxyoctyl) Phthalate - COP	15.03	2.28	84	16.85	1.34	382	18.90	3.20	102	21.93	2.87	362
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	11.92	1.26	85	10.66	0.56	382	**16.30**	**1.10**	**102 ****	12.90	0.87	360
Mono-n-butyl Phthalate - MBP	8.73	0.86	85	9.35	0.73	372	**14.33**	**1.08**	**101 *****	9.98	0.56	358
Mono-(3-carboxypropyl) Phthalate - MC1	2.68	0.75	83	2.51	0.21	364	2.82	0.35	94	2.92	0.28	347
Mono-ethyl Phthalate -MEP	44.21	6.89	85	53.83	5.62	382	62.70	9.49	102	58.77	6.80	362
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.24	0.67	85	6.74	0.38	382	8.92	0.79	102	7.56	0.43	361
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	4.89	0.49	85	4.54	0.26	380	**6.34**	**0.49**	**102 ***	5.06	0.30	362
Mono-benzyl Phthalate - MZP	4.02	0.62	84	3.54	0.29	376	**6.97**	**0.86**	**101 ****	4.38	0.25	357
Mono-isobutyl Phthalate - MIB	6.75	0.57	84	5.60	0.32	379	**7.99**	**0.58**	**100 ***	6.59	0.35	358
Bisphenol A - BPA	1.54	0.23	76	1.37	0.07	366	1.55	0.10	98	1.71	0.11	339

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.15 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by Animal Fluency Cut-Off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.42	0.31	43	2.31	0.17	151	2.72	0.36	47	2.83	0.20	364
Mono (carboxyoctyl) Phthalate - COP	25.51	5.19	43	19.01	1.45	151	18.33	3.09	47	20.09	2.12	364
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	20.88	2.23	43	16.97	1.03	151	13.97	1.62	47	11.47	0.66	363
Mono-n-butyl Phthalate - MBP	15.33	2.05	43	13.36	0.89	149	10.65	1.19	47	9.17	0.64	357
Mono-(3-carboxypropyl) Phthalate - MC1	3.21	0.61	41	2.72	0.28	143	2.91	0.82	45	2.77	0.26	350
Mono-ethyl Phthalate -MEP	102.55	38.82	43	101.55	13.06	151	42.85	7.74	47	51.94	5.22	364
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	10.63	1.56	43	10.14	0.67	151	8.17	0.86	47	6.93	0.37	363
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	7.07	0.91	43	6.45	0.45	151	5.69	0.64	47	4.69	0.27	362
Mono-benzyl Phthalate - MZP	**6.02**	**0.94**	**43 *****	3.41	0.29	151	6.25	1.32	47	3.92	0.23	357
Mono-isobutyl Phthalate - MIB	10.39	1.04	43	8.85	0.46	151	6.83	0.69	46	5.64	0.28	361
Bisphenol A - BPA	1.60	0.22	40	1.62	0.17	144	1.59	0.20	43	1.54	0.10	349
EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.79	0.15	75	2.03	0.13	169	3.85	1.80	20	1.86	0.20	58
Mono (carboxyoctyl) Phthalate - COP	14.28	1.90	74	14.47	1.38	169	10.28	3.12	22	13.62	2.80	60
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.65	1.20	75	10.12	0.84	168	12.10	1.26	22	12.80	0.90	60
Mono-n-butyl Phthalate - MBP	10.99	0.92	75	10.43	0.67	165	13.81	2.37	21	14.13	3.07	59
Mono-(3-carboxypropyl) Phthalate - MC2	2.16	0.26	73	2.24	0.19	163	2.96	0.71	18	2.52	0.46	55
Mono-ethyl Phthalate -MEP	67.52	10.35	75	81.93	9.22	169	43.72	11.08	22	50.84	15.95	60
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.08	0.75	75	7.02	0.64	169	5.62	0.83	22	7.39	0.84	60
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.67	0.52	75	4.59	0.37	169	4.06	0.55	22	4.79	0.59	60
Mono-benzyl Phthalate - MZP	5.29	0.95	73	4.30	0.37	168	2.71	0.45	22	5.03	2.21	57
Mono-isobutyl Phthalate - MIB	7.64	0.70	74	7.46	0.61	165	6.74	1.27	21	9.90	2.14	60
Bisphenol A - BPA	1.37	0.11	73	1.42	0.06	163	1.70	0.66	18	1.37	0.23	49

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.16 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by Verbal Fluency Score for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	≤13 / ≥14	Unadjusted Odds Ratio [1]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #1 [2]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	42/192	1.00		41/192	1.00		38/187	1.00	
≥ 50th percentile	43/190	0.925	0.535-1.597	43/190	0.950	0.512-1.762	42/184	1.044	0.498-2.186
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	65/166	1.00		65/167	1.00		62/160	1.00	
≥ 50th percentile	37/196	0.471	0.268-0.827	37/194	0.664	0.386-1.142	35/187	0.577	0.315-1.057
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	38/195	1.00		38/195	1.00		36/189	1.00	
≥ 50th percentile	47/187	0.675	0.290-1.570	46/187	0.782	0.305-2.008	44/182	0.753	0.265-2.138
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	59/173	1.00		59/172	1.00		56/166	1.00	
≥ 50th percentile	43/189	0.751	0.413-1.367	43/189	0.873	0.494-1.540	41/181	0.884	0.450-1.739
ECP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	40/193	1.00		40/193	1.00		36/189	1.00	
≥ 50th percentile	45/189	0.998	0.451-2.210	44/189	0.672	0.303-1.491	44/182	0.570	0.195-1.663
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	45/187	1.00		45/186	1.00		43/179	1.00	
≥ 50th percentile	57/175	1.598	0.936-2.728	57/175	1.610	0.896-2.895	54/168	1.174	0.520-2.653
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	37/196	1.00		37/196	1.00		33/192	1.00	
≥ 50th percentile	48/186	1.509	0.698-3.260	47/186	0.919	0.389-2.171	47/179	1.136	0.432-2.987
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	41/191	1.00		41/190	1.00		38/184	1.00	
≥ 50th percentile	61/171	**2.369 ****	**1.392-4.031**	61/171	**2.080 ***	**1.151-3.757**	59/163	**2.437 ***	**1.190-4.989**
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	40/193	1.00		40/193	1.00		38/187	1.00	
≥ 50th percentile	45/189	0.909	0.378-2.185	44/189	0.936	0.346-2.528	42/184	0.766	0.252-2.329
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	60/172	1.00		60/171	1.00		57/165	1.00	
≥ 50th percentile	42/190	0.581	0.317-1.066	42/190	0.584	0.321-1.065	40/182	0.489	0.278-0.858
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	43/190	1.00		43/190	1.00		40/185	1.00	
≥ 50th percentile	42/192	0.711	0.379-1.337	41/192	0.626	0.316-1.240	40/186	0.589	0.281-1.235
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	47/185	1.00		47/184	1.00		43/179	1.00	
≥ 50th percentile	55/177	1.280	0.831-1.972	55/177	1.060	0.641-1.753	54/168	1.364	0.809-2.301
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	42/191	1.00		41/192	1.00		38/187	1.00	
≥ 50th percentile	43/191	1.668	0.975-2.852	43/190	1.423	0.777-2.607	42/184	1.432	0.642-3.193
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	46/186	1.00		46/185	1.00		45/177	1.00	
≥ 50th percentile	56/176	**1.861 ***	**1.078-3.212**	56/176	1.790	1.019-3.144	52/170	1.332	0.633-2.802
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	40/193	1.00		40/193	1.00		37/188	1.00	
≥ 50th percentile	45/189	1.638	0.678-3.955	44/189	1.197	0.430-3.332	43/183	1.207	0.372-3.921
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	46/185	1.00		46/186	1.00		44/177	1.00	
≥ 50th percentile	56/177	1.692	0.957-2.990	56/175	1.540	0.806-2.944	53/170	1.262	0.595-2.676
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	41/192	1.00		41/192	1.00		39/186	1.00	
≥ 50th percentile	44/190	0.905	0.435-1.886	43/190	0.965	0.463-2.012	41/185	0.896	0.404-1.983
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	35/197	1.00		35/196	1.00		34/188	1.00	
≥ 50th percentile	67/165	**2.610 *****	**1.573-4.332**	67/165	**2.175 ****	**1.281-3.692**	63/159	1.787	0.933-3.424
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	35/198	1.00		34/199	1.00		33/192	1.00	
≥ 50th percentile	50/184	1.665	0.699-3.969	50/183	1.377	0.563-3.366	47/179	1.263	0.532-2.998
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	43/189	1.00		42/189	1.00		41/181	1.00	
≥ 50th percentile	59/173	**2.205 ****	**1.323-3.675**	60/172	**2.051 ***	**1.111-3.786**	56/166	1.947	0.957-3.963
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	44/189	1.00		44/189	1.00		43/182	1.00	
≥ 50th percentile	41/193	0.957	0.516-1.773	40/193	0.953	0.537-1.691	37/189	0.861	0.437-1.697
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	52/180	1.00		52/179	1.00		51/172	1.00	
≥ 50th percentile	50/182	1.011	0.613-1.669	50/182	1.139	0.659-1.969	46/175	1.068	0.597-1.911

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2]Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Digit Symbol Substitution Test (DSST) Scores and Exposure to BPA and Phthalates:

Tables 1.17 to 1.21 present the GMs and GSEs of urinary phthalates and BPA levels among subjects with DSST scores. Table 1.17 presents GMs and GSEs for subjects who have measurable phthalate and BPA levels over the LOD, by DSST cut-off scores. Of the ten phthalates, seven of the phthalates have GMs that were higher in subjects with a DSST score ≤ 27 than with a DSST score ≥ 28. These phthalates are ECP, MBP, MEP, MHH, MOH, MZP, and MIB. Furthermore, GMs were significant for ECP ($p<0.01$), MBP ($p<0.05$), MHH ($p<0.05$), and MOH ($p<0.05$), in subjects with a DSST score ≤ 27 compared to those with a DSST score ≥ 28. Table 1.18 gives age-specific GMs and GSEs for phthalate and BPA levels by DSST cut-off scores. In the 60-69-year group, the GM for phthalate MBP is significantly higher in subjects with scores ≤ 27 compared to subjects who scored ≥ 28 group ($p<0.05$). For the phthalates CNP and COP, they are significantly higher in subjects with scores ≥ 28 compared to those with scores ≤ 27 ($p<0.001$ and $p<0.01$). No significant findings were found in the 70-79 age group. In the 80+ age group, the concentrations for the phthalate MEP were significantly higher subjects with scores ≤ 27 compared to those with scores ≥ 28 ($p<0.05$) (Table 1.18). Table 1.19 gives gender-specific GM and GSE for phthalate and BPA concentrations by DSST cut-off score. In males, ECP ($p<0.01$), MHH ($p<0.05$), and MOH ($p<0.05$) concentrations are significantly higher in the DSST Score ≤ 27 group compared to the DSST Score ≥ 28 group. In females, MBP ($p<0.05$) concentrations were significantly higher in the DSST Score ≤ 27 group compared to the DSST Score ≥ 28 group. Table 1.20 presents race-specific GMs and GSEs for phthalates and BPA concentrations by DSST cut-off scores. In Hispanics, MEP is significantly higher ($p<0.05$) in subjects with

a score of ≤ 27 compared to those with a score of ≥ 28. CNP and COP are significantly higher in subjects with a score of ≥ 28 compared to those with a score of ≤ 27 (CNP, $p<0.05$; COP, $p<0.05$). In Non-Hispanic Whites, ECP, MOH, and MZP are significantly higher in subjects with a score of ≤ 27 compared to those with a score of ≥ 28 (ECP, $p<0.05$; MOH, $p<0.05$; MZP, $p<0.05$). In the Asian/others, MEP and MZP are significantly higher in subjects with a score of ≥ 28 compared to those with a score of ≤ 27 (MEP, $p<0.01$; MZP, $p<0.05$). Table 1.21 presents estimated ORs and 95% CI of phthalate and BPA concentrations by DSST cut-off scores. For the phthalate ECP, males in the ≥ 50th percentile compared to the reference group, ECP concentration was significantly associated with lower DSST scores adjusted model #2 (OR=2.302, 95% CI: 1.031-5.141). For MBP, females in the ≥ 50th percentile compared to the reference group were found to have MBP levels significantly associated with lower DSST scores (OR=2.650, 95% CI: 1.342-5.236). MBP in females was not significant in the adjusted models. For MOH, males in the ≥ 50th percentile compared to the reference group were found to have MOH concentrations significantly associated with lower DSST scores in adjusted model #2 (OR=2.132, 95% CI: 1.019-4.462). For MZP, females in the ≥ 50th percentile compared to the reference group were found to have MZP concentrations that were associated with lower DSST scores in the unadjusted model (OR=1.763, 95% CI: 1.003-3.099). Subsequent adjusted models were not significant.

Table 1.17 Geometric Mean Urinary Phthalate and BPA Levels by Digit Symbol Substitution Test (DSST) Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)					
	DSST Score ≤ 27			**DSST Score** ≥ 28		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	2.14	0.22	128	2.67	0.14	759
Mono (carboxyoctyl) Phthalate - COP	15.48	1.67	129	19.00	1.58	761
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**15.86**	**1.65**	**129 ****	11.59	0.56	760
Mono-n-butyl Phthalate - MBP	**12.55**	**1.09**	**127 ***	9.63	0.54	749
Mono-(3-carboxypropyl) Phthalate - MC1	2.69	0.36	120	2.70	0.19	727
Mono-ethyl Phthalate -MEP	71.91	13.31	129	53.51	4.57	762
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**9.11**	**0.91**	**129 ***	7.05	0.32	761
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**6.31**	**0.39**	**129 ***	4.74	0.22	760
Mono-benzyl Phthalate - MZP	4.74	0.60	129	4.03	0.21	750
Mono-isobutyl Phthalate - MIB	6.89	0.61	127	6.14	0.27	755
Bisphenol A - BPA	1.62	0.17	121	1.52	0.08	720

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.18 Age-Specific Geometric Mean Urinary Phthalate and BPA Levels by Digit Symbol Substitution (DSST) Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	DSST Score ≤ 27			**DSST Score** ≥ 28			**DSST Score** ≤ 27			**DSST Score** ≥ 28			**DSST Score** ≤ 27			**DSST Score** ≥ 28		
	GM	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**	**GM**	**GSE**	**N**
Mono (carboxynonyl) Phthalate - CNP	1.62	0.13	52	**2.56**	**0.18**	**428 *****	2.41	0.31	40	2.95	0.28	228	2.42	0.44	36	2.45	0.19	103
Mono (carboxyoctyl) Phthalate - COP	11.80	1.66	53	**18.27**	**2.07**	**428 ****	20.21	3.56	40	22.08	2.27	230	15.66	2.59	36	15.32	1.79	103
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	14.90	2.45	53	10.59	0.75	427	16.35	3.00	40	13.35	0.72	230	16.26	2.37	36	11.90	0.71	103
Mono-n-butyl Phthalate - MBP	**12.83**	**1.58**	**51 ***	9.10	0.61	422	11.94	2.02	40	10.02	0.85	227	12.81	1.97	36	11.22	1.32	100
Mono-(3-carboxypropyl) Phthalate - MC1	2.06	0.36	47	2.50	0.21	409	3.12	0.91	37	3.09	0.32	220	2.89	0.38	36	2.68	0.33	98
Mono-ethyl Phthalate -MEP	91.95	19.23	53	58.27	6.55	429	77.66	24.26	40	56.85	6.79	230	**56.43**	**12.84**	**36 ***	31.55	2.83	103
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.77	1.44	53	6.56	0.46	428	10.20	2.39	40	8.11	0.45	230	8.63	0.89	36	6.69	0.53	103
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.65	0.97	53	4.27	0.29	428	6.99	1.57	40	5.53	0.27	230	6.36	0.64	36	5.04	0.42	102
Mono-benzyl Phthalate - MZP	5.18	1.37	53	3.98	0.31	424	4.78	0.91	40	3.80	0.29	227	4.42	0.75	36	4.97	0.49	99
Mono-isobutyl Phthalate - MIB	8.21	1.07	52	6.37	0.37	427	7.42	0.96	40	6.14	0.36	226	5.70	0.91	35	5.25	0.49	102
Bisphenol A - BPA	1.71	0.21	51	1.48	0.10	408	1.71	0.36	36	1.66	0.11	215	1.50	0.29	34	1.39	0.16	97

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.19 Geometric Mean Urinary Phthalate and BPA Levels by Digit Symbol Substitution (DSST) Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	DSST Score ≤ 27			DSST Score ≥ 28			DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.95	0.23	69	2.38	0.13	384	2.31	0.30	59	2.98	0.27	375
Mono (carboxyoctyl) Phthalate - COP	13.79	2.22	69	16.71	1.23 3	86	16.94	2.38	60	21.56	2.83	375
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**15.28**	**1.95**	**69 ****	10.50	0.50	387	16.32	2.40	60	12.78	0.83	373
Mono-n-butyl Phthalate - MBP	10.29	1.41	68	9.23	0.71	378	**14.67**	**1.57**	**59 ***	10.05	0.59	371
Mono-(3-carboxypropyl) Phthalate - MC1	2.67	0.52	64	2.50	0.20	372	2.70	0.35	56	2.92	0.29	355
Mono-ethyl Phthalate -MEP	63.90	14.22	69	51.25	5.44	387	78.84	19.27	60	55.84	6.21	375
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**8.69**	**1.10**	**69 ***	6.66	0.36	387	9.45	1.24	60	7.44	0.42	374
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**6.01**	**0.75**	**69 ***	4.48	0.23	385	6.54	0.89	60	5.02	0.30	375
Mono-benzyl Phthalate - MZP	3.88	0.51	69	3.58	0.29	380	5.55	1.01	60	4.53	0.25	370
Mono-isobutyl Phthalate - MIB	6.01	0.75	68	4.48	0.23	384	6.54	0.89	59	5.02	0.30	371
Bisphenol A - BPA	1.66	0.17	65	1.36	0.07	366	1.59	0.23	56	1.71	0.11	354

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.20 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by Digit Symbol Substitution (DSST) Cut-Off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.89	0.16	49	**2.49**	**0.18**	**129 ***	2.77	0.48	23	2.77	0.17	377
Mono (carboxyoctyl) Phthalate - COP	17.64	2.56	49	**20.22**	**2.08**	**129 ***	17.77	3.28	23	19.67	1.91	377
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	20.06	2.68	49	16.34	1.01	129	**19.10**	**3.50**	**23 ***	11.33	0.61	376
Mono-n-butyl Phthalate - MBP	13.68	1.29	49	13.80	1.18	127	12.98	2.48	23	9.10	0.60	370
Mono-(3-carboxypropyl) Phthalate - MC1	2.53	0.38	44	2.85	0.33	124	3.82	0.78	23	2.72	0.23	360
Mono-ethyl Phthalate -MEP	**169.71**	**38.53**	**49 ****	83.07	9.44	129	48.78	11.50	23	49.43	4.83	377
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	11.70	2.01	49	9.66	0.69	129	10.02	1.80	23	6.86	0.35	376
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	7.22	1.20	49	6.18	0.44	129	**7.65**	**1.33**	**23 ***	4.65	0.24	375
Mono-benzyl Phthalate - MZP	3.94	0.68	49	3.69	0.26	129	**6.71**	**1.71**	**23 ***	3.97	0.22	270
Mono-isobutyl Phthalate - MIB	10.00	0.80	49	8.84	0.57	129	4.58	0.80	23	5.73	0.25	373
Bisphenol A - BPA	1.75	0.18	43	1.53	0.15	127	1.66	0.42	22	1.54	0.09	359
EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.81	0.14	48	1.96	0.12	182	1.92	0.59	8	2.35	0.38	71
Mono (carboxyoctyl) Phthalate - COP	12.98	2.20	48	14.70	1.16	181	8.60	3.00	9	14.35	2.98	74
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	9.96	1.09	48	10.62	0.81	181	13.12	4.13	9	13.14	0.76	74
Mono-n-butyl Phthalate - MBP	9.91	1.34	47	11.12	0.69	179	18.37	4.63	8	13.69	2.69	73
Mono-(3-carboxypropyl) Phthalate - MC2	1.94	0.21	45	2.25	0.18	177	1.80	0.58	8	2.92	0.43	66
Mono-ethyl Phthalate -MEP	64.41	17.59	48	84.59	8.39	182	17.26	6.05	9	**60.95**	**16.85**	**74 ****
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	6.32	0.82	48	7.30	0.58	182	7.54	2.88	9	7.19	0.74	74
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	4.45	0.61	48	4.82	0.33	182	5.00	1.81	9	4.73	0.47	74
Mono-benzyl Phthalate - MZP	4.78	0.96	48	4.57	0.42	180	1.89	0.49	9	**4.92**	**1.81**	**71 ***
Mono-isobutyl Phthalate - MIB	7.93	0.84	46	7.49	0.47	180	6.09	1.61	9	9.86	1.79	73
Bisphenol A - BPA	1.53	0.17	47	1.39	0.06	175	1.38	0.46	9	1.43	0.23	59

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.21 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by Digit Symbol Substitution Test (DSST) Score for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	≤27 / ≥28	Unadjusted Odds Ratio [1]	95% CI	≤27 / ≥28	Adjusted Odds Ratio #1 [2]	95% CI	≤27 / ≥28	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	38/190	1.00		37/190	1.00		36/186	1.00	
≥ 50th percentile	31/197	0.764	0.436-1.337	31/197	0.928	0.487-1.767	30/191	1.326	0.639-2.750
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	37/180	1.00		38/179	1.00		33/177	1.00	
≥ 50th percentile	23/195	0.406	0.209-0.789	22/195	0.477	0.214-1.061	22/187	0.568	0.248-1.300
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	39/189	1.00		39/188	1.00		37/184	1.00	
≥ 50th percentile	30/198	0.704	0.342-1.452	29/199	0.687	0.318-1.484	29/193	0.889	0.386-2.046
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	29/188	1.00		29/188	1.00		25/184	1.00	
≥ 50th percentile	31/187	0.827	0.440-1.555	31/186	1.029	0.543-1.953	30/180	1.087	0.495-2.388
ECP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	26/202	1.00		26/201	1.00		24/197	1.00	
≥ 50th percentile	43/185	2.095	0.965-4.547	42/186	1.593	0.621-4.088	42/180	**2.302 ***	**1.031-5.141**
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	27/190	1.00		27/190	1.00		24/185	1.00	
≥ 50th percentile	33/185	1.539	0.662-3.579	33/184	1.295	0.469-3.578	31/179	1.118	0.359-3.485
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	31/197	1.00		30/197	1.00		29/192	1.00	
≥ 50th percentile	38/190	1.608	0.732-3.532	38/190	0.902	0.388-2.098	37/185	0.839	0.366-1.924
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	25/192	1.00		25/192	1.00		23/186	1.00	
≥ 50th percentile	35/183	**2.650 ** **	**1.342-5.236**	35/182	2.106	0.973-4.555	32/178	2.366	0.824-6.790
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	37/191	1.00		37/190	1.00		36/185	1.00	
≥ 50th percentile	32/196	0.949	0.382-2.359	31/197	1.252	0.571-2.744	30/192	1.197	0.518-2.763
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	33/184	1.00		33/184	1.00		29/180	1.00	
≥ 50th percentile	27/191	0.706	0.327-1.523	27/190	0.723	0.269-1.941	26/184	0.608	0.270-1.367
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	27/201	1.00		27/200	1.00		26/195	1.00	
≥ 50th percentile	42/186	1.329	0.622-2.842	41/187	1.071	0.458-2.508	40/182	0.956	0.416-2.193
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	27/190	1.00		27/190	1.00		24/185	1.00	
≥ 50th percentile	33/185	1.246	0.599-2.591	33/184	1.121	0.466-2.698	31/179	2.504	0.725-8.643
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	30/198	1.00		29/198	1.00		27/194	1.00	
≥ 50th percentile	39/189	1.353	0.727-2.517	39/189	1.012	0.500-2.048	39/183	1.538	0.658-3.596
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	30/187	1.00		30/187	1.00		27/182	1.00	
≥ 50th percentile	30/188	1.559	0.778-3.125	30/187	1.266	0.646-2.481	28/182	1.150	0.479-2.760
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	28/200	1.00		27/200	1.00		26/195	1.00	
≥ 50th percentile	41/187	1.840	0.932-3.635	41/187	1.444	0.730-2.856	40/182	**2.132 ***	**1.019-4.462**
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	27/190	1.00		27/190	1.00		24/185	1.00	
≥ 50th percentile	33/185	1.880	0.901-3.923	33/184	1.533	0.739-3.182	31/179	1.359	0.526-3.509
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	30/198	1.00		30/197	1.00		29/192	1.00	
≥ 50th percentile	39/189	1.230	0.628-2.409	38/190	0.955	0.471-1.934	37/185	0.960	0.519-1.775
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	25/192	1.00		25/192	1.00		23/186	1.00	
≥ 50th percentile	35/183	**1.763 ***	**1.003-3.099**	35/182	1.356	0.722-2.544	32/178	1.148	0.441-2.985
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	29/199	1.00		28/199	1.00		26/195	1.00	
≥ 50th percentile	40/188	1.281	0.733-2.239	40/188	0.789	0.474-1.315	40/182	1.073	0.554-2.079
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	25/192	1.00		25/192	1.00		23/186	1.00	
≥ 50th percentile	35/183	1.421	0.825-2.446	35/182	0.882	0.469-1.658	32/178	1.234	0.501-3.037
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	30/198	1.00		30/198	1.00		30/191	1.00	0.515-1.885
≥ 50th percentile	39/189	1.069	0.573-1.996	38/189	1.111	0.523-2.362	36/186	0.885	0.444-1.763
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	30/187	1.00		30/187	1.00		28/181	1.00	
≥ 50th percentile	30/188	0.820	0.397-1.692	30/187	0.810	0.333-1.966	27/183	0.446	0.193-1.027

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2]Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Associations between Exposures to Phthalate and BPA and Memory Function

Exposures to the 12 phthalate metabolites and BPA and three memory function indicators: 1) During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse?; 2) During the past 7 days, how often have you had trouble remembering where you put things?; 3) Are you limited in any way because of difficulty remembering or because you experience periods of confusion?) summarized in tables 1.22 to 1.36. Memory function have been included as a surrogate indicator of brain health as declining memory function can indicate the development of mild cognitive impairment, dementia, AD, or other memory-related neurodegenerative disease.

Worsening memory past 12 months and Exposure to BPA and Phthalates: Table 1.22 presents crude GMs and GSEs for subjects with phthalates and BPA concentrations over the LOD, by responses to the question, "During the past 12 months, have you experience confusion or memory loss that is happening more often or getting worse?". The GMs of three of the phthalate metabolites, MBP, MZP, and MIB, were found to be significantly higher in those who responded "yes" to experiencing confusion or memory loss in the past year than those who responded "no" (MBP, MZP, MIB, $p<0.05$).

Table 1.23 presents age-specific GMs and GSEs for subjects with phthalates and BPA concentrations over the LOD who responded to having memory loss or confusion over the past year. In the 60-69-year age group, three phthalate metabolites, MHH, MOH, MIB, were found to have GMs significantly higher ($p<0.05$) in subjects who answered "yes" versus those who answered "no". In the 70-79-year age group, the phthalate metabolite, COP, was found to have a significantly higher GM in the "no" group

compared to the "yes" group ($p<0.05$). In the 80+ age group, the phthalate metabolite, MIB, was found to have a significantly higher GM in the "yes" group compared to the "no" group ($p<0.05$).

Table 1.24 presents gender-specific GMs and GSEs for subjects with phthalate and BPA concentrations over the LOD who responded having memory loss or confusion over the past year. Among females, the phthalate metabolites MZP and MIB had significantly higher GMs in those who experienced memory issues in the past year, than those who did not ($p<0.05$).

Table 1.25 presents race-specific GMS and GSEs for subjects with phthalates and BPA concentrations over the LOD who to having memory loss or confusion over the past year. In the Non-Hispanic White group, the phthalate metabolite MIB was found to have a higher GM among the "yes" group compared to the "no" group ($p<0.05$). No other significant observations were observed.

Table 1.26 presents estimated ORs and 95% CIs for phthalate metabolites and BPA concentrations by responses to experiencing memory and confusion problems the last 12 months. For the phthalate metabolite MBP, concentrations among males in the ≥ 50th percentile compared to the reference group, were found to be significantly associated with experiencing memory loss or confusion over the past year in the unadjusted model (OR=2.844, 95% CI: 1.170-6.912) and the 1st adjusted model (OR=3.184, 95% CI: 1.081-9.381). For the phthalate metabolite MZP, among females in the ≥ 50th percentile group compared to the reference group, MZP concentrations were found to be significantly associated with experiencing memory loss or confusion over the past year in the unadjusted model (OR=2.277, 95% CI 1.183-4.383) and the 1st adjusted

model (OR=2.214, 95% CI: 1.055-4.647). For the phthalate metabolite MIB among females in the≥ 50th percentile group compared to the reference group, concentrations were found to be significantly associated with experiencing memory loss or confusion over the past year in the 2nd adjusted model (OR=2.180, 95% CI: 1.137-1.332).

Table 1.22 Geometric Mean Urinary Phthalate and BPA Levels by responses, "During the past 12 months, experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.82	0.43	178	2.63	0.13	843
Mono (carboxyoctyl) Phthalate - COP	18.63	2.34	181	19.14	1.55	843
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	13.51	1.12	180	12.02	0.63	843
Mono-n-butyl Phthalate - MBP	**11.80**	**0.81**	**179 ***	9.80	0.55	831
Mono-(3-carboxypropyl) Phthalate - MC1	2.79	0.28	173	2.74	0.18	805
Mono-ethyl Phthalate -MEP	54.91	6.40	181	56.30	4.95	844
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.27	0.64	181	7.25	0.35	843
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.63	0.39	181	4.88	0.24	842
Mono-benzyl Phthalate - MZP	**5.24**	**0.65**	**179 ***	4.06	0.22	831
Mono-isobutyl Phthalate - MIB	**7.29**	**0.38**	**180 ***	6.19	0.30	835
Bisphenol A - BPA	1.46	0.11	166	1.54	0.08	800

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.23 Age-Specific Geometric Mean Urinary Phthalate and BPA Levels by responses, "During the past 12 months, experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Yes			No			Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	4.15	1.79	67	2.42	0.14	464	2.13	0.29	51	3.09	0.30	249	2.58	0.33	60	2.56	0.20	130
Mono (carboxyoctyl) Phthalate - COP	23.65	6.18	69	18.08	2.09	463	15.10	2.46	52	**22.84**	**2.27**	**250 ***	18.31	4.15	60	16.19	2.02	130
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	15.20	2.97	68	10.63	0.73	463	11.72	1.47	52	14.10	0.78	250	13.96	1.57	60	13.72	0.74	130
Mono-n-butyl Phthalate - MBP	11.11	1.73	68	9.24	0.64	456	11.47	1.34	52	10.01	0.86	247	12.94	1.44	59	11.78	1.12	128
Mono-(3-carboxypropyl) Phthalate - MC1	2.96	0.84	66	2.51	0.22	440	2.27	0.39	49	3.19	0.32	238	3.24	0.67	58	2.77	0.30	127
Mono-ethyl Phthalate -MEP	58.11	10.79	69	58.27	6.45	464	66.14	12.94	52	59.22	7.33	250	42.46	12.03	60	43.84	3.23	130
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**9.18**	**1.25**	**69 ***	6.56	0.46	463	7.88	1.12	52	8.47	0.46	250	7.82	1.07	60	7.60	0.47	130
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**5.67**	**0.74**	**69 ***	4.30	0.29	463	5.31	0.66	52	5.75	0.28	250	5.94	0.69	60	5.59	0.36	129
Mono-benzyl Phthalate - MZP	5.59	1.48	69	4.01	0.30	456	4.19	0.76	52	3.83	0.27	247	6.28	0.82	58	4.87	0.43	128
Mono-isobutyl Phthalate - MIB	**8.12**	**0.69**	**69 ***	6.39	0.37	460	6.55	0.49	52	6.25	0.38	246	**7.32**	**0.84**	**59 ***	5.33	0.51	129
Bisphenol A - BPA	1.52	0.13	65	1.51	0.09	442	1.36	0.20	45	1.69	0.13	234	1.50	0.21	56	1.39	0.12	124

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.24 Geometric Mean Urinary Phthalate and BPA Levels by responses, "During the past 12 months, experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.05	0.29	78	2.40	0.14	437	3.40	0.85	100	2.89	0.21	406
Mono (carboxyoctyl) Phthalate - COP	11.94	2.06	80	17.41	1.31	437	24.11	4.08	101	21.13	2.65	406
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	11.80	1.46	80	10.86	0.57	438	14.62	1.94	100	13.38	0.91	405
Mono-n-butyl Phthalate - MBP	10.25	1.03	79	9.25	0.67	429	12.81	1.22	100	10.38	0.60	402
Mono-(3-carboxypropyl) Phthalate - MC1	2.32	0.42	77	2.56	0.19	420	3.12	0.51	96	2.96	0.26	385
Mono-ethyl Phthalate -MEP	49.63	8.64	80	53.52	5.07	438	58.21	8.77	101	59.36	7.04	406
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.24	0.86	80	6.80	0.38	438	8.93	0.86	101	7.74	0.46	405
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	4.92	0.58	80	4.59	0.25	436	6.08	0.53	101	5.19	0.33	406
Mono-benzyl Phthalate - MZP	3.40	0.67	78	3.74	0.31	432	**6.70**	**1.13**	**101 ***	4.42	0.24	399
Mono-isobutyl Phthalate - MIB	6.18	0.58	79	5.80	0.32	435	**8.00**	**0.60**	**101 ***	6.62	0.37	400
Bisphenol A - BPA	1.33	0.19	70	1.40	0.08	419	1.53	0.13	96	1.72	0.11	381

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.25 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by responses, "During the past 12 months, experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.62	0.34	38	2.31	0.15	177	2.98	0.57	86	2.79	0.18	356
Mono (carboxyoctyl) Phthalate - COP	19.08	3.69	38	19.89	2.27	177	19.05	2.72	86	20.33	2.06	356
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	19.61	2.27	38	17.72	1.01	177	12.69	1.29	86	11.66	0.70	355
Mono-n-butyl Phthalate - MBP	13.60	1.89	38	13.73	0.89	175	11.03	0.92	86	9.11	0.65	349
Mono-(3-carboxypropyl) Phthalate - MC1	2.69	0.34	36	2.85	0.30	167	2.81	0.35	82	2.82	0.24	342
Mono-ethyl Phthalate -MEP	80.38	11.12	38	99.65	14.07	17	52.33	7.80	86	50.66	5.16	356
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	11.31	1.56	38	10.22	0.69	177	7.88	0.70	86	6.99	0.39	355
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	7.66	0.90	38	6.53	0.45	177	5.37	0.43	86	4.74	0.28	354
Mono-benzyl Phthalate - MZP	4.42	0.98	38	3.90	0.30	177	5.41	0.85	85	4.00	0.23	350
Mono-isobutyl Phthalate - MIB	8.66	0.92	38	9.31	0.58	177	**6.78**	**0.40**	**85 ***	5.65	0.28	353
Bisphenol A - BPA	1.80	0.35	35	1.57	0.14	170	1.44	0.13	79	1.57	0.10	340
EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.88	0.21	31	1.98	0.10	231	2.65	0.73	23	2.25	0.36	79
Mono (carboxyoctyl) Phthalate - COP	15.13	2.09	31	15.13	2.09	230	17.86	7.65	26	12.78	1.76	80
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.22	2.32	30	10.85	0.63	231	16.71	2.96	26	12.62	0.92	80
Mono-n-butyl Phthalate - MBP	12.34	1.85	31	10.84	0.57	227	18.31	4.03	24	14.37	2.68	80
Mono-(3-carboxypropyl) Phthalate - MC2	2.28	0.31	29	2.19	0.15	225	3.19	0.90	26	2.65	0.41	71
Mono-ethyl Phthalate -MEP	59.29	14.35	31	83.59	7.95	231	50.46	17.02	26	53.22	14.57	80
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.87	1.61	31	7.28	0.45	231	8.28	1.87	26	7.15	0.78	80
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	6.13	1.27	31	4.87	0.26	231	5.50	1.06	26	4.74	0.56	80
Mono-benzyl Phthalate - MZP	5.56	1.29	31	4.60	0.44	228	4.59	1.11	25	4.31	1.49	76
Mono-isobutyl Phthalate - MIB	8.99	1.74	31	7.46	0.38	226	9.51	2.05	26	9.12	1.70	79
Bisphenol A - BPA	1.34	0.13	30	1.42	0.06	224	1.40	0.26	22	1.31	0.23	66

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.26 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by responses, "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	52/206	1.00		52/207	1.00		45/195	1.00	
≥ 50th percentile	28/232	0.649	0.283-1.491	28/230	0.586	0.248-1.386	72/214	0.712	0.295-1.722
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	52/202	1.00		52/201	1.00		44/190	1.00	
≥ 50th percentile	49/204	0.921	0.451-1.882	48/204	0.984	0.466-2.080	43/190	1.102	0.497-2.448
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	48/211	1.00		48/210	1.00		46/194	1.00	
≥ 50th percentile	32/227	0.570	0.284-1.146	32/227	0.575	0.300 1.104	26/215	0.421	0.199-0.887
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	46/207	1.00		45/207	1.00		38/195	1.00	
≥ 50th percentile	55/199	1.457	0.813-2.610	55/198	1.690	0.944-3.026	49/185	1.889	0.942-3.790
ECP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	42/217	1.00		42/216	1.00		36/204	1.00	
≥ 50th percentile	38/221	1.073	0.422-2.733	38/221	0.661	0.245-1.788	36/205	0.705	0.240-2.074
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	51/202	1.00		50/202	1.00		40/193	1.00	
≥ 50th percentile	50/204	0.962	0.565-1.638	50/203	0.966	0.550-1.697	47/187	1.089	0.576-2.059
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	33/226	1.00		33/225	1.00		27/213	1.00	
≥ 50th percentile	47/212	**2.844 ***	**1.170-6.912**	47/212	2.465	0.913-6.656	45/196	**3.184 ***	**1.081-9.381**
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	44/209	1.00		44/208	1.00		39/194	1.00	
≥ 50th percentile	57/197	1.260	0.697-2.277	56/197	1.175	0.651-2.118	48/186	1.109	0.569-2.161
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	48/210	1.00		48/210	1.00		43/197	1.00	
≥ 50th percentile	50/203	0.704	0.378-1.309	32/227	0.606	0.317-1.158	29/212	0.581	0.305-1.108
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	50/203	1.00		49/203	1.00		42/192	1.00	
≥ 50th percentile	51/203	1.001	0.626-1.602	51/202	1.080	0.673-1.733	45/188	1.008	0.556-1.825
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	41/218	1.00		41/217	1.00		38/202	1.00	
≥ 50th percentile	39/220	0.901	0.487-1.667	39/220	1.006	0.538-1.883	34/207	0.971	0.473-1.993
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	53/200	1.00		53/199	1.00		43/190	1.00	
≥ 50th percentile	48/206	1.236	0.658-2.322	47/206	1.320	0.678-2.570	44/190	1.589	0.701-3.603
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	38/221	1.00		38/220	1.00		32/208	1.00	
≥ 50th percentile	42/217	1.383	0.797-2.400	42/217	1.080	0.608-1.920	40/201	1.152	0.636-2.089
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	46/207	1.00		46/206	1.00		39/194	1.00	
≥ 50th percentile	55/199	1.343	0.806-2.239	54/199	1.258	0.757-2.091	48/186	1.302	0.724-2.342
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	41/218	1.00		41/217	1.00		34/206	1.00	
≥ 50th percentile	39/220	0.940	0.421-2.099	39/220	0.630	0.264-1.503	38/203	0.681	0.293-1.585
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	49/205	1.00		48/204	1.00		40/193	1.00	
≥ 50th percentile	52/201	1.109	0.643-1.912	52/201	1.088	0.596-1.988	47/187	1.066	0.541-2.101
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	48/211	1.00		48/210	1.00		42/198	1.00	
≥ 50th percentile	32/227	0.649	0.276-1.527	32/227	0.618	0.265-1.441	30/211	0.690	0.296-1.610
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	37/216	1.00		37/215	1.00		33/200	1.00	
≥ 50th percentile	64/190	**2.277 ***	**1.183-4.383**	63/190	**2.214 ***	**1.055-4.647**	54/180	2.173	0.925-5.108
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	36/223	1.00		36/222	1.00		32/208	1.00	
≥ 50th percentile	44/215	1.270	0.652-2.473	44/215	1.297	0.629-2.672	40/201	1.159	0.497-2.704
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	47/206	1.00		47/205	1.00		39/194	1.00	
≥ 50th percentile	54/200	1.765	0.984-3.165	53/200	1.826	0.978-3.409	48/186	**2.180 ***	**1.137-4.177**
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	44/215	1.00		44/215	1.00		40/200	1.00	
≥ 50th percentile	36/223	0.847	0.433-1.659	36/222	0.829	0.469-1.464	32/209	0.749	0.400-1.401
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	51/202	1.00		50/201	1.00		42/191	1.00	
≥ 50th percentile	50/204	0.960	0.562-1.640	50/204	0.982	0.563-1.715	45/189	1.262	0.650-2.448

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDC levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Trouble remembering past 7 days and Exposure to BPA and Phthalates:

Table 1.27 presents crude GMs and GSEs for phthalate and BPA concentrations over the LOD for subjects who provided a response to the question "During the past 7 days, how often have you had trouble remembering where you put things?" The phthalate metabolite, MIB, was found to be significantly higher in those who experienced memory issues in the past week ($p<0.05$). Table 1.28 presents age-specific GMs and GSEs. No significant findings were observed. Table 1.29 presents gender-specific GMs and GSEs. Among males, GMs the for-phthalate metabolites ECP, MHH, and MOH were found to be significantly higher in those that experienced memory issues in the past week (ECP, $p<0.05$; MHH, $p<0.05$; MOH, $p<0.05$). Table 1.30 presents race-specific GMs and GSEs. Among Hispanics, the phthalate metabolite MBP was found to be significantly higher ($p<0.05$) in subjects that experienced memory issues in the past week.

Table 1.31 presents the estimated ORs and 95% CIs. For the phthalate metabolite ECP, among females in the ≥ 50th percentile group compared to the reference group, ECP concentrations were found to be significantly associated with the having trouble remembering in the past week in adjusted model #1 (OR=1.673, 95% CI: 1.007-2.780) and adjusted model #2 (OR=1.927, 95% CI: 1.131-3.283). For the phthalate metabolite MBP, among females in the ≥ 50th percentile group compared to the reference group, MBP concentrations were found to be significantly associated with having trouble remembering in the past week (OR=1.955, 95% CI: 1.030-3.711) in the 2nd adjusted model.

For the phthalate metabolite MHH, among females in the ≥ 50th percentile group, MHH concentrations were found to be significantly associated with having trouble remembering in the past week (OR=1.821, 95% CI: 1.104-3.005) in the 2nd adjusted model.

Table 1.27 Geometric Mean Urinary Phthalate and BPA Levels by Responses, "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.64	0.18	187	2.67	0.15	780
Mono (carboxyoctyl) Phthalate - COP	17.79	1.83	188	19.45	1.66	782
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.55	0.58	188	11.94	0.64	781
Mono-n-butyl Phthalate - MBP	10.41	0.78	186	9.95	0.57	770
Mono-(3-carboxypropyl) Phthalate - MC1	2.36	0.24	178	2.84	0.19	748
Mono-ethyl Phthalate -MEP	63.99	8.74	188	53.71	4.47	783
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.60	0.41	188	7.19	0.38	782
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.07	0.30	187	4.86	0.26	782
Mono-benzyl Phthalate - MZP	4.38	0.38	186	4.12	0.24	771
Mono-isobutyl Phthalate - MIB	**7.04**	**0.47**	**187 ***	6.15	0.30	775
Bisphenol A - BPA	1.42	0.12	180	1.53	0.07	736

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.30 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.56	0.30	42	2.37	0.18	150	2.70	0.20	89	2.85	0.20	333
Mono (carboxyoctyl) Phthalate - COP	21.13	2.39	42	20.10	2.41	150	18.83	2.65	89	20.58	2.15	333
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	20.53	1.85	42	17.62	1.11	150	11.71	0.66	89	11.60	0.71	332
Mono-n-butyl Phthalate - MBP	**17.40**	**1.96**	**41 ***	13.72	0.90	149	9.22	0.76	89	9.32	0.70	326
Mono-(3-carboxypropyl) Phthalate - MC1	3.06	0.48	39	2.96	0.35	143	2.24	0.29	85	2.94	0.26	319
Mono-ethyl Phthalate -MEP	104.73	24.56	42	93.49	13.03	150	53.54	6.98	89	49.61	4.96	333
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	12.24	1.33	42	10.12	0.78	150	7.11	0.47	89	6.95	0.43	332
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	7.80	0.81	42	6.52	0.48	150	4.82	0.36	88	4.72	0.30	332
Mono-benzyl Phthalate - MZP	4.31	0.68	42	3.87	0.35	150	4.30	0.47	88	4.09	0.26	327
Mono-isobutyl Phthalate - MIB	10.41	0.87	42	9.20	0.67	150	**6.22**	**0.44**	**89**	5.67	0.29	329
Bisphenol A - BPA	1.69	0.33	39	1.56	0.12	144	1.36	0.14	85	1.57	0.10	316

EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.02	0.23	39	1.93	0.09	216	3.09	1.76	17	2.15	0.24	81
Mono (carboxyoctyl) Phthalate - COP	14.77	1.89	39	13.82	1.05	215	9.67	2.84	18	15.14	2.25	84
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.30	1.61	39	10.58	0.72	215	13.88	2.39	18	13.39	1.06	84
Mono-n-butyl Phthalate - MBP	12.07	1.58	39	10.72	0.52	212	16.55	2.98	17	14.82	3.01	83
Mono-(3-carboxypropyl) Phthalate - MC2	2.11	0.24	38	2.18	0.15	209	3.29	1.04	16	2.63	0.37	77
Mono-ethyl Phthalate -MEP	106.02	19.93	39	77.01	8.27	216	121.49	80.49	18	40.44	8.13	84
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.59	1.14	39	7.16	0.50	216	7.11	1.44	18	7.42	0.83	84
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.43	0.81	39	4.87	0.31	216	4.47	0.94	18	4.99	0.56	84
Mono-benzyl Phthalate - MZP	5.77	0.96	39	4.48	0.44	214	3.81	0.91	17	4.29	1.55	80
Mono-isobutyl Phthalate - MIB	8.32	0.91	39	7.38	0.44	212	12.99	4.20	17	8.55	1.56	84
Bisphenol A - BPA	1.39	0.16	39	1.43	0.06	209	1.97	0.46	17	1.14	0.17	67

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.28 Age-Specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Yes			No			Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.08	0.22	88	2.66	0.20	418	3.29	0.41	59	2.81	0.26	227	2.99	0.37	40	2.42	0.23	135
Mono (carboxyoctyl) Phthalate - COP	13.62	3.26	89	19.52	2.29	418	22.11	4.08	59	21.49	2.29	229	21.35	5.33	40	15.67	2.08	135
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	11.59	1.25	89	10.81	0.84	417	13.68	1.09	59	13.36	0.88	229	12.81	1.55	40	13.58	0.79	135
Mono-n-butyl Phthalate - MBP	9.91	1.07	87	9.33	0.67	412	9.92	1.07	59	10.20	0.94	226	12.33	1.92	40	11.98	1.13	132
Mono-(3-carboxypropyl) Phthalate - MC1	2.02	0.38	83	2.66	0.24	400	2.54	0.41	56	3.14	0.36	217	2.80	0.67	39	2.94	0.39	131
Mono-ethyl Phthalate -MEP	67.84	17.75	89	55.88	5.88	419	70.60	17.55	59	58.83	8.50	229	49.12	11.23	40	38.75	2.85	135
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	6.95	0.77	89	6.68	0.51	418	8.88	0.67	59	8.01	0.55	229	7.13	0.94	40	7.55	0.56	135
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	4.33	0.47	89	4.39	0.32	418	5.90	0.48	59	5.47	0.34	229	5.46	0.76	39	5.53	0.36	135
Mono-benzyl Phthalate - MZP	4.87	0.83	88	3.99	0.32	413	3.51	0.42	59	3.91	0.35	226	5.03	0.92	39	5.17	0.47	132
Mono-isobutyl Phthalate - MIB	7.70	0.82	89	6.29	0.36	416	6.98	0.59	58	6.09	0.39	226	5.98	0.95	40	5.81	0.47	133
Bisphenol A - BPA	1.44	0.16	87	1.50	0.10	396	1.55	0.17	54	1.63	0.12	212	1.21	0.27	39	1.48	0.11	128

NHANES sampling weight applied before calculating the geometric mean.
The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.29 Gender-Specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.65	0.40	71	2.35	0.14	423	2.64	0.26	116	3.06	0.30	357
Mono (carboxyoctyl) Phthalate - COP	15.02	2.58	71	16.96	1.25	425	19.27	3.21	117	22.61	3.13	357
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**13.27**	**1.21**	**71 ***	10.47	0.55	426	12.22	0.86	117	13.82	1.06	355
Mono-n-butyl Phthalate - MBP	9.71	1.28	71	9.36	0.69	416	10.76	0.88	115	10.64	0.72	354
Mono-(3-carboxypropyl) Phthalate - MC1	2.28	0.42	68	2.57	0.22	408	2.39	0.37	110	3.18	0.30	340
Mono-ethyl Phthalate -MEP	56.35	11.19	71	52.19	4.99	426	67.94	11.77	117	55.44	5.65	357
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**8.06**	**0.75**	**71 ***	6.53	0.37	426	7.40	0.53	117	7.99	0.52	356
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**5.66**	**0.51**	**70 ***	4.40	0.25	425	4.82	0.39	117	5.42	0.36	357
Mono-benzyl Phthalate - MZP	3.41	0.43	70	3.74	0.33	419	4.91	0.58	116	4.58	0.31	352
Mono-isobutyl Phthalate - MIB	6.31	0.82	71	5.73	0.31	422	7.41	0.59	116	6.66	0.38	353
Bisphenol A - BPA	1.38	0.24	65	1.37	0.08	404	1.44	0.12	115	1.75	0.12	332

NHANES sampling weight applied before calculating the geometric mean.
The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.31 Estimated ORs (95% CI) of Urinary Phthalate and BPA by Responses, "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	36/212	1.00		36/212	1.00		34/197	1.00	
≥ 50th percentile	35/214	0.873	0.412-1.853	35/213	0.871	0.444-1.708	34/198	1.009	0.453-2.250
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	59/178	1.00		59/177	1.00		52/166	1.00	
≥ 50th percentile	58/179	1.024	0.518-2.023	57/179	1.012	0.472-2.166	54/164	1.036	0.487-2.204
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	39/209	1.00		39/209	1.00		39/192	1.00	
≥ 50th percentile	32/217	1.326	0.653-2.694	32/216	1.256	0.606-2.603	29/203	1.328	0.689-2.560
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	60/177	1.00		59/177	1.00		53/165	1.00	
≥ 50th percentile	57/180	1.059	0.567-1.978	57/179	1.007	0.531-1.910	53/165	0.955	0.475-1.918
ECP - Above/Below 50th Percentile - Males									
≥ 50th percentile	40/209	0.637	0.323-1.257	40/208	0.899	0.439-1.838	38/194	1.014	0.425-2.423
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	62/175	1.00		62/174	1.00		54/164	1.00	
≥ 50th percentile	55/182	1.543	0.979-2.429	54/182	**1.673 ***	**1.007-2.780**	52/166	**1.927 ***	**1.131-3.283**
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	34/214	1.00		34/214	1.00		32/199	1.00	
≥ 50th percentile	37/212	0.744	0.350-1.582	37/211	0.865	0.391-1.912	36/196	0.910	0.380-2.176
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	59/178	1.00		59/177	1.00		54/164	1.00	
≥ 50th percentile	58/179	1.417	0.841-2.389	57/179	1.551	0.904-2.660	52/166	**1.955 ***	**1.030-3.711**
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	37/211	1.00		37/211	1.00		35/196	1.00	
≥ 50th percentile	34/215	1.036	0.429-2.501	34/214	1.039	0.426-2.537	33/199	1.033	0.421-2.536
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	62/175	1.00		61/175	1.00		56/162	1.00	
≥ 50th percentile	55/182	1.345	0.708-2.556	55/185	1.292	0.681-2.452	50/168	1.399	0.696-2.813
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	31/217	1.00		31/217	1.00		29/202	1.00	
≥ 50th percentile	40/209	0.824	0.384-1.771	40/208	0.804	0.365-1.768	39/193	0.744	0.351-1.580
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	51/186	1.00		50/186	1.00		46/172	1.00	
≥ 50th percentile	66/171	0.784	0.470-1.308	66/170	0.726	0.425-1.242	60/158	0.761	0.396-1.460
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	27/221	1.00		27/221	1.00		26/205	1.00	
≥ 50th percentile	44/205	0.536	0.268-1.070	44/204	0.622	0.305-1.271	42/190	0.643	0.296-1.394
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	59/178	1.00		59/177	1.00		54/164	1.00	
≥ 50th percentile	58/178	1.294	0.812-2.060	57/179	1.367	0.867-2.155	52/166	**1.821 ***	**1.104-3.005**
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	30/218	1.00		30/218	1.00		29/202	1.00	
≥ 50th percentile	41/208	0.555	0.257-1.199	41/207	0.691	0.291-1.637	39/193	0.788	0.315-1.970
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	59/178	1.00		58/178	1.00		53/165	1.00	
≥ 50th percentile	58/179	1.333	0.824-2.157	58/178	1.323	0.804-2.177	53/165	1.720	0.983-3.011
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	38/210	1.00		38/210	1.00		36/195	1.00	
≥ 50th percentile	33/216	1.508	0.837-2.719	33/215	1.479	0.818-2.674	32/200	1.625	0.881-2.996
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	54/183	1.00		54/182	1.00		50/168	1.00	
≥ 50th percentile	63/174	0.757	0.413-1.388	62/174	0.780	0.427-1.426	56/162	0.795	0.394 -1.603
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	26/222	1.00		26/222	1.00		25/206	1.00	
≥ 50th percentile	45/204	0.568	0.251-1.282	45/203	0.567	0.239-1.341	43/189	0.623	0.248-1.563
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	59/178	1.00		59/177	1.00		53/165	1.00	
≥ 50th percentile	58/179	1.009	0.501-2.031	57/179	1.084	0.533-2.207	53/165	1.303	0.604-2.812
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	38/211	1.00		38/209	1.00		36/195	1.00	
≥ 50th percentile	33/215	1.073	0.552-2.087	33/216	1.136	0.577-2.237	32/200	1.283	0.685-2.403
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	61/177	1.00		60/176	1.00		56/162	1.00	
≥ 50th percentile	56/180	1.392	0.810-2.390	56/180	1.347	0.787-2.304	50/168	1.460	0.738-2.889

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Limitations Due to Difficulty Remembering or Confusion and Exposure to BPA and Phthalates: Table 1.32 presents crude GMs and GSEs for subjects with phthalate and BPA levels above the LOD who responded to the question, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?". The phthalate metabolites ECP, MBP, MHH, MOH, MZP, and MIB were found to be significantly higher among individuals who are limited because of difficulty remembering or confusion (ECP, $p<0.05$; MBP, $p<0.01$; MHH, $p<0.01$; MOH, $p<0.05$; MZP, $p<0.01$; MIB, $p<0.001$) (

Table 1.33 presents age-specific GMs and GSEs. For the age group 60-69, the phthalate metabolites ECP, MBP, MHH, MOH, MZP, and MIB were found to be significantly higher in those who are limited due to difficulty remembering or confusion (ECP, $p<0.01$; MBP, $p<0.05$; MHH, $p<0.01$; MOH, $p<0.05$; MZP, $p<0.05$; MIB, $p<0.01$). In the age group 70-79, the phthalate metabolite MIB was found to be significantly higher in those who are limited due to difficulty remembering or confusion ($p<0.05$). In the age group 80+, the phthalate metabolite MIB was found to be significantly higher in those who experienced memory issues or confusion ($p<0.05$). Table 1.34 presents gender-specific GMs and GSEs. For males, the phthalate metabolites ECP, MHH, MOH, and MIB were found to be significantly higher in those who are limited due to memory issues or confusion (ECP, $p<0.05$; MHH, $p<0.05$; MOH, $p<0.05$; MIB, $p<0.001$). For females, the phthalate metabolites MBP, MZP, and MIB were found to be significantly higher in those in those who are limited due to memory issues or confusion (MBP, $p<0.05$; MZP, $p<0.001$; MIB, $p<0.05$). In females, BPA was found to be significantly higher in those that significantly higher in those in those who are not limited due to memory issues or

confusion ($p<0.05$). Table 1.35 presents race-specific GMs and GSEs. Among non-Hispanic whites, the phthalate metabolites MZP and MIB were found to be significantly higher among those that are limited due to memory issues or confusion (MZP, $p<0.01$; MIB, $p<0.05$). Table 1.36 presents estimated ORs and 95% CI for phthalate metabolites and BPA among subjects who responded to "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?". For the phthalate metabolite MBP among females in the ≥ 50th percentile group compared to the reference group, MBP concentrations were found to be significantly associated with having limitations due to memory issues or confusion (OR=1.721, 95% CI: 1.083-2.735) in the unadjusted model. The adjusted models were not significant. For the phthalate metabolite MHH, among males in the ≥ 50th percentile group compared to the reference group, MHH concentrations were found to be significantly associate with limitations due to memory issues or confusion in the unadjusted model, adjusted model #1, and adjusted model #2 (OR=2.460, 95% CI: 1.392-4.350, OR=2.444, 95% CI: 1.278-4.675, OR=3.029, 95% CI: 1.441=6.366). For the phthalate metabolite MOH, among males in the ≥ 50th percentile group compared to the reference group, MOH concentrations were significantly associated with limitations due to memory issues or confusion the unadjusted model (OR=2.050, 95% CI: 1.016-4.136).

For the phthalate metabolite MZP, among females in the ≥ 50th percentile group compared to the reference group, MZP concentrations were significantly associated with limitations due to memory issues or confusion in the unadjusted and both adjusted models (OR=3.135, 95% CI: 1.965-5.001, OR=2.863, 95% CI: 1.719-4.768, OR=2.124, 95% CI: 1.151-3.922). For the phthalate metabolite MIB, among males in the ≥ 50th

percentile group compared to the reference group, MIB concentrations were significantly associated with limitations due to memory issues or confusion in the unadjusted and both adjusted models (OR=3.779, 95% CI: 1.756-8.131; OR=3.818, 95% CI: 1.742-8.369; OR=3.953, 95% CI: 1.691-9.242). Among females in the ≥ 50th percentile compared to the reference group, MIB concentrations were significantly associated with limitations due to memory issues or confusion in only the unadjusted model (OR=1.786, 95% CI: 1.046-3.049).

Table 1.32 Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.44	0.20	164	2.69	0.15	856
Mono (carboxyoctyl) Phthalate - COP	17.74	2.76	165	19.29	1.56	858
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**14.51**	**0.94**	**164 ***	11.98	0.59	858
Mono-n-butyl Phthalate - MBP	**12.25**	**0.81**	**164 ****	9.83	0.51	845
Mono-(3-carboxypropyl) Phthalate - MC1	2.63	0.37	160	2.77	0.19	818
Mono-ethyl Phthalate -MEP	55.64	7.67	165	56.20	4.65	859
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**8.62**	**0.53**	**165 ****	7.26	0.33	858
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**5.86**	**0.36**	**165 ***	4.89	0.23	857
Mono-benzyl Phthalate - MZP	**5.73**	**0.59**	**165 ****	4.05	0.21	845
Mono-isobutyl Phthalate - MIB	**8.42**	**0.65**	**165 *****	6.11	0.27	850
Bisphenol A - BPA	1.42	0.13	154	1.55	0.07	811

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.35 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.54	0.22	50	2.32	0.14	165	2.62	0.26	58	2.84	0.20	383
Mono (carboxyoctyl) Phthalate - COP	20.87	3.32	50	19.39	2.13	165	18.46	3.70	58	20.37	2.02	383
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	19.36	1.52	50	17.66	1.10	165	13.47	1.32	58	11.66	0.66	382
Mono-n-butyl Phthalate - MBP	13.36	1.85	50	13.82	0.91	163	10.99	1.06	58	9.23	0.61	376
Mono-(3-carboxypropyl) Phthalate - MC1	2.72	0.42	46	2.85	0.32	157	2.61	0.52	57	2.84	0.24	367
Mono-ethyl Phthalate -MEP	97.76	15.35	50	95.22	14.73	165	44.74	7.32	58	51.67	5.12	383
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	11.61	1.46	50	10.06	0.75	165	7.74	0.66	58	7.08	0.37	382
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	7.58	0.80	50	6.47	0.48	165	5.41	0.42	58	4.79	0.26	381
Mono-benzyl Phthalate - MZP	4.50	0.92	50	3.84	0.30	165	**6.12**	**0.97**	**58 ****	4.01	0.22	377
Mono-isobutyl Phthalate - MIB	8.86	0.64	50	9.30	0.63	165	**7.71**	**0.84**	**58 ***	5.64	0.26	380
Bisphenol A - BPA	1.67	0.25	48	1.59	0.15	157	1.38	0.20	52	1.57	0.09	366

EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.77	0.26	35	2.01	0.10	227	2.08	0.58	21	2.40	0.38	81
Mono (carboxyoctyl) Phthalate - COP	16.00	3.51	35	13.90	0.89	226	11.67	3.88	22	14.48	2.23	84
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	13.47	2.27	34	10.63	0.58	227	15.54	2.61	22	12.98	0.96	84
Mono-n-butyl Phthalate - MBP	11.89	1.51	35	10.86	0.65	223	22.74	4.89	21	13.66	2.47	83
Mono-(3-carboxypropyl) Phthalate - MC2	2.58	0.43	35	2.14	0.14	219	2.64	0.52	22	2.82	0.45	75
Mono-ethyl Phthalate -MEP	49.05	13.22	35	87.39	7.79	227	100.51	62.86	22	44.15	8.71	84
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	9.08	1.69	35	7.20	0.42	227	9.70	2.15	22	6.88	0.72	84
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	6.42	0.14	35	4.79	0.25	227	5.59	1.42	22	4.74	0.50	84
Mono-benzyl Phthalate - MZP	6.17	0.98	35	4.49	0.44	224	5.21	1.31	22	4.16	1.41	79
Mono-isobutyl Phthalate - MIB	8.88	1.06	35	7.43	0.42	222	12.81	4.31	22	8.42	1.41	83
Bisphenol A - BPA	1.17	0.13	34	1.46	0.07	220	1.66	0.26	20	1.25	0.20	68

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.33 Age-Specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Yes			No			Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.26	0.19	74	2.58	0.19	457	2.34	0.31	36	2.97	0.27	264	2.72	0.41	54	2.54	0.17	135
Mono (carboxyoctyl) Phthalate - COP	17.00	2.86	75	18.73	2.12	457	15.80	3.19	36	21.95	2.09	266	20.14	5.55	54	15.98	1.80	135
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**15.04**	**1.28**	**74 ****	10.67	0.78	457	13.81	1.71	36	13.65	0.73	266	14.43	1.51	54	13.72	0.7918.	135
Mono-n-butyl Phthalate - MBP	**12.01**	**1.24**	**74 ***	9.19	0.62	450	10.96	1.18	36	10.17	0.81	263	13.50	1.62	54	11.75	1.09	132
Mono-(3-carboxypropyl) Phthalate - MC1	2.39	0.32	73	2.57	0.24	433	2.49	0.73	34	3.08	0.30	253	3.03	0.74	53	2.86	0.32	132
Mono-ethyl Phthalate -MEP	60.87	18.15	75	58.00	6.47	458	78.19	16.52	36	58.73	6.76	266	39.85	9.80	54	44.95	3.76	135
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**9.27**	**0.93**	**75 ****	6.57	0.46	457	9.27	1.26	36	8.28	0.45	266	7.57	0.89	54	7.84	0.48	135
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**5.81**	**0.61**	**75 ***	4.30	0.30	457	6.08	0.76	36	5.63	0.27	266	5.76	0.55	54	5.76	0.38	134
Mono-benzyl Phthalate - MZP	**6.16**	**1.00**	**75 ***	3.98	0.30	450	5.01	0.78	36	3.79	0.30	263	5.81	0.77	54	5.07	0.45	132
Mono-isobutyl Phthalate - MIB	**8.96**	**1.09**	**75 ****	6.34	0.34	454	**8.73**	**1.26**	**36 ***	6.09	0.34	262	**7.66**	**0.83**	**54 ****	5.34	0.46	134
Bisphenol A - BPA	1.62	0.20	73	1.50	0.10	434	1.28	0.28	30	1.66	0.10	249	1.30	0.19	51	1.48	0.14	128

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.34 Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.22	0.25	72	2.38	0.14	442	2.60	0.34	92	3.05	0.27	414
Mono (carboxyoctyl) Phthalate - COP	15.30	3.29	72	16.88	1.30	444	19.62	3.96	93	22.02	2.68	414
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**14.22**	**1.45**	**72 ***	10.68	0.55	445	14.70	1.19	92	13.44	0.90	413
Mono-n-butyl Phthalate - MBP	9.91	0.84	72	9.32	0.68	435	**14.16**	**1.28**	**92 ***	10.35	0.55	410
Mono-(3-carboxypropyl) Phthalate - MC1	2.49	0.69	71	2.53	0.19	426	2.73	0.37	89	3.03	0.29	392
Mono-ethyl Phthalate -MEP	61.56	7.92	72	52.27	5.08	445	51.93	10.58	93	60.39	6.37	414
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**8.70**	**0.77**	**72 ***	6.70	0.36	445	8.56	0.84	93	7.86	0.45	413
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**5.87**	**0.53**	**72 ***	4.53	0.24	443	5.85	0.53	93	5.28	0.33	414
Mono-benzyl Phthalate - MZP	4.31	0.87	72	3.64	0.30	438	**6.96**	**0.73**	**93 *****	4.51	0.25	407
Mono-isobutyl Phthalate - MIB	**8.47**	**0.82**	**72 *****	5.61	0.29	442	**8.38**	**0.88**	**93 ***	6.65	0.33	408
Bisphenol A - BPA	1.61	0.28	64	1.38	0.07	424	1.32	0.12	90	**1.75**	**0.11**	**387 ***

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.36 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by Responses, "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	42/217	1.00		42/216	1.00		37/202	1.00	
≥50th percentile	30/228	0.645	0.348-1.194	30/228	0.614	0.352-1.069	27/214	0.642	0.337-1.220
CNP - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	48/206	1.00		48/205	1.00		42/192	1.00	
≥50th percentile	45/208	1.018	0.555-1.870	44/208	1.389	0.747-2.584	42/191	1.649	0.833-3.264
COP - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	41/217	1.00		41/217	1.00		38/202	1.00	
≥50th percentile	31/228	1.031	0.445-2.393	31/227	1.129	0.525-2.431	26/214	1.074	0.504-2.291
COP - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	46/207	1.00		45/207	1.00		40/193	1.00	
≥50th percentile	47/207	0.923	0.467-1.823	47/206	1.177	0.568-2.437	44/190	1.288	0.553-3.002
ECP - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	35/223	1.00		35/223	1.00		30/210	1.00	
≥50th percentile	37/222	1.537	0.770-3.068	37/221	1.275	0.564-2.887	34/206	1.405	0.504-3.917
ECP - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	43/210	1.00		42/210	1.00		35/198	1.00	
≥50th percentile	50/204	1.128	0.666-1.909	50/203	1.027	0.554-1.903	49/185	1.097	0.599-2.008
MBP - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	31/227	1.00		31/227	1.00		25/215	1.00	
≥50th percentile	41/218	1.800	0.803-4.033	41/217	1.562	0.679-3.591	39/201	2.272	0.853-6.049
MBP - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	36/217	1.00		36/216	1.00		33/200	1.00	
≥50th percentile	57/197	**1.721 ***	**1.083-2.735**	56/197	1.350	0.820-2.221	51/183	1.183	0.728-1.923
MC1 - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	43/216	1.00		43/214	1.00		39/201	1.00	
≥50th percentile	29/229	0.943	0.323-2.750	29/230	0.907	0.331-2.487	25/215	0.917	0.290-2.901
MC1 - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	46/207	1.00		45/207	1.00		41/193	1.00	
≥50th percentile	47/207	0.877	0.466-1.650	47/206	0.994	0.516-1.915	43/190	0.808	0.408-1.600
MEP - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	28/230	1.00		28/230	1.00		27/213	1.00	
≥50th percentile	44/215	1.605	0.955-2.698	44/214	1.765	0.948-3.287	37/203	1.866	0.927-3.757
MEP - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	48/205	1.00		47/205	1.00		41/192	1.00	
≥50th percentile	45/209	0.915	0.511-1.640	45/208	0.900	0.467-1.733	43/191	1.215	0.557-2.652
MHH - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	27/231	1.00		27/231	1.00		23/217	1.00	
≥50th percentile	45/214	**2.460 ****	**1.392-4.350**	45/213	**2.444 ****	**1.278-4.675**	41/199	**3.029 ****	**1.441-6.366**
MHH - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	38/215	1.00		38/214	1.00		34/199	1.00	
≥50th percentile	55/199	1.560	0.845-2.879	54/199	1.297	0.667-2.523	50/184	1.173	0.593-2.321
MOH - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	28/230	1.00		28/230	1.00		25/215	1.00	
≥50th percentile	44/215	**2.050 ***	**1.016-4.136**	44/214	1.744	0.868-3.504	39/201	1.767	0.756-4.128
MOH - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	42/212	1.00		41/211	1.00		36/197	1.00	
≥50th percentile	51/202	1.172	0.677-2.029	51/202	1.008	0.557-1.827	48/186	0.922	0.511-1.663
MZP - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	38/220	1.00		38/220	1.00		34/206	1.00	
≥50th percentile	34/225	1.179	0.489-2.844	34/224	1.084	0.491-2.395	30/210	1.117	0.465-2.683
MZP - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	29/224	1.00		29/223	1.00		27/206	1.00	
≥50th percentile	64/190	**3.135 *****	**1.965-5.001**	63/190	**2.863 *****	**1.719-4.768**	57/177	**2.124 *****	**1.151-3.922**
MIB - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	24/234	1.00		24/234	1.00		21/219	1.00	
≥50th percentile	48/211	**3.779 ****	**1.756-8.131**	48/210	**3.818 ****	**1.742-8.369**	43/197	**3.953 ****	**1.691-9.242**
MIB - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	39/214	1.00		39/213	1.00		35/198	1.00	
≥50th percentile	54/200	**1.786 ***	**1.046-3.049**	53/200	1.487	0.759-2.913	49/185	1.541	0.768-3.090
BPA - Above/Below 50th Percentile - Males									
<LOD to 50th percentile (reference)	37/221	1.00		37/221	1.00		32/208	1.00	
≥50th percentile	35/224	1.044	0.496-2.200	35/223	0.959	0.512-1.797	32/208	0.945	0.443-2.014
BPA - Above/Below 50th Percentile - Females									
<LOD to 50th percentile (reference)	53/200	1.00		52/199	1.00		46/187	1.00	
≥50th percentile	40/214	0.513	0.249-1.058	40/214	0.544	0.249-1.187	38/196	0.567	0.254-1.270

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Associations Between Exposures to Phthalate and BPA and Taste/Smell Function

Exposures to the 12 phthalate metabolites and BPA and two indicators of taste/smell function: 1) Do you sometimes smell an unpleasant, bad, or burning odor when nothing is there (phantosmia), and 2) During the past 12 months have you had a taste or other sensation in your mouth that does not go away? Taste and smell indicators have been included as a surrogate indicator of brain health as taste and smell dysfunction is a possible pre-clinical indicator in the development of AD and other memory-related neurodegenerative diseases.

Smell Dysfunction and Exposure to BPA and Phthalates: Table 1.37 presents crude GMs and GSEs for subjects with phthalate metabolite and BPA measurements over the LOD who provided a response to the question, "Do you sometimes smell an unpleasant, bad, or burning odor when nothing is there?". The GM for the phthalate metabolite MIB was found to be significantly higher in those that experienced phantosmia ($p<0.05$). Table 1.38 presents age-specific GMs and GSEs. In the 60-69 age group, the GM for the phthalate MIB was found to be significantly higher in those that experienced phantom odors ($p<0.05$). In the 70-79 age group, the GM for the phthalate MEP was found to be significantly higher in those that experienced phantom odors ($p<0.01$). Table 1.39 presents gender-specific GMs and GSEs. In females, the GMs for the phthalate metabolites MBP and MOH were significantly higher in those that experienced phantom odors (MBP, $p<0.01$; MOH, $p<0.05$). Table 1.40 presents race-specific GMs and GSEs. Among non-Hispanic blacks, the GM for phthalate metabolite MC1 was significantly higher in those that experienced phantom odors ($p<0.01$). The GM for BPA among Asian/other was significantly higher in those that experienced phantom odors ($p<0.05$).

Table 1.41 presents estimated ORs and 95% CI for subjects with measurable phthalate metabolite and BPA levels who responded to the question "Do you sometimes smell and unpleasant, bad, or burning odor when nothing is there?". For the phthalate metabolite MEP, among females in the ≥ 50th percentile compared to the reference group, MEP concentrations are significantly associated with phantom odor (OR=2.036, 95% CI: 1.047-3.958) in the unadjusted model (Table 1.41).

Table 1.37 Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.51	0.27	73	2.67	0.14	947
Mono (carboxyoctyl) Phthalate - COP	21.90	3.90	74	18.91	1.48	949
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	13.63	1.69	74	12.16	0.56	948
Mono-n-butyl Phthalate - MBP	11.55	1.32	74	10.00	0.52	935
Mono-(3-carboxypropyl) Phthalate - MC1	2.50	0.37	70	2.77	0.18	907
Mono-ethyl Phthalate -MEP	75.21	16.90	74	55.11	4.33	950
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.36	1.16	73	7.34	0.31	950
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.51	0.74	74	4.96	0.23	948
Mono-benzyl Phthalate - MZP	4.84	0.73	73	4.19	0.23	936
Mono-isobutyl Phthalate - MIB	**7.57**	**0.66**	**74 ***	6.28	0.28	940
Bisphenol A - BPA	1.51	0.18	70	1.53	0.07	895

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.40 Race-specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	1.93	0.30	21	2.43	0.13	194	2.68	0.34	25	2.82	0.18	417
Mono (carboxyoctyl) Phthalate - COP	15.73	3.97	21	20.28	1.65	194	24.01	5.79	25	19.94	1.90	417
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	16.79	1.91	21	18.21	1.05	194	13.28	2.47	25	11.74	0.60	416
Mono-n-butyl Phthalate - MBP	12.02	2.26	21	13.93	0.99	192	11.13	1.85	25	9.29	0.60	410
Mono-(3-carboxypropyl) Phthalate - MC1	2.49	0.37	18	2.86	0.27	185	2.45	0.52	24	2.84	0.23	400
Mono-ethyl Phthalate -MEP	141.12	46.34	21	91.49	11.53	194	68.51	22.09	25	50.11	4.51	417
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	9.96	1.25	21	10.47	0.73	194	8.19	1.63	24	7.07	0.34	417
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	6.42	0.82	21	6.76	0.48	194	5.38	1.04	25	4.81	0.25	415
Mono-benzyl Phthalate - MZP	4.09	0.87	21	3.98	0.36	194	5.24	1.18	24	4.13	0.26	411
Mono-isobutyl Phthalate - MIB	9.59	1.13	21	9.14	0.48	194	7.31	0.92	25	5.74	0.27	413
Bisphenol A - BPA	1.57	0.33	21	1.62	0.17	184	1.61	0.26	23	1.55	0.09	396

EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.06	0.46	21	1.96	0.10	241	3.91	1.70	6	2.23	0.34	95
Mono (carboxyoctyl) Phthalate - COP	22.09	6.62	21	13.66	0.79	240	17.73	5.57	7	13.74	2.11	98
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.44	2.33	21	10.89	0.63	240	12.93	2.83	7	13.53	0.96	98
Mono-n-butyl Phthalate - MBP	10.82	1.83	21	11.03	0.58	237	18.60	5.19	7	15.02	2.59	96
Mono-(3-carboxypropyl) Phthalate - MC1	**3.30**	**0.56**	**21 ****	2.12	0.12	233	1.70	0.62	7	2.90	0.40	89
Mono-ethyl Phthalate -MEP	64.66	17.91	21	81.72	8.27	241	58.36	35.50	7	52.76	11.50	98
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.05	1.81	21	7.40	0.46	241	7.27	2.00	7	7.41	0.77	98
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.44	1.08	21	4.97	0.27	241	5.00	1.26	7	4.90	0.54	98
Mono-benzyl Phthalate - MZP	4.93	0.77	21	4.69	0.44	238	2.94	0.89	7	4.55	1.36	93
Mono-isobutyl Phthalate - MIB	6.76	0.82	21	7.72	0.46	236	7.87	0.78	7	9.46	1.56	97
Bisphenol A - BPA	1.30	0.29	21	1.42	0.06	233	0.78	0.20	5	**1.37**	**0.16**	**82 ***

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.38 Age-specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Yes			No			Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.74	0.30	50	2.53	0.18	480	2.19	0.46	16	2.93	0.25	284	1.78	0.56	7	2.60	0.15	183
Mono (carboxyoctyl) Phthalate - COP	22.71	5.04	50	18.27	2.08	481	24.11	10.69	17	21.17	2.09	285	13.28	5.05	7	16.93	1.81	183
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	12.64	2.18	50	10.88	0.77	480	17.20	2.61	17	13.53	0.68	285	14.03	2.02	7	13.79	0.75	183
Mono-n-butyl Phthalate - MBP	11.16	1.66	50	9.28	0.62	473	12.02	3.07	17	10.18	0.78	282	13.64	1.27	7	12.08	1.11	180
Mono-(3-carboxypropyl) Phthalate - MC1	2.31	0.46	47	2.58	0.22	458	3.07	1.28	16	3.02	0.30	271	2.81	0.77	7	2.91	0.28	178
Mono-ethyl Phthalate -MEP	63.02	19.27	50	57.93	6.37	482	**155.45**	**43.22**	**17 ****	58.02	6.61	285	52.46	15.91	7	43.15	3.89	183
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.61	1.43	49	6.72	0.47	482	9.87	1.70	17	8.31	0.44	285	11.39	2.22	7	7.57	0.47	183
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.00	0.90	50	4.37	0.30	481	6.73	1.11	17	5.63	0.27	285	7.23	1.01	7	5.65	0.33	182
Mono-benzyl Phthalate - MZP	4.86	0.97	50	4.86	0.97	474	4.49	1.00	16	3.87	0.29	283	5.52	2.23	7	5.25	0.45	179
Mono-isobutyl Phthalate - MIB	**8.12**	**0.76**	**50 ***	6.43	0.38	478	7.23	1.42	17	6.27	0.32	281	4.96	1.10	7	5.89	0.46	181
Bisphenol A - BPA	1.36	0.19	50	1.52	0.10	456	1.88	0.41	15	1.62	0.10	264	2.42	0.84	5	1.41	0.13	175

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.39 Gender-specific Geometric Mean Urinary Phthalate and BPA Levels by Responses, "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.62	0.36	30	2.34	0.12	484	2.42	0.35	43	3.02	0.25	463
Mono (carboxyoctyl) Phthalate - COP	21.12	7.05	31	16.45	1.15	485	22.56	4.12	43	21.61	2.53	464
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	11.11	2.70	31	10.95	0.50	486	16.07	2.01	43	13.45	0.86	462
Mono-n-butyl Phthalate - MBP	8.03	1.66	31	9.45	0.66	476	**15.49**	**1.62**	**43 ****	10.55	0.57	459
Mono-(3-carboxypropyl) Phthalate - MC1	2.48	0.68	30	2.53	0.18	466	2.52	0.35	40	3.02	0.26	441
Mono-ethyl Phthalate -MEP	84.50	39.48	31	51.73	4.49	486	68.45	9.74	43	58.56	5.94	464
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.08	1.88	31	6.84	0.33	486	9.62	1.34	42	7.86	0.43	464
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	4.57	1.27	31	4.63	0.23	484	**6.42**	**0.64**	**43 ***	5.29	0.31	464
Mono-benzyl Phthalate - MZP	4.22	1.24	31	3.68	0.31	478	5.43	0.53	42	4.75	0.27	458
Mono-isobutyl Phthalate - MIB	7.26	1.13	31	5.78	0.31	482	7.83	0.64	43	6.81	0.35	458
Bisphenol A - BPA	1.33	0.26	29	1.40	0.07	459	1.68	0.22	41	1.68	0.10	436

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.41 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by Responses, "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	15/243	1.00		15/242	1.00		13/227	1.00	
≥ 50th percentile	16/243	1.254	0.483-3.256	16/243	1.532	0.510-4.600	13/227	1.601	0.659-3.890
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	26/228	1.00		26/227	1.00		23/211	1.00	
≥ 50th percentile	17/236	0.649	0.274-1.537	17/235	0.694	0.312-1.540	17/216	0.906	0.396-2.075
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	12/246	1.00		12/246	1.00		10/230	1.00	
≥ 50th percentile	19/240	1.403	0.292-6.732	19/239	1.258	0.253-6.258	16/224	0.839	0.129-5.478
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	17/236	1.00		17/235	1.00		16/217	1.00	
≥ 50th percentile	26/228	1.880	0.814-4.339	26/227	1.981	0.892-4.401	24/210	2.317	0.891-6.022
ECP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	13/245	1.00		13/245	1.00		12/228	1.00	
≥ 50th percentile	18/241	1.741	0.449-6.744	18/240	2.210	0.582-8.389	14/226	1.264	0.305-5.247
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	18/235	1.00		18/234	1.00		15/218	1.00	
≥ 50th percentile	25/229	1.724	0.701-4.240	25/228	1.708	0.672-4.341	25/209	1.755	0.702-4.388
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	17/241	1.00		17/241	1.00		14/226	1.00	
≥ 50th percentile	14/245	0.980	0.252-3.817	14/244	1.056	0.222-5.026	12/228	1.577	0.315-7.881
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	18/235	1.00		18/234	1.00		18/215	1.00	
≥ 50th percentile	25/229	1.945	0.907-4.168	25/228	1.843	0.912-3.724	22/215	1.539	0.719-3.294
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	17/242	1.00		17/240	1.00		15/225	1.00	
≥ 50th percentile	14/244	1.016	0.265-3.899	14/245	1.095	0.251-4.771	11/229	0.887	0.167-4.702
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	21/232	1.00		21/231	1.00		18/216	1.00	
≥ 50th percentile	23/232	0.806	0.436-1.492	22/231	0.807	0.424-1.537	22/211	0.939	0.471-1.871
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	10/248	1.00		10/248	1.00		8/232	1.00	
≥ 50th percentile	21/238	1.749	0.431-7.096	21/237	1.457	0.387-5.484	18/222	1.318	0.220-7.899
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	16/237	1.00		17/235	1.00		16/217	1.00	
≥ 50th percentile	27/227	**2.036 ***	**1.047-3.958**	26/227	1.693	0.811-3.535	24/210	1.819	0.706-4.685
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	14/244	1.00		14/244	1.00		12/228	1.00	
≥ 50th percentile	17/242	1.390	0.392-4.936	17/241	1.596	0.416-6.118	14/226	1.420	0.348-5.800
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	19/234	1.00		19/233	1.00		17/216	1.00	
≥ 50th percentile	24/230	1.143	0.449-2.905	24/229	1.080	0.422-2.764	23/211	1.060	0.380-2.957
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	15/243	1.00		15/243	1.00		13/227	1.00	
≥ 50th percentile	16/243	1.014	0.270-3.813	16/242	1.155	0.287-4.645	13/227	0.962	0.172-5.377
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	18/236	1.00		18/234	1.00		15/218	1.00	
≥ 50th percentile	25/228	1.715	0.782-3.761	25/228	1.630	0.690-3.855	25/209	1.871	0.823-4.253
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	16/242	1.00		16/242	1.00		15/225	1.00	
≥ 50th percentile	15/244	0.633	0.159-2.519	15/243	0.504	0.144-1.757	11/229	0.303	0.064-1.442
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	18/235	1.00		18/234	1.00		16/217	1.00	
≥ 50th percentile	25/229	1.539	0.652-3.636	25/228	1.474	0.577-3.766	24/210	1.493	0.444-5.021
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	11/247	1.00		11/247	1.00		11/229	1.00	
≥ 50th percentile	20/239	1.664	0.402-6.880	20/238	1.330	0.363-4.877	15/225	1.032	0.263-4.048
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	21/232	1.00		20/232	1.00		18/215	1.00	
≥ 50th percentile	22/232	1.452	0.710-2.969	23/230	1.331	0.620-2.859	22/212	1.449	0.709-2.960
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	11/248	1.00		11/246	1.00		9/231	1.00	
≥ 50th percentile	20/238	2.216	0.511-9.613	20/239	2.079	0.426-10.141	17/223	1.352	0.257-7.104
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	24/229	1.00		24/227	1.00		22/211	1.00	
≥ 50th percentile	19/235	0.756	0.327-1.750	19/235	0.783	0.321-1.910	18/216	0.879	0.337-2.295

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, , high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Taste Dysfunction and Exposure to BPA and Phthalates: Table 1.42 presents crude GMs and GSEs for subjects who have phthalate metabolite and BPA levels over the LOD who responded to the question, "During the past 12 months, you had a problem with your ability to taste sweet, sour, salty or bitter foods and drinks?". The GMs phthalate metabolites COP, ECP, MBP, MHH, MOH, and MIB were found to be significantly higher in those that had persistent sensation in their mouth the past 12 months compared to those that did not have it (COP, MIB, $p<0.05$; MBP, MHH, MOH, $p<0.01$; ECP, $p<0.001$) (Table 1.42). Table 1.43 presents age-specific GMs and GSEs. Among the 60-69 age group, GMs for the phthalate metabolites ECP, MBP, MHH, MOH, and MIB were significantly higher in those with persistent sensation in their mouths compared to those who did not have persistent sensation (ECP, MHH, MOH, $p<0.01$; MBP, MIB, $p<0.05$). Among the 80+ age group, GMs for the phthalate metabolites CNP, ECP, MHH, and MOH were significantly higher in those with persistent sensation in their mouths compared to those who did not have persistent sensation (CNP, ECP, MHH, $p<0.05$; MOH, $p<0.01$) (Table 1.43). Table 1.44 presents gender-specific GMs and GSEs. Among males, the phthalate metabolites MBP and MIB were significantly higher in those that experienced persistent sensations in their mouths compared to those who did not have those sensations (MBP, MIB, $p<0.05$). In females, ECP, MBP, MHH, and MOH were observed to be significantly higher in those that experience persistent sensation in their mouths (ECP, MBP, MHH, MOH, $p<0.01$) (Table 1.44). Table 1.45 presents race-specific GMs and GSEs. Among non-Hispanic Whites, the phthalate metabolites COP, ECP, MBP, MHH, MOH, and MIB were found to be significantly higher in

those with persistent sensation in their mouths (ECP, MBP, $p<0.001$; MHH, $p<0.01$; COP, MOH, MIB, $p<0.05$). Among Asians/Others, the phthalate metabolite MHH was found to be significantly higher in those with persistent taste or sensation in their mouths (MHH, $p<0.05$).

Table 1.46 presents ORs and 95% CI for those with Yes/No responses to the question "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" and phthalates and BPA stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. For the phthalate COP, males in the ≥ 50th percentile compared to the reference group were found to have COP concentrations significantly associated gustatory sensations that would not go away in the unadjusted model and both adjusted models (OR=3.649, 95% CI: 1.054-12.639; OR=4.1.280, 95% CI: 1.386-12.603; OR=4.608, 95% CI: 1.130-18.787). For the phthalate ECP, males in the ≥ 50th percentile compared to the reference group were found to have ECP concentrations significantly associated with gustatory sensations that would not go away in the unadjusted model and both adjusted models (OR=8.673, 95% CI: 2.471-30.448; OR=4.180, 95% CI: 1.386-12.603; OR=4.608, 95% CI: 1.130-18.787) and in females ECP concentrations were significant in the second adjusted model (OR=3.411; 95% CI: 1.013-11.483). For the phthalate MBP, males in the ≥ 50th percentile compared to the reference group were found to have MBP concentrations significantly associated with gustatory sensations that would not go away in the unadjusted model and second adjusted model (OR=4.548, 95% CI: 1.339-15.445; OR=5.547, 95% CI: 1.137-27.073), and in females MBP concentrations were significant in the unadjusted and first adjusted

model (OR=2.153, 95% CI: 1.063-4.358; OR=2.229, 95% CI: 1.055-4.706). For the phthalate MC1, males in the ≥ 50th percentile compared to the reference group were found to have MC1 concentrations significantly associated with gustatory sensations that would not go away in the second adjusted model (OR=4.545, 95% CI: 1.488-13.877). For the phthalate MHH, males in the ≥ 50th percentile compared to the reference group were found to have MHH concentrations significantly associated with gustatory sensations that would not go away in the unadjusted model, first adjusted model, and second adjusted model (OR=4.611, 95% CI: 1.360-15.633; OR=4.628, 95% CI: 1.068-20.065; OR=5.525, 95% CI: 1.487-20.519) with the same observation in females (OR=3.255, 95% CI: 1.261-8.401; OR=3.386, 95% CI: 1.313-8.734; OR=3.025, 95% CI: 1.223-7.480). For the phthalate MOH, females in the ≥ 50th percentile compared to the reference group were found to have MOH concentrations significantly associated with gustatory sensations that would not go away in the unadjusted model, first adjusted model, and second adjusted model (OR=3.576, 95% CI: 1.345-9.506; OR=3.671, 95% CI: 1.341-10.047; OR=3.571, 95% CI: 1.343-9.494). For the phthalate MOH, females in the ≥ 50th percentile compared to the reference group were found to have MZP concentrations significantly associated with gustatory sensations that would not go away in the unadjusted model, first adjusted model, and second adjusted model (OR=2.743, 95% CI: 1.003-7.498; OR=3.055, 95% CI: 1.088-8.581; OR=4.161, 95% CI: 1.299-13.324).

Table 1.42 Geometric Mean Urinary Phthalate and BPA Levels by Responses, "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	3.30	0.45	66	2.63	0.13	954
Mono (carboxyoctyl) Phthalate - COP	**25.12**	**3.25**	**66 ***	18.77	1.46	957
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**17.83**	**1.63**	**66 *****	11.99	0.56	956
Mono-n-butyl Phthalate - MBP	**14.00**	**1.19**	**65 ****	9.91	0.51	944
Mono-(3-carboxypropyl) Phthalate - MC1	3.22	0.59	63	2.72	0.17	914
Mono-ethyl Phthalate -MEP	68.42	18.48	66	55.46	4.35	958
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**10.19**	**1.04**	**66 ****	7.27	0.31	957
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**7.01**	**0.72**	**66 ****	4.89	0.22	956
Mono-benzyl Phthalate - MZP	5.05	0.68	66	4.18	0.22	943
Mono-isobutyl Phthalate - MIB	**8.30**	**0.89**	**66 ***	6.25	0.28	948
Bisphenol A - BPA	1.72	0.19	64	1.52	0.07	901

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.45 Race-specific Geometric Mean Phthalate and BPA Levels by Responses, "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.2342	0.2408	26	2.3859	0.1460	189	3.9106	0.6435	25	2.7724	0.1817	417
Mono (carboxyoctyl) Phthalate - COP	17.9850	2.9303	26	19.9700	1.6055	189	**30.6082**	**4.9858**	**25 ***	19.7210	1.9011	417
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	17.1142	2.3004	26	18.1769	1.0721	189	**18.7852**	**2.1194**	**25 *****	11.5447	0.6015	416
Mono-n-butyl Phthalate - MBP	11.4422	1.7341	25	14.0124	1.0539	188	**14.9867**	**1.7298**	**25 *****	9.1628	0.5846	410
Mono-(3-carboxypropyl) Phthalate - MC1	2.2833	0.4231	23	2.8941	0.2699	180	3.7968	0.8898	25	2.7757	0.2247	399
Mono-ethyl Phthalate -MEP	109.36	29.9294	26	94.2364	12.4476	189	63.4905	23.6845	25	50.3623	4.6046	417
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	8.8961	1.3089	26	10.6238	0.7541	189	**10.6166**	**1.362**	**25 ****	6.9825	0.3365	416
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	6.184	0.8758	26	6.791	0.4969	189	**7.3103**	**0.9166**	**25 ***	4.7364	0.2406	415
Mono-benzyl Phthalate - MZP	3.2295	0.4627	26	4.0989	0.4304	189	5.6186	0.9783	25	4.1235	0.2376	410
Mono-isobutyl Phthalate - MIB	8.9868	0.9808	26	9.214	0.5559	189	**7.9277**	**1.0725**	**25 ***	5.7226	0.2659	413
Bisphenol A - BPA	1.7619	0.3249	26	1.5904	0.1517	179	1.834	0.2932	24	1.5382	0.08534	395

EEDC	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.4360	0.8530	8	1.9588	0.0971	254	1.9807	0.7439	7	2.3450	0.3556	94
Mono (carboxyoctyl) Phthalate - COP	14.5821	4.3951	8	14.1855	0.9590	253	11.3284	5.0000	7	13.8170	2.1139	98
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	11.9787	2.2455	8	10.9773	0.697	253	15.592	2.713	7	13.245	0.9117	98
Mono-n-butyl Phthalate - MBP	10.838	1.5849	8	11.0157	0.5595	250	14.1343	4.2605	7	15.1841	2.4725	96
Mono-(3-carboxypropyl) Phthalate - MC1	1.9788	0.4841	8	2.2092	0.1326	246	1.8634	0.7431	7	2.7594	0.369	89
Mono-ethyl Phthalate -MEP	74.1442	33.8916	8	80.3933	7.68	254	37.2185	10.0307	7	53.0442	11.4011	98
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.2754	2.0263	8	7.458	0.4859	254	**12.7003**	**3.0819**	**8 ***	7.0862	0.7082	98
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.2183	1.4067	8	4.9967	0.2934	254	8.0265	2.3301	8	4.7063	0.5009	96
Mono-benzyl Phthalate - MZP	6.338	0.8961	8	4.669	0.4342	251	4.6039	1.1814	7	4.3551	1.2852	93
Mono-isobutyl Phthalate - MIB	7.0111	1.7604	8	7.6527	0.4326	249	12.6603	4.9063	7	8.975	1.4887	97
Bisphenol A - BPA	1.1639	0.2892	8	1.4181	0.05666	246	1.024	0.2724	6	1.3599	0.1736	81

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.43 Age-Specific Geometric Urinary Mean Phthalate and BPA Levels by Responses, "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EED Metabolite	Geometric Mean (ng/ml) (GSE, N), Age 60-69						Geometric Mean (ng/ml) (GSE, N), Age 70-79						Geometric Mean (ng/ml) (GSE, N), Age 80 +					
	Yes			No			Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	3.35	0.68	40	2.51	0.18	490	2.26	0.48	13	2.92	0.23	287	**4.62**	**1.26**	**13 ***	2.47	0.14	177
Mono (carboxyoctyl) Phthalate - COP	27.27	5.54	40	18.10	2.15	491	21.59	6.09	13	21.27	1.93	289	22.80	7.30	13	16.47	1.81	177
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	**17.18**	**2.06**	**40 ****	10.69	0.77	490	15.91	1.72	13	13.59	0.70	289	**22.35**	**4.65**	**13 ***	13.37	0.65	177
Mono-n-butyl Phthalate - MBP	**12.49**	**1.18**	**39 ***	9.24	0.61	484	16.00	3.58	13	10.10	0.77	286	17.20	4.02	13	11.85	1.08	174
Mono-(3-carboxypropyl) Phthalate - MC1	3.14	0.82	38	2.51	0.23	467	3.50	1.83	12	3.00	0.27	275	3.20	0.67	13	2.88	0.29	172
Mono-ethyl Phthalate -MEP	46.34	12.77	40	59.02	6.59	492	115.71	48.63	13	59.06	7.01	289	131.42	86.95	13	40.42	3.06	177
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	**10.31**	**1.53**	**40 ****	6.60	0.45	491	9.06	1.35	13	8.34	0.45	289	**11.07**	**2.00**	**13 ***	7.49	0.44	177
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	**6.75**	**1.01**	**40 ****	4.30	0.29	491	6.29	0.81	13	5.65	0.27	289	**8.72**	**1.36**	**13 ****	5.54	0.31	176
Mono-benzyl Phthalate - MZP	4.79	0.92	40	4.10	0.30	484	4.70	1.12	13	3.87	0.30	286	3.69	0.49	13	4.28	0.15	173
Mono-isobutyl Phthalate - MIB	**8.83**	**1.23**	**40 ***	6.41	0.36	488	8.33	1.45	13	6.24	0.35	285	6.84	2.00	13	5.80	0.45	175
Bisphenol A - BPA	1.78	0.29	39	1.49	0.09	467	1.44	0.33	13	1.64	0.10	266	1.85	0.54	12	1.40	0.12	168

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.44 Geometric Mean Phthalate and BPA Levels by Responses, "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

EEDC	Geometric Mean (ng/ml) (GSE, N)						Geometric Mean (ng/ml) (GSE, N)					
	Male						Female					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Mono (carboxynonyl) Phthalate - CNP	2.5467	0.5328	25	2.3497	0.1165	490	3.8577	0.5860	41	2.9296	0.2575	464
Mono (carboxyoctyl) Phthalate - COP	21.1371	3.8864	25	16.4962	1.0825	492	27.8631	5.0511	41	21.2872	2.6031	465
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	15.4782	1.8068	25	10.8085	0.5128	493	**19.4138**	**2.4171**	**41 ****	13.2772	0.8424	463
Mono-n-butyl Phthalate - MBP	**13.3296**	**1.8758**	**25 ***	9.2284	0.6392	483	**14.4154**	**1.5417**	**40 ****	10.6012	0.5494	461
Mono-(3-carboxypropyl) Phthalate - MC1	2.8000	0.8309	24	2.5171	0.1717	473	3.5122	0.6441	39	2.9426	0.2706	441
Mono-ethyl Phthalate -MEP	60.8717	21.0466	25	52.7528	5.0023	493	73.3896	24.0038	41	60.4769	12.894	465
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH	7.9262	0.7366	25	6.8088	0.3495	493	**11.8474**	**1.8728**	**41 ****	7.7421	0.4146	464
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	5.7843	0.7892	25	4.5876	0.2355	491	**7.8603**	**1.1761**	**41 ****	5.2125	0.2944	465
Mono-benzyl Phthalate - MZP	4.1234	1.1159	25	3.6835	0.2944	485	5.6951	1.0655	41	4.7335	0.2481	458
Mono-isobutyl Phthalate - MIB	**8.1351**	**1.0605**	**25 ***	5.7655	0.2965	489	8.3956	1.2826	41	6.7734	0.335	459
Bisphenol A - BPH	1.6569	0.3623	24	1.3829	0.06966	465	1.756	0.2112	40	1.6725	0.09923	436

NHANES sampling weight applied before calculating the geometric mean.

The EEDCs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and EEDCs levels below the LOD were taken into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

Table 1.46 Estimated ORs (95% CI) of Urinary Phthalate and BPA Levels by Responses, "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes / No	Unadjusted Odds Ratio	95% CI	Yes / No	Adjusted Odds Ratio	95% CI	Yes / No	Adjusted Odds Ratio	95% CI
CNP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	15/243	1.00		15/244	1.00		11/162	1.00	
≥ 50th percentile	10/250	0.679	0.185-2.493	10/248	0.751	0.211-2.678	4/169	0.511	0.101-2.581
CNP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	19/233	1.00		19/232	1.00		13/165	1.00	
≥ 50th percentile	22/232	1.703	0.699-4.147	22/231	1.685	0.719-3.950	13/165	2.005	0.757-5.306
COP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	11/248	1.00		11/247	1.00		8/165	1.00	
≥ 50th percentile	14/245	**3.649 ***	**1.054 -12.639**	14/245	**4.180 ***	**1.386-12.603**	7/166	**4.608 ***	**1.130-18.787**
COP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	19/234	1.00		19/233	1.00		10/168	1.00	
≥ 50th percentile	22/231	1.696	0.732-3.928	22/230	1.620	0.735-3.571	16/162	2.850	0.937-8.670
ECP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	7/252	1.00		7/251	1.00		5/168	1.00	
≥ 50th percentile	18/241	**8.673 ****	**2.471-30.448**	18/241	**9.359 ***	**1.753-49.967**	10/163	**13.311 ****	**2.090-84.762**
ECP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	15/238	1.00		15/237	1.00		6/172	1.00	
≥ 50th percentile	26/227	2.195	0.927-5.199	26/226	2.128	0.831-5.448	20/158	**3.411 ***	**1.013-11.483**
MBP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	12/247	1.00		12/246	1.00		10/230	1.00	
≥ 50th percentile	13/246	**4.548 ***	**1.339-15.445**	13/246	4.517	0.970-21.040	12/229	**5.547 ***	**1.137-27.073**
MBP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	16/237	1.00		16/236	1.00		15/228	1.00	
≥ 50th percentile	25/228	**2.153 ***	**1.063-4.358**	25/227	**2.229 ***	**1.055-4.706**	24/209	2.257	0.919-5.541
MC1 - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	11/247	1.00		11/247	1.00		9/231	1.00	
≥ 50th percentile	14/246	2.848	0.941-8.623	14/245	3.084	0.987-9.635	13/228	**4.545 ****	**1.488-13.877**
MC1 - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	21/232	1.00		21/231	1.00		20/212	1.00	
≥ 50th percentile	20/233	1.554	0.660-3.657	20/232	1.513	0.641-3.570	19/215	1.602	0.652-3.938
MEP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	11/248	1.00		11/247	1.00		9/231	1.00	
≥ 50th percentile	14/245	1.915	0.474-7.743	14/245	1.831	0.403-8.330	13/228	1.738	0.396-7.627
MEP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	19/234	1.00		19/233	1.00		18/215	1.00	
≥ 50th percentile	22/231	1.517	0.633-3.638	22/230	1.317	0.492-3.526	21/212	1.599	0.519-4.924
MHH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	10/249	1.00		10/248	1.00		8/232	1.00	
≥ 50th percentile	15/244	**4.611 ***	**1.360-15.633**	15/244	**4.628 ***	**1.068-20.065**	14/227	**5.525 ***	**1.487-20.519**
MHH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	13/240	1.00		13/239	1.00		13/220	1.00	
≥ 50th percentile	28/225	**3.255 ***	**1.261-8.401**	28/224	**3.386 ***	**1.313-8.734**	26/207	**3.025 ***	**1.223-7.480**
MOH - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	10/249	1.00		10/248	1.00		8/232	1.00	
≥ 50th percentile	15/244	2.375	0.571-9.871	15/244	2.193	0.490-9.814	14/227	2.159	0.533-8.743
MOH - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	12/240	1.00		12/240	1.00		12/221	1.00	
≥ 50th percentile	29/225	**3.576 ***	**1.345-9.506**	29/223	**3.671 ***	**1.341-10.047**	27/206	**3.571 ***	**1.343-9.494**
MZP - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	14/245	1.00		14/244	1.00		12/228	1.00	
≥ 50th percentile	11/248	2.145	0.746-6.168	11/248	1.990	0.747-5.303	10/231	2.089	0.777-5.619
MZP - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	15/238	1.00		15/237	1.00		13/220	1.00	
≥ 50th percentile	26/227	**2.743 ***	**1.003-7.498**	26/226	**3.055 ***	**1.088-8.581**	26/207	**4.161 ***	**1.299-13.324**
MIB - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	12/247	1.00		12/246	1.00		10/230	1.00	
≥ 50th percentile	13/246	2.789	0.923-8.426	13/246	2.165	0.816-5.742	12/229	2.442	0.787-7.580
MIB - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	14/239	1.00		14/238	1.00		13/220	1.00	
≥ 50th percentile	27/226	2.048	0.880-4.766	27/225	2.049	0.768-5.466	26/207	1.995	0.656-6.071
BPA - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	12/247	1.00		12/247	1.00		10/230	1.00	
≥ 50th percentile	13/246	1.232	0.317-4.792	13/245	1.172	0.290-4.740	12/229	1.199	0.233-6.165
BPA - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	18/234	1.00		18/235	1.00		16/217	1.00	
≥ 50th percentile	23/231	1.619	0.729-3.595	23/228	1.661	0.718-3.843	23/210	2.362	0.918-5.484

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

DISCUSSION

This study takes a novel approach in the assessment of exposure to phthalates and BPA in the development of cognitive dysfunction and neurodegenerative disease using surrogates of brain health. The study examined an older geriatric-aged population of US adults 60 years of age and older. We first assessed the bioburden of urinary phthalates and BPA by calculating and comparing the GMs of each EEDCs versus each surrogate of brain health, looking at age, gender, and race and subsequently used ORs and 95% CI to determine the risk of developing cognitive dysfunction.

Major Findings: Overall, we observed a higher bioburden of phthalates in the GMs of subjects who scores lower on the four cognitive tests, had memory function deficits from our three memory questions, and had taste/smell deficits on our two taste and smell questions (Tables 1.2, 1.7, 1.12, 1.17, 1.22, 1.27, 1.32, 1.37, and 1.47). In our analyses of GMs by age, gender, and race, we accounted for subjects that have extreme creatinine measurements and examined subjects who had phthalate and BPA levels over the LOD. A higher bioburden of phthalates was observed according to gender (Tables 1.3, 1.9, 1.14, 1.19, 1.24, 1.29, 1.34, 1.39, 1.33, 1.48 and 1.49). This trend was more prominent in females (Table 1.48 and 1.49). We did not observe any meaningful trends when examining GMs by age, as the age grouping was skewed towards the 60-69-year-old age group, with the number of subjects decreasing in the 70-79-year-old and 80+ year old age group. We also did not observe any meaningful observations in our analyses of race, where large majority of participants were in the Non-Hispanic White age group. BPA was not observed to be significantly higher in

those who experienced adverse brain health versus those who did not in any of analyses.

Table 1.47 - Summary Table of EEDCs overall signficance of GMs by Surrogate of Brain Health Indicators (* p<0.05, ** p<0.01, *** p<0.001)	Immediate Recall Score (n=940)		Delayed Recall Score (n=930)		Animal Fluency Score (n=931)		Digit Symbol Substitution Test Score (n=891)		Past 12 months, memory getting worse? (n=1,025)		Past 7 days, trouble remembering? (n=971)		Limited due to difficulty remembering or confusion? (n=1,024)		Phantom Odor? (n=1,024)		Sensation in mouth that does not go away? (n=1024)	
	≤ 13	≥ 14	≤ 3	≥ 4	≤ 11	≥ 12	≤ 27	≥ 28	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Mono (carboxynonyl) Phthalate - CNP																		
Mono (carboxyoctyl) Phthalate - COP																	*	
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	*				*		**						*				***	
Mono-n-butyl Phthalate - MBP					*		*		*				**				**	
Mono-(3-carboxypropyl) Phthalate - MC1																		
Mono-ethyl Phthalate -MEP																	**	
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH							*						**				**	
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH							*						*					
Mono-benzyl Phthalate - MZP					*				*				**				*	
Mono-isobutyl Phthalate - MIB					*				*		*		***		*		*	
Bisphenol A - BPA																		

Table 1.48 - Summary Table of EEDCs overall signficance of GMs by Surrogate of Brain Health Indicators in males (* p<0.05, ** p<0.01, *** p<0.001)	Immediate Recall Score (n=940)		Delayed Recall Score (n=930)		Animal Fluency Score (n=931)		Digit Symbol Substitution Test Score (n=891)		Past 12 months, memory getting worse? (n=1,025)		Past 7 days, trouble remembering? (n=971)		Limited due to difficulty remembering or confusion? (n=1,024)		Phantom Odor? (n=1,024)		Sensation in mouth that does not go away? (n=1024)	
	≤ 13	≥ 14	≤ 3	≥ 4	≤ 11	≥ 12	≤ 27	≥ 28	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Mono (carboxynonyl) Phthalate - CNP																		
Mono (carboxyoctyl) Phthalate - COP																		
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP							**				*		*					
Mono-n-butyl Phthalate - MBP																	*	
Mono-(3-carboxypropyl) Phthalate - MC1																		
Mono-ethyl Phthalate -MEP																		
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH							*				*		*					
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH							*				*		*					
Mono-benzyl Phthalate - MZP																		
Mono-isobutyl Phthalate - MIB													***				*	
Bisphenol A - BPA																		

Table 1.49 - Summary Table of EEDCs overall signficance of GMs by Surrogate of Brain Health Indicators in females (* p<0.05, ** p<0.01, *** p<0.001)	Immediate Recall Score (n=940)		Delayed Recall Score (n=930)		Animal Fluency Score (n=931)		Digit Symbol Substitution Test Score (n=891)		Past 12 months, memory getting worse? (n=1,025)		Past 7 days, trouble remembering? (n=971)		Limited due to difficulty remembering or confusion? (n=1,024)		Phantom Odor? (n=1,024)		Sensation in mouth that does not go away? (n=1024)	
	≤ 13	≥ 14	≤ 3	≥ 4	≤ 11	≥ 12	≤ 27	≥ 28	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Mono (carboxynonyl) Phthalate - CNP																		
Mono (carboxyoctyl) Phthalate - COP																		
Mono-(2-ethyl-5-carboxypentyl) Phthalate -ECP	*		*		**												**	
Mono-n-butyl Phthalate - MBP	***		***		***		**						**		**		**	
Mono-(3-carboxypropyl) Phthalate - MC1																		
Mono-ethyl Phthalate -MEP																		
Mono (2-ethyl-5-hydroxy hexyl) Phthalate - MHH																	**	
Mono-(2-ethyl-5-oxohexyl) Phthalate -MOH	*		*		*										*		**	
Mono-benzyl Phthalate - MZP			*		**				*				***					
Mono-isobutyl Phthalate - MIB					*				*				*					
Bisphenol A - BPA																		

The analysis of odds of having a cognitive dysfunction among our nine surrogates of brain health varied by the surrogate and type of model. Although a number of the phthalates examined were significant in our unadjusted models and first adjusted model (controlling for age, education, and gender) a number of them were still significant after adjusting for all the known and suspected risk factors of cognitive dysfunction and AD. The final adjusted model accounts for the following

covariates: age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, and head trauma status.

For immediate recall, ECP in females was the only phthalate metabolite to be found significantly associated with lower immediate recall scores after controlling for the known and suspected risk factors. For delayed recall, MEP in males was the only phthalate to be found significantly associated with lower delayed recall scores after controlling for the known and suspected risk factors. For animal fluency, the phthalate MBP in females was the only phthalate to be found significantly associated with lower animal fluency scores. For DSST, the phthalate metabolites ECP and MOH in males were found to be significantly associated with lower DSST scores after controlling for the known and suspected risk factors.

Among those who had reported issues with memory in the past year, the phthalate metabolites MBP in males and MIB in females were found to be significantly associated with having memory issues in the past year after controlling for the known and suspected risk factors. Those who had reported memory issues in the past week, the phthalate metabolites ECP, MBP, and MHH in females were found to be significantly associated with having memory issues in the past year after controlling for the known and suspected risk factors.

Among those who had reported experiencing phantom odors, no phthalate or BPA was found to be significant in the second adjusted models. Those who had reported experiencing gustatory sensations that do not go away, the phthalate metabolites COP, ECP, MBP, MC1, and MHH in males were significantly associated

with experiencing gustatory sensations that did not go away. In females, this was observed with the phthalate metabolites ECP, MHH, MOH, and MZP. It should be noted that due to a smaller number of cases with taste and smell variables, diabetes status was left out of the final model since it contributed to a quasi-separation of data, making the model validity questionable, due to having zero cases among those who had diabetes. The large standard errors among the taste and smell variables indicate that the results should be interpreted with caution.

The higher bioburden of phthalates among females are in line with an earlier study that examined the urinary levels of phthalate metabolites in the US population using the NHANES 1999-2000 data sets [8], which found females to have a higher bioburden of phthalates overall. Another study using the NHANES 2003-2004 data sets found BPA to be higher in females than in males [25]. It is speculated that this increase is due to the use of phthalate containing products marketed to a female population in addition to everyday exposures to phthalates [8]. A recent study of NHANES 2009 to 2012 cycle years found gender-specific increases in product use and phthalate bioburden in males and females [103].

There are few epidemiological studies that specifically look at an older population with respect to phthalate bioburden and brain health. Shiue (2015) found a higher bioburden of phthalates, but not BPA in those having difficulties thinking or remembering and those with memory issues in the past week [23] from the 2011-2012 NHANES data sets. These findings are consistent with our study. Human epidemiological studies regarding phthalates and BPA have focused on the pre-natal, post-natal, and childhood exposures. These studies have found phthalate exposure to

be associated with social deficits [18], decreased visual recognition memory [19] and decreased IQ [20]. However there is evidence to suggests inconsistent cognitive and behavioral effects in children with regards to phthalate type and gender [21,22]. The few human epidemiological studies have concentrated on pre-natal BPA exposure and exposure in children which have been associated with significant behavioral issues in children [35,47–50]. These studies support the hypothesis of phthalates and BPA having an effect on the brain.

We also observed an increase in EEDC bioburden in females vs. males. Among females, geometric means of the EEDCs were generally higher in females than males, both significant and insignificant. Gender plays large role in the development of neurodegenerative diseases [104] and estrogen has been suspected to play a large role in the development of neurodegenerative disease [105], possibly due to its many neuroprotective effects it has on the brain [106]. The increase in bioburden is females versus males was observed in all surrogates of brain health that were examined. Studies have greater bioburden of phthalates in the mother can is associated with developmental dysfunction in children [11], which give credence to a higher bioburden of EEDCs in women. An increase in the bioburden of EEDCs in females, can affect estrogen balance in the female body, which can contribute to a higher incidence of neurodegenerative disease in females. Geometric means of EEDCs were also observed to generally increase as age increases.

Our study also observed specific phthalates reoccurring with significant associations in our surrogates of brain health. The phthalates ECP (Mono-(2-ethyl-5-carboxypentyl) Phthalate), MOH (Mono-(2-ethyl-5-oxohexyl) Phthalate), MBP

(Mono-n-butyl Phthalate), MHH, and MIB were found to be have more significant results among our surrogates of brain health compared to the other phthalates and BPA. Literature is limited regarding the specific phthalates and their effects on gender and neurodegenerative disease.

Biological Mechanisms and Brain Health: With respect to biological mechanisms, phthalate and BPA's effects have focused on mechanisms affecting the pre, peri, and postnatal stages of development and much of what is known in older human populations is based off of animal and neuronal cell line studies [11,107]. Both phthalates and BPA have been demonstrated to have affinity for estrogen receptors [9,10,26]. BPA, although having a low affinity for ER receptor binding, is also thought to exert effects through other non-classical pathways [26], which allows for phthalates and BPA to mimic and interfere with estrogen. Estrogen itself has been demonstrated to have roles in neuroprotection as well as exert anti-inflammatory effects on the brain [106,108–112]. Animal studies have also demonstrated estrogens significant role in the modulation and promotion of neuroplasticity and synaptogenesis [113–117]. Estrogen has also been demonstrated to protect and regulate mitochondrial function in the brain, where mitochondrial dysfunction is implicated as one of the causes of neurodegenerative disease [118–120]. This leads to the possibility of phthalates and BPA interfering with the function of estrogen and its protective and restorative effects on the brain.

Animal studies are numerous and have shown phthalates to adversely affect brain function and gives an idea of the possible mechanisms involved. These adverse effects include negatively affecting learning [12,13], negatively affecting

memory [13,14], interfering with locomotion [14], negative affecting social behavior [12], and producing cellular effects such as cell death, synaptic loss, and synaptic dysfunction [15]. Some animal studies have reported an improvement in memory [16], and possible dose-dependent effects, where memory improves one dose, but degrades it in another dose [17]. A recent studies, examining phthalates effects on neuronal cells found an increase in ROS concentrations after exposure [121], increase neuronal cell death [122], and disturbances to dendritic outgrowth.

Animal studies have shown BPA to also adversely brain function. Animal studies are numerous and have demonstrated BPA's negative effects on brain health and function. In animal studies BPA has been shown to negatively affect memory [27–41], negatively affect neurogenesis [33,42], negatively affect the structure of dendritic spines and synaptogenesis [27,29,32,38,40,43], and negatively affect cellular processes, protein expression and expression [31,36,39,41]. There are also animal studies that shows BPA exerts no negative effects on spatial and working memory [44–46].

BPA has been found is post-mortem brain tissue [123] and phthalates have shown to adversely affect brain neuroplasticity and affect neurodevelopment [107]. Although the mechanisms are not completely understood, both EEDCs appear to have the ability to cross the blood brain barrier.

Furthermore, genes that have been implicated in the development of neurodegenerative disease such as AD which are also estrogen-responsive are also pathway for BPA and phthalates to exert their effects on the aging brain. Genes that are estrogen-responsive, BPA-responsive, interfere with mitochondrial energetics, and implicated in AD include APBB2, DPYSL2, EIF2S1, ENO1, MAPT, and

PAXIP1 [11]. Genes that are estrogen-responsive, phthalate-responsive, interfere with mitochondrial energetics, and implicated in AD include DPYSL2, EIFS1, ENO1, and MAPT [11]. Additionally, a recent search of the Comparative Toxicogenomic Database (CTD) reveals that from 88 genes implicated in AD, 61 of those genes are estrogen and BPA responsive [124]. A search of the phthalates most associated with adverse brain health in men and women from our analyses, ECP, MBP, MHH, MOH, and MIB, for any estrogen-responsive AD genes found none for ECP, MOH, MHH, and MIB and two for MBP (EPHA1 and PPARG), which may indicate previously unknown gene/chemical interactions that affect brain health [124]. The results from our study can result from any of the possible biological mechanisms observations that have been referenced.

Strengths and Limitations: Our study has several limitations. The cross-sectional design of our study with self-reported data lends itself to misclassification bias. We cannot account for day to day variability with those who responded to our different brain health indicators. Neurodegeneration and neurodegenerative disease have a number of other risk factors. Genetic susceptibility as well as other direct measures of risk factors such as blood lipid profiles, were either not included, lacked the sufficient number of subjects, or did not use the appropriate sampling weights. We could also not account for estrogen levels as there were not measurements and we lacked the subjects required for oral contraceptive and hormone replacement therapy in our analyses. We used surrogates of brain health to link neurodegenerative disease development to EEDC exposure. The surrogates, as valid as they can be, are not clinical endpoints which cannot be used solely to diagnose neurodegenerative

conditions. Taste and smell variables have a large number of confounders associated with them and including all of them in the regression model testing would have affected the overall validity of the model.

Our study had a number of strengths. The ability to combine data cycles greatly increased our sample size and the availability of EEDC measurements allowed us a way to compare large groups together. The availability of surrogate brain health indicators made it possible to assess bioburdens and odds of adverse brain health and generalize it to the US population. The study is novel in approach and is one of the first studies to examine the role of EEDCs in an older US population.

CONCLUSION

Based on our findings for our study, increased levels of specific phthalates play a role in the development of neurodegenerative disease. Surprisingly, BPA did not appear to be significant in any of our brain health surrogates. The examination of this older population can give us a sense of a possible lifetime of exposure and how it can lead to the pre-conditions of Alzheimer's disease, Parkinson's disease, and others. Further research is needed with biologically plausible clinical endpoints and robust epidemiological studies in order to fully assess the effects of phthalate exposure on brain health and the development of neurodegenerative disease.

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CHAPTER VI

MANUSCRIPT III

EXPOSURE TO METALLOESTROGENS AND ASSOCIATIONS WITH BRAIN HEALTH: NHANES 2011-2014

ABSTRACT

BACKGROUND: The role of estrogenic endocrine disrupting chemicals (EEDCs) and their role in the development of neurodegenerative disease is of great public health concern, due to increasing exposures to these chemicals and increasingly aging population. Evidence suggests EEDCs exposure plays a role in the development of neurodegenerative disease. Metalloestrogens are known estrogenic endocrine disrupting chemicals (EEDCs) that are also heavy metals, and have been shown to exert estrogenic activity, which affects estrogen and its protective effects on brain health.

OBJECTIVE: The objective of this study is to investigate the relationship between surrogate brain health indicators and exposure to metalloestrogens among the older individuals of the United States (US) population.

METHODS: In this study, we analyzed participants from the Center for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) in the survey cycles 2011-2012 and 2013-2014. The participants were 60 years of age and older who had urine samples taken during the examination. Other data pertaining to covariates and demographics were also obtained. In total, three metallogestrogens were selected. The three analyzed metalloestrogens were the

following: cadmium (Cd), manganese (Mn), and arsenic (As). These EEDCs were analyzed versus various brain health indicators available in the form of test scores and questionnaires, available in the NHANES datasets. The brain health indicators test scores were the following: immediate recall test scores; delayed recall test scores; animal fluency test scores; digit symbol substitution test scores. The brain health indicator questions were as follows: worsening memory over the past 12 months; trouble remembering over the past week; difficulty remembering or because you experience periods of confusion. The following smell and taste questions were also included as brain health indicators due to their potential as pre-clinical indicators of cognitive impairment: phantom odor (phantosmia) and persistent taste in mouth over the past 12 months. Geometric means were calculated to compare yes/no or low score/high score dichotomous responses to the brain health indicators versus the EEDC concentrations. Logistic regression was then used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Three logistic regression models were presented in our study with all of them stratified by gender: unadjusted; age, race, education; age, race, education, body mass index (BMI), smoking status, blood pressure, diabetes status, alcohol use, coronary heart disease status, heart attack status, stroke status, head injury status, and physical activity status.

RESULTS: Cd and Mn bioburdens were found to be more evident in individuals who have lower cognitive scores and/or have memory cognition issues. In our logistic regression models, Cd stood out as the metalloestrogen that plays a larger role in the development of neurodegenerative disease and adverse brain health in an older population.

CONCLUSION: Cd and to a lesser extent, Mn, may play a role in adverse brain health and the development of some neurodegenerative condition. Further research is necessary due to the cross-sectional nature of our study.

Exposure to Metalloestrogens and Associations with Brain Health: NHANES 2011-2014

INTRODUCTION

The role of exposure to EEDCs and neurodegenerative disease development is of great public health concern as stated by the World Health Organization (WHO) [1], due to cognitive health and neurodegenerative disease emerging as great public health concerns due to an increasingly aging population [2]. Exposures to EEDCs have been linked to neurodegenerative diseases and other adverse brain health conditions, such as Alzheimer's disease (AD). In this study, we examine the associations of three of the mostly widely present Metalloestrogens, Cd, Mn, and As, and their associations with brain health in an older US population.

The role of exposure to EEDCs, brain health, and neurodegenerative disease development is of great public health concern as stated by the World Health Organization (WHO) since exposure to endocrine disrupting chemicals can lead to the development of various human disease, which include neurodegenerative diseases [1].

Cadmium is a naturally occurring metal in the earth's crust and a natural constituent of ocean water [3]. Populations are exposed through food, cigarettes, smoke, drinking water, and air [3]. Cadmium is introduced into the food chain through soil and food

contact surfaces, and through foods such as leafy vegetables, grains, legumes, and organ meats [3]. Occupation exposures are highest in occupations involving cadmium-containing products, and occupations involved in alloy, battery, plastics, and coloring production [3]. Inhalation and oral routes of exposure are predominant, followed by dermal exposure [3]. Current evidence supports the toxicity of cadmium and its effects on the developing organism, reproductive toxicity, hepatic effects, hematological effects, and immunological effects [3].

Studies on human populations have also shown cadmium's adverse effects on adult brain function. A cross-sectional study using NHANES III data from 1988 to 1994 compared neurocognitive test scores and urinary cadmium concentrations found individuals with no smoking history, or known occupational cadmium exposure were found to have lower attention/perception scores with increasing urinary cadmium levels [4]. In a cross-sectional study of rural elderly Chinese persons, it was found that increasing serum cadmium and copper levels was significant associated with lower composite cognitive scores [5] Another cross-sectional study examined the cerebrospinal fluid of ALS patients found elevated levels of various metals, including cadmium, which her higher than the measured blood levels and indicative of bioaccumulation [6]. A case-control study examining heavy metal levels in a group of Mongolian people found elevated cadmium, as well as other heavy metals in those with Parkinson-like symptoms in hair samples taken [7].

Arsenic is an element in the environment, found in the earth's crust, and is considered a metalloid [8]. Populations are usually exposed through the air, drinking water, and food, with food being the main source of arsenic in a population, with some areas

having naturally high levels of arsenic [8]. Occupational exposure occurs through individuals working in metal smelting, wood treatment, and those in working in the production and application of pesticides and herbicides [8]. Arsenic is also used in the animal and poultry feed as an antimicrobial additive [8]. The major routes of exposure are inhalation and oral, with dermal exposure being considered a minor route [8]. Arsenic has been associated with various health conditions, which include respiratory disorders, cardiovascular outcomes, diabetes, ocular effects, immune response disturbances, impaired neurological function, developmental effects, and cancers [8] Genetic polymorphisms are suspected of contributing to the sensitivity towards arsenic [8].

In cross-sectional study consisting of 133 men and 201 women from the Project FRONTIER, a rural healthcare study, long-term low level exposure to arsenic from groundwater was found to be associated with poorer scores in language, visuospatial skills, and executive functioning, global cognition, processing speed, and immediate memory [9]. In another cross-sectional study from Project Frontier, consisting of 526 subjects genotyped according to the AS3MT gene, exposure to higher low level arsenic in groundwater reduced cognitive functioning, but the results differed with amongst the different SNPs [10]. In a cross-sectional study measuring heavy metal serum levels in 89 Ad patients and 188 cognitively normal controls, there was no difference in serum arsenic levels between the AD group and controls [11]. Another cross-sectional study conducted by Edwards et al. [12] with a cohort consisting of 733 AD patients, 127 individuals with mild CI, and 530 individuals of normal cognition,

found that exposure to low level arsenic exposure from groundwater was found to be associated with poorer neuropsychological performance.

Manganese is a metal that is an essential nutrient required as a cofactor for various enzymes and is found naturally in grains and fruit [13]. Manganese is found in various industrial processes and products and exposure can occur through inhalation, oral, dermal, and occupational routes [13]. Manganese has the potential to accumulate in lower level organisms in the food chain and has been linked to various health issues including inflammation, impaired lung function, and adverse neurological effects [13].

Recent epidemiological studies have assessed the effects of manganese on brain health. A cross-sectional study by Hozumi et al. [14], analyzed the cerebrospinal fluid of various neurodegenerative disease patients and found a higher level of manganese among PD patients. In another cross-sectional study assessing children's intellectual functioning and arsenic and manganese exposure, blood manganese levels were negatively associated with full scale IQ test scores, working memory, and perceptual memory [15]. A cross-sectional study by Kim et al.[16] examining low-level manganese exposure in adults of a Ohio community found subtle subclinical effects in UPDRS and postural sway test for PD. A cross-sectional study of school-aged children in Brazil found inverse scores on executive function and attention tests with manganese levels [17]. A study amongst school-children in Canada found low-level manganese exposure in drinking water was associated with poorer neurobehavioral functions [18]. Koc et al. [19] found higher levels of metal, including manganese, in hair samples of AD patients compared to controls.

A case-control study Miyake et al. [20], assessing dietary intake of heavy metals amongst PD patients found no association with manganese intake. A case-control study by Roos et al. [6] found elevated manganese levels in cerebrospinal fluid of ALS patients. A study by Kumudini et al.[21] found not correlation between manganese blood levels in PD patients compared to controls. A case control study by Garzillo et al.[22] found no association between manganese levels in ALS patients vs controls. A study by Kihira et al. [23] found elevated manganese levels in ALS patients vs controls from hair samples. Another study by Arain et al. [24] found higher levels of manganese and aluminum in hair samples of patients suffering from neurodegenerative disease.

A small cohort study that followed 26 welders exposed to manganese found after a 3.5-year follow-up found worsened olfactory, extrapyramidal, and mood disturbances [25]. A cohort study following asymptomatic welder trainees with no previous manganese exposure found low-level exposure to cause sub-clinical brain changes in subjects before any measurable learning deficits may occur [26].

Cadmium, arsenic, and manganese have been found to all have estrogenic activity and affinity for estrogen receptors [27] and have been found to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [28] Heavy metals have also been demonstrated to affect and cross the blood brain barrier [29–31].

OBJECTIVE

There is limited information regarding exposures to metalloestrogens the development of cognitive dysfunction and neurodegenerative disease in older

populations. In this study we examine the relationship between three metalloestrogens, Cd, Mn, and As, with surrogate brain health indicators, from the CDC's NHANES 2011-2012 and 2013-2014 data cycles. The objectives of the study are as follows: 1) to assess the mean Cd, Mn, and As levels in older adults in the US, 60 years of age and above with the surrogate brain health indicators in the US population, 2) assess the association between Cd, Mn, and As levels and surrogate brain health indicators in older adults in the US, to find the risk of poor cognitive function and possible development of mild cognitive impairment, dementia, and AD.

METHODS

Study Design and Population: NHANES is a continuous cross-sectional data collection utilizing a complex multi-stage sampling design that creates a survey representative of the non-institutionalized population of the United States [32,33]. The survey has been conducted since 1999 and consists of an at-home questionnaires followed by a standardized physical examination and specimen collection conducted in mobile examination centers (MEC) [32,33]. Eligibility is determined using preset selection probabilities for the desired demographic subdomains [33]. A household screener is performed before to determine if any household members are eligible for the interview and examination [33]. The interview collects demographic, health, nutrition, and household information, while the physical examination includes physical measurements, dental examination, and the collection of blood and urine specimens for laboratory testing [33]. Prior to any to interviews and examinations, informed consent was obtained and all procedures were approved by the CDC Institutional Review Board [34]

In our study, we merged the NHANES 2011-2012 and 2013-2014 data cycles. All our analyses were limited to individuals 60 years of age and older who have recorded responses to cognitive test scores and/or memory and taste/smell questions and have select metalloestrogen urine measurements.

Inclusion/Exclusion Criteria

Inclusion criteria:

9. Males and females, 60 years of age and older
10. Available metalloestrogen urine measurements (Cd, Mn, As)
11. Urine creatinine measurements >30 mg/dl and >300 mg/dl.
12. Complete responses to identified outcome variables.

Exclusion criteria:

9. Males and females, 59 years of age and younger
10. Unavailable metalloestrogen urine measurements (Cd, Mn, As)
11. Urine creatinine measurements <30mg/dl and >300mg/dl
12. Complete responses to identified outcome variables.

Cadmium Exposure Assessment Measurements

Cadmium were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [35–37] . The laboratory inductively coupled-plasma dynamic reaction cell-mass spectrometry to analyze urine Cadmium levels and was consistently used in both survey cycles [35–37]. Cadmium levels were provided in ug/L and was used in our analyses. Urinary cadmium was used in our analyses and coded

as URXUCD, with a limit of detection variable coded as URDUCDLC. The limits of detection were 0.056 ug/L for 2011-2012 and 0.036 ug/L for 2013-2014.

The limit of detection variables indicates if subjects have urine Cadmium levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy Cadmium level of the LOD divided by the square root of two [38]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [39].

Manganese Exposure Assessment and Measurements

Manganese were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [35–37] . The laboratory inductively coupled-plasma dynamic reaction cell-mass spectrometry to analyze urine Manganese levels and was consistently used in both survey cycles [35–37]. Manganese levels were provided in ug/L and was used in our analyses. The following Manganese metabolites were used in our analyses. Urinary manganese was used in our analyses and coded as URXUMN, with a limit of detection variable coded as URDUMNLC. The limits of detection were 0.08 ug/L for 2011-2012 and 0.013 ug/L for 2013-2014.

The limit of detection variables indicates if subjects have urine Manganese levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy Manganese level of the LOD divided by the

square root of two [38]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [39].

Arsenic Exposure Assessment and Measurements

Arsenic were measured from urine samples taken from a representative and random one-third subsample of individuals 6 years of age and older in the 2011-2012 and 2013-2014 survey cycles [35–37] . The laboratory inductively coupled-plasma dynamic reaction cell-mass spectrometry to analyze urine arsenic levels and was consistently used in both survey cycles [35–37]. Arsenic levels were provided in ug/L and was used in our analyses. Total urinary arsenic was used in our analyses and coded as URXUAS, with a limit of detection variable coded as URDUASLC. The limits of detection were 1.25 ug/L for 2011-2012 and 0.26 ug/L for 2013-2014.

Only total arsenic was analyzed in the study. The limit of detection variables indicates if subjects have urine arsenic levels above the limit of detection. A value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy arsenic level of the LOD divided by the square root of two [38]. Some LODs differ between survey cycles and a conservative approach was used to account for differing LODs per survey cycle [39]. The specific arsenic metabolites were selected as >60% of study subjects had urine arsenic levels above the LOD.

Assessment of Surrogate Brain Health Indicators – Cognitive Scores

CERAD Word Learning Subtest – Immediate Recall and Delayed Recall:

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word assesses both immediate and delayed learning [40,41]. The delayed and immediate

recall tests available in NHANES assess the ability to process new verbal information [40,41]. The tests are part of the neuropsychological assessment for the entire CERAD testing protocol, which was initially created to standardize AD assessment and diagnosis [42]. The tests in the neuropsychological assessment itself were chose because of their ability to assess cognitive functions inherent in AD [42]. The assessments have the ability to differentiate those of adequate cognitive status versus those who have mild cognitive impairment or dementia [42–45]. Although developed for use in the assessment of AD, the CERAD assessments have shown utility in use for Parkinson's disease [45] and frontotemporal lobar degeneration [46].

Immediate Recall: For immediate recall, , the subjects are asked to read aloud a sequence of 10 unrelated words as they are presented to them and immediately after, they are asked to recall as many words as possible [40,41]. This is done in three trials with the order of the words differing in each trial. [40,41]. Each trial has a maximum score of 10, with a maximum overall score of 30 [40,41,43].

In our study, we included individuals 60 years of age and older who completed all immediate recall word list trials identified as: CFDCST1, CFDCST2, and CFDCST3 in the 2011-2012 and 2013-2014 NHANES data cycles. Those who did not have three trials completed were not included in the immediate recall analysis. We summed the total of the three trials and created a new variable with cut-off scores named IMMEDIATERECALL. A cut-off score of ≤ 13 and ≥ 14 was used as it is the standard in other assessments [43,47]. A total of 3,149 subjects from the 2011-2012 and 2013-2014 responded with complete immediate recall trials. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme

creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our immediate recall study population consisted of 940 subjects, 146 subjects ≤ 13 and 794 subjects ≥ 14.

Delayed Recall: For delayed recall, the subject is asked to repeat the sequence of 10 unrelated words after the other cognitive tests are completed, which is typical 8 to 10 minutes after the start of the word learning trials [40,41]. The maximum score is 10 for delayed recall [40,41].

In our study, we included subjects 60 years of age and older who completed the delayed recall trial, identified as CFDCSR, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with the cut-off scores named DELAYEDRECALL. A cut-off score of ≤ 13 and ≥ 14 was used as it is the standard in other assessments [43,47,49]. A total of 3,126 subjects from the 2011-2012 and 2013-2014 responded with a complete delayed recall trial. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our study population consisted of 930 subjects,157 subjects ≤ 3 and 776 subjects ≥ 4.

Animal Fluency: The animal fluency test is used to determine categorical verbal fluency, which is part of executive function and can differentiate between with normal cognition versus those with MCI and more severe cognitive impairment [40,41]. Since the test uses animal names, it does not require cultural consideration or formal education experience [40,41]. In the test, subjects are asked to name as many animals in a

one minute span, with a maximum range of 40 words in the NHANES 2011-2014 data set. [40,41]. A sample test is given to each subject before the actual test [40,41].

In our study, we included subjects 60 years of age and older who completed the animal fluency trial, identified as CFDAST, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with cut-off scores named VERBALFLUENCY. cut-off score of ≤ 11 and ≥ 12 was used as it is the standard in other assessments [43,47,49,50]. A total of 3,110 subjects from the 2011-2012 and 2013-2014 responded with a complete delayed recall trial. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our study population consisted of 931 subjects,187 subjects ≤ 11 and 744 subjects ≥ 12.

Digit Symbol Substitution Test: The Digit Symbol Substitution Test (DSST) is part of the Wechsler Adult Intelligence Scale (WAIS III) [40,41,51]. The test measures processing speed, sustained attention, and working memory [40,41,51]. The subtests have shown utility in the identification of dementia and other neurodegenerative disorders [52–54]. The test is given in paper form, with a key that has 9 numbers paired to different symbols. The subject has 2 minutes to match each symbol to 133 boxes with a number associated to it, with the score as the total correct matches with a maximum score of 105 in the 2011-2014 NHANES dataset. [40,41]. A sample test is given to each subject before the actual test [40,41].

In our study, we included subjects 60 years of age and older who completed the animal fluency trial, identified as CFDDS, for the 2011-2012 and 2013-2014

NHANES data cycles. After we created a new variable with cut-off scores named DSST. cut-off score of ≤ 27 and ≥ 28 was used as it is the standard in other assessments [55–57]. A total of 3,104 subjects from the 2011-2012 and 2013-2014 responded with a complete delayed recall trial. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our study population consisted of 891 subjects,129 subjects ≤ 27 and 744 subjects ≥ 28.

Assessment of Surrogate Brain Health Indicators – Memory Function

During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse?: In our study we included subjects 60 years of age and older who had metalloestrogens samples taken and responded to the yes=0/no=1 question," During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" [58]. Memory issues, such as confusion and memory loss often precede the development of dementia and neurodegeneration[2,59], which makes this question a potential surrogate for the development of memory issues. 3,628 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our delayed recall study population consisted of 1,025 subjects,181 subjects answered "yes" and 844 subjects answered "no".

During the past 7 days, how often have you had trouble remembering where you put things?: In our study we included subjects 60 years of age and older who had metalloestrogens samples taken and responded to the question," During the past 7 days, how often {have you/has SP} had trouble remembering where {you/he/she} put things, like {your/his/her} keys or {your/his/her} wallet?" [58]. Memory issues, such as confusion and memory loss often precede the development of dementia and neurodegeneration[2,59], which makes this question a potential surrogate for the development of memory issues. 3,448 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

The question is multi-leveled, where 1,993 subjects answered "Never" =0, 809 subjects answered "About once" =1, 544 subjects answered "Two or three times" =2, 175 subjects answered "Nearly every day" =3, and 102 subjects answered "Several times a day" =4. We created a new variable named MCQ380_WK, which combines responses coded as 0/Never and 1/About once into a variable =2 and 2/Two or three times, 3/Nearly every day and 4/Several times a day into a variable =1.

We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our study population consisted of 1,074 subjects,188 subjects answered "1" and 783 subjects answered "2".

Are you limited in any way because of difficulty remembering or because you experience periods of confusion?: In our study we included subjects 60 years of age and older who had metalloestrogens samples taken and responded to the question,"

{Are you/Is SP} limited in any way because of difficulty remembering or because {you/s/he} experience{s} periods of confusion?" [58]. Limitations in physical movement due to difficulty remembering and confusion can indicate the development of cognition issues [60]. 3,629 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our study population consisted of 1,133 subjects,181 subjects answered yes and 952 subjects answered no.

Assessment of Surrogate Brain Health Indicators – Taste and Smell Function

It has been observed that neurodegenerative disease has been shown to be preceded by smell and taste disorders [61–64]. The causes of these disorders have been linked to genetic alterations [61], overexpression of key proteins[62], and direct effect of some environmental chemicals on the olfactory mucosa [65], which can have associations with exposure to EEDCs [61,62,64,65]. However, issues with olfaction can also be caused by upper respiratory tract infections, sino-nasal disease, head trauma, idiopathic causes, surgery of the nasal area, and congenital loss of smell [66].

The two most common and prevalent neurodegenerative diseases, AD and PD have been shown to be preceded by smell disorders [67–72]. These disorders manifest themselves when evidence of pathological changes in the olfactory system are evident [72]. These are characterized by the build-up of pathological proteins, which cause the death of olfactory cells [72]. Several human epidemiological studies have also alluded

to the utility of using sensory biomarkers as an early detection for neurodegenerative diseases [73–76]

Do you sometimes smell and unpleasant, bad, or burning odor when nothing is there?: In our study we included subjects 60 years of age and older who had metalloestrogens samples taken and responded to the question," {Do you/Does SP} sometimes smell an unpleasant, bad or burning odor when nothing is there?" [58]. 3,617 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle. We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our study population consisted of 1,050 subjects, 74 subjects answered yes and 950 subjects answered no.

During the past 12 months have you had a taste or other sensation in your mouth that does not go away?: In our study we included subjects 60 years of age and older who had metalloestrogens samples taken and responded to the question," During the past 12 months {have you/has SP} had a taste or other sensation in {your/his/her} mouth that does not go away?"[58]. 3,623 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for those who were measured for metalloestrogens and accounted for those with extreme creatinine scores (<30 and >300 mg/dl), as these extreme values can affect analyses by being too dilute or concentrated [48]. After, our study population consisted of 1,024 subjects, 66 subjects answered yes and 958 subjects answered no.

Covariates

In our study we included a number of covariates, based off a review of literature and well-known risk factors for neurodegenerative diseases, if they were available in the NHANES datasets.

The demographic variables are as follows: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade) [58].

Modifiable health variables and risk factors are as follows: ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [58].

Statistical Analysis

Statistical analysis was performed using SAS software [77]. The 2011-2012 and 2013-2014 survey cycles were merged and a four-year sampling weight was calculated to account for the complex sampling design in order to calculate correct statistical estimates and standard errors when calculating means, geometric means, and other statistics [78].

For metalloestrogens variables, a value of "0" indicates above the limit of detection and a value of "1" indicates below the limit of detection. Individuals with a below the limit of detection were given a dummy phthalate level of the LOD divided by the square root of two [38]. Some LODs differ between survey cycles and a conservative

approach was used to account for differing LODs per survey cycle, where the LOD for that year was used to make a determination if the EEDC was above or below the LOD. [39]. We log-transformed and then adjusted for creatinine all metalloestrogens variables [79–81] since environmental chemical data is not normally distributed and urine dilution varies from person to person.

We used the SAS Survey procedures to account for the complex sampling design of the NHANES data sets [82].

We used PROC SURVEYFREQ was used to obtain descriptive statistics for the different populations we were examining in our study which accounts for the complex survey design of the NHANES data sets [82]. Descriptive statistics were organized based on the following categories per variable: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade), ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [58].

We used PROC SURVEYREG and guidance provided by the SAS institute to directly to determine the geometric mean of the EEDC to test if they were significant between the responses of our outcome variables [82,83]. The standard errors were calculated using the Taylor Series linearization method, which is the default method in the survey procedures to calculate standard error [82]. Geometric means (GM),

geometric standard errors (GSE), and number of subjects were reported for the results of the outcome variables for all subjects that had EEDCs over the LOD. We looked at geometric means between the outcome variables (yes vs. no, low test score vs. high test score), and also performed age-specific, gender-specific, and race/ethnicity-specific geometric means between the responses to the outcome variable. Due to the smaller range of ages in our dataset, 60 years and older, we calculated age-specific rates in lieu of age-standardized rates.

We used PROC SURVEYLOGISTIC to find the unadjusted and adjusted odds ratios (ORs) and the 95% confidence intervals (CI) to examine the association between our outcome variables and exposures to metalloestrogens [82]. Analysis was done per EEDC per outcome variable. We presented three logistic regression models which were stratified by gender and presented the EEDC as a continuous variable as well as a ranked variable < LOD to 50^{th} percentile (reference) and $\geq 50^{th}$ percentile: unadjusted, adjusted for known risk factors, age, education, race/ethnicity, adjusted for known and suspected risk factors, age, education, race/ethnicity, smoking, blood pressure history, history of coronary heart disease, stroke, heart attack, diabetes status, head trauma, and alcohol use. We did not include income, OC and HRT use as variables as they significantly reduced the size of the population.

RESULTS

Descriptive statistics for the Surrogates of Brain Health Indicators and Covariates: Descriptive statistics of the study populations are described in table 1.1 and 1.1a for each of our 9 outcomes with their respective covariates.

Table 1.1 - Descriptive Statistics -- Surrogate brain health indicators and covariates for Cd and Mn	Immediate Recall Score (n=1378)				Delayed Recall Score (n=930)				Animal Fluency Score (n=931)				Digit Symbol Substitution Test Score (n=891)				Past 12 months, memory getting worse? (1,025)				Past 7 days, trouble remembering? (n=971)				Limited due to difficulty remembering or confusion? (n=1,024)				Phantom Odor? (n=1,024)				Sensation in mouth that does not go away? (n=1024)			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total Population	≤ 13		≥ 14		≤ 3		≥ 4		≤ 11		≥ 12		≤ 27		≥ 28		Yes		No		Yes		No		Yes		No		Yes		No		Yes		No	
	173	8.93	1205	91.07	243	14.14	1124	85.86	282	14.52	1078	85.48	231	9.75	1095	90.25	259	16.39	1207	83.61	238	15.44	1152	84.56	219	11.81	1249	88.19	70	4.19	1395	95.81	93	5.09	1374	94.91
Gender (n, %)																																				
Male	108	5.31	592	43.77	143	8.04	553	41.18	139	6.90	555	42.55	131	4.91	550	44.46	135	8.98	616	40.07	111	6.93	610	42.57	89	5.26	664	43.97	30	1.80	722	47.45	41	2.20	712	47.04
Female	65	3.62	613	47.30	100	6.10	571	44.68	143	7.62	523	42.93	100	4.84	545	45.78	124	7.41	591	43.54	127	8.51	542	42.00	130	6.55	585	44.22	40	2.39	673	48.36	52	2.89	662	47.87
Age (years) (n, %)																																				
60-69	69	2.48	663	51.06	94	4.89	630	48.69	109	4.37	613	49.00	99	3.35	619	51.04	111	6.47	661	46.48	115	7.20	617	46.01	106	4.70	668	48.41	54	3.25	717	49.81	57	3.13	716	49.97
70-79	52	3.34	382	29.01	74	4.58	359	27.85	100	5.69	327	26.69	80	3.43	333	28.87	70	5.08	389	27.19	73	4.85	367	27.44	52	3.10	407	29.06	12	0.73	447	31.46	24	1.37	435	30.80
80 +	52	3.11	160	11.00	75	4.67	135	9.32	73	4.45	138	9.79	52	2.97	143	10.34	78	4.84	157	9.94	50	3.39	168	11.11	61	4.01	174	10.72	4	0.21	231	14.53	12	0.60	223	14.13
Race/Ethnicity (n, %)																																				
Hispanic	38	1.18	227	6.53	63	1.93	201	5.80	58	1.69	205	6.07	84	2.49	163	4.81	58	1.72	228	6.28	50	1.47	207	6.09	59	1.61	227	6.37	14	0.42	272	7.57	32	0.90	254	7.08
Non-Hispanic White	71	6.16	584	73.00	102	10.23	201	5.80	103	9.42	103	69.94	63	4.88	579	74.97	131	12.67	546	65.36	112	11.66	535	66.67	94	8.37	585	69.74	25	2.93	654	75.26	32	3.37	647	74.76
Non-Hispanic Black	37	0.89	287	8.06	59	1.49	548	68.97	91	2.65	224	6.08	69	1.92	235	6.72	32	0.81	310	8.23	52	1.55	279	7.60	32	0.83	310	8.18	26	0.68	314	8.28	20	0.61	322	8.41
Non-Hispanic Asian/Other	27	0.69	107	3.48	19	0.49	262	7.43	30	0.76	101	3.40	15	0.47	118	3.75	38	1.18	123	3.73	24	0.75	131	4.20	34	1.00	127	3.90	5	0.18	155	4.70	9	0.22	151	4.66
Education (n, %)																																				
<12th Grade	89	3.25	295	14.30	103	3.64	278	13.88	124	4.82	252	12.58	135	4.35	216	12.35	91	3.91	349	15.55	68	2.56	343	16.62	91	3.85	349	15.54	23	0.80	415	18.54	34	1.35	405	18.03
Completed High School	36	2.37	278	18.69	58	4.37	250	16.57	90	5.03	217	15.59	53	2.59	247	18.13	56	3.39	275	17.59	73	4.17	243	16.69	64	3.47	267	17.44	20	0.96	311	19.98	26	1.67	305	19.25
>12 Grade	46	3.28	630	58.12	80	6.10	594	55.44	65	4.62	608	57.36	42	2.80	631	59.78	110	9.06	581	50.49	97	8.73	562	51.23	62	4.46	631	55.23	2	2.44	665	57.29	33	2.08	660	57.63
BMI (kg/m2) (n, %)																																				
Underweight (<18.5)	6	0.45	36	2.65	15	0.88	27	2.24	13	0.71	29	2.43	10	0.69	28	2.39	16	0.93	35	2.23	9	0.47	33	2.31	20	0.95	31	2.19	3	0.17	48	2.98	6	0.30	45	2.85
Normal Weight (18.5 to 24.9)	52	2.96	289	20.40	54	3.09	284	20.15	69	3.77	270	19.79	52	1.91	279	21.51	73	4.66	302	19.63	55	3.59	301	20.48	69	4.03	306	20.18	9	0.28	365	23.92	17	0.70	357	23.49
Overweight (25.0 to 29.9)	68	3.10	419	35.19	104	6.11	380	32.31	102	4.76	381	33.81	84	3.49	387	34.73	82	5.42	426	32.15	83	5.78	403	32.44	60	2.81	448	34.63	18	0.98	490	36.49	33	1.80	475	35.65
Obese (30.0+)	47	2.41	461	32.83	70	4.06	433	31.16	98	5.28	398	29.45	85	3.66	401	31.62	88	5.38	444	29.61	91	5.61	415	29.32	70	4.01	464	31.19	40	2.76	492	32.41	37	2.29	497	32.92
Alcohol Use (n, %)																																				
Yes	93	5.09	816	67.98	143	9.13	764	64.03	148	7.98	756	65.61	142	5.73	753	67.96	157	11.35	766	60.51	146	11.08	729	60.60	105	6.26	820	65.70	50	3.27	874	68.73	58	3.58	866	68.37
No	66	3.45	366	23.47	89	4.78	338	22.06	119	6.16	302	20.25	82	3.88	321	22.42	83	4.70	384	23.44	73	3.93	369	24.39	90	4.91	377	23.13	16	0.91	449	27.09	30	1.49	437	26.56
Ever Smoked (n, %)																																				
Yes	88	4.42	618	48.44	112	6.91	590	46.11	140	6.74	558	46.39	129	5.44	549	47.23	146	9.39	601	43.25	122	7.91	588	44.73	106	6.13	643	46.66	38	2.72	710	50.10	51	3.32	698	49.48
No	85	4.51	587	42.63	131	7.23	534	39.75	142	7.78	520	39.10	102	4.31	546	43.02	113	7.00	606	40.36	116	7.53	564	39.83	113	5.68	606	41.53	32	1.48	685	45.70	42	1.77	676	45.42
Physically Active? (n, %)																																				
Yes	50	2.63	450	37.21	69	4.51	427	35.39	64	3.10	433	37.05	52	2.18	433	37.82	80	4.88	437	34.08	67	4.49	424	34.33	65	3.29	452	35.53	20	1.35	497	37.51	24	1.04	492	37.77
No	123	6.30	755	53.86	174	9.63	697	50.47	218	11.42	645	48.44	179	7.57	662	52.43	179	11.51	770	49.53	171	10.95	728	50.23	154	8.52	797	52.66	50	2.84	898	58.30	69	4.05	882	57.14
Diabetes (n, %)																																				
Yes	54	2.20	272	16.41	65	3.03	259	15.61	90	4.19	228	14.41	89	3.12	219	15.32	59	3.55	291	15.02	54	2.73	275	15.48	64	3.66	286	14.85	22	1.54	326	16.93	33	1.76	316	16.63
No	111	6.37	870	69.64	164	10.22	809	65.75	173	9.45	800	66.65	135	6.40	816	69.88	186	12.12	855	63.99	173	12.29	815	64.27	152	8.08	891	68.11	39	2.06	1003	74.18	53	2.68	990	73.53
Borderline	8	0.36	63	5.03	14	0.89	56	4.50	19	0.88	50	4.42	7	0.23	60	5.05	14	0.72	61	4.60	11	0.41	62	4.81	3	0.07	72	5.22	9	0.60	66	4.70	7	0.56	68	4.74
Blood Pressure (n, %)																																				
Normal	118	5.71	817	67.08	154	9.36	772	63.46	179	9.11	742	63.46	132	5.68	771	67.26	171	11.44	822	61.23	168	11.46	775	61.39	157	8.19	836	64.23	54	3.38	937	69.04	56	3.49	937	68.95
High	55	3.22	388	23.99	89	4.78	352	22.40	103	5.41	336	22.02	99	4.08	324	22.99	88	4.95	385	22.38	70	3.98	377	23.17	62	3.62	413	23.96	16	0.81	458	26.76	37	1.60	437	25.95
Myocardial Infarction (n, %)																																				
Yes	26	1.63	89	7.95	33	2.87	81	6.74	28	1.88	84	7.75	26	1.42	81	8.04	44	2.78	77	6.77	30	2.05	78	6.64	29	2.41	92	7.11	11	1.01	110	8.51	13	1.18	108	8.34
No	147	7.30	1116	83.12	210	11.27	1043	79.12	254	12.64	994	77.73	205	8.33	1014	82.20	215	13.61	1130	76.84	208	13.39	1074	77.92	190	9.40	1157	81.08	59	3.18	1285	87.29	80	3.91	1266	86.57
Stroke (n, %)																																				
Yes	17	0.52	72	5.24	29	1.92	60	3.87	34	1.82	52	3.92	29	1.16	50	4.30	29	1.88	78	4.61	22	2.04	76	4.17	35	2.17	72	4.31	12	1.13	94	5.32	7	0.99	100	5.49
No	156	8.43	1130	85.81	214	12.24	1061	81.97	245	12.53	1026	81.73	202	8.60	1044	85.94	230	14.53	1126	78.97	216	13.43	1073	80.37	182	9.62	1176	83.90	58	3.07	1298	90.48	86	4.12	1271	89.41
Coronary Heart Disease (n, %)																																				
Yes	27	1.80	93	7.06	42	2.85	78	6.05	31	1.85	89	7.12	25	1.20	89	7.53	42	2.69	88	6.23	25	1.54	97	7.13	24	1.39	106	7.50	4	0.35	126	8.55	10	0.45	120	8.44
No	142	7.10	1105	84.04	197	11.28	1039	79.82	247	12.67	982	78.37	203	8.23	1002	83.03	213	13.67	1112	77.41	209	13.58	1048	77.75	190	10.36	1137	80.75	1258	3.87	1258	87.24	83	4.67	1243	86.44
Head Trauma (n, %)																																				
Yes	24	1.75	153	15.63	31	2.76	145	14.63	22	1.65	151	15.80	19	1.22	150	16.13	56	4.94	126	12.05	49	3.60	115	12.87	44	3.34	138	13.59	12	1.32	170	15.63	12	1.21	170	15.72
No	147	7.14	1052	75.48	210	11.35	979	71.27	258	12.83	927	69.72	212	8.53	945	74.11	201	11.42	1081	71.59	189	11.85	1035	71.69	173	8.44	1111	74.63	58	2.87	1281	80.18	81	3.88	1202	79.18
Used Birth Control (n, %)																																				
Yes	18	2.51	371	62.23	41	5.87	347	58.89	69	6.87	316	57.66	35	3.50	349	62.13	52	7.68	343	55.97	72	11.41	305	53.37	46	5.30	349	58.35	21	3.28	16	1.48	36	4.69	358	58.95
No	43	4.63	220	30.63	59	6.67	202	28.57	70	8.57	187	26.90	62	6.28	179	28.09	64	6.87	215	29.48	46	5.39	207	29.83	75	7.49	204	28.86	374	60.46	277	36.26	13	1.00	266	35.36
Used Female Hormones (n, %)																																				
Yes	11	1.51	257	51.22	28	3.95	239	48.67	35	4.16	231	48.37	25	2.27	243	51.55	36	5.02	235	46.70	35	6.27	219	45.82	37	4.12	234	47.60	12	2.38	25	2.39	19	2.38	252	49.36
No	46	5.28	330	41.99	68	8.32	307	39.06	102	11.13	267	36.34	70	7.35	281	38.83	75	8.53	320	39.75	79	9.83	289	38.09	78	7.87	317	40.41	259	49.41	368	45.82	30	3.32	364	44.94

Table 1.1a - Descriptive Statistics -- Surrogate brain health indicators and covariates for As	Immediate Recall Score (n=1378)				Delayed Recall Score (n=930)				Animal Fluency Score (n=931)				Digit Symbol Substitution Test Score (n=891)				Past 12 months, memory getting worse? (1,025)				Past 7 days, trouble remembering? (n=971)				Limited due to difficulty remembering or confusion? (n=1,024)				Phantom Odor? (n=1,024)				Sensation in mouth that does not go away? (n=1024)			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total Population	≤ 13		≥ 14		≤ 3		≥ 4		≤ 11		≥ 12		≤ 27		≥ 28		Yes		No		Yes		No		Yes		No		Yes		No		Yes		No	
	125	10.45	784	89.55	167	14.94	733	85.06	184	14.07	713	85.93	148	9.38	726	90.62	174	16.41	803	83.59	157	15.37	765	84.63	150	12.30	828	87.70	53	4.32	923	95.68	63	5.23	914	94.77
Gender (n, %)																																				
Male	75	6.07	387	42.69	97	8.71	361	40.20	89	6.56	368	42.45	82	4.49	368	44.49	88	8.53	413	40.30	71	6.59	408	42.66	61	5.34	441	43.62	22	1.77	479	47.19	27	2.20	475	46.77
Female	50	4.39	397	46.87	70	6.22	372	44.86	95	7.51	345	43.48	66	4.88	358	46.13	86	7.88	390	43.30	86	8.78	357	41.97	89	6.96	387	44.08	31	2.55	444	48.50	36	3.04	439	47.99
Age (years) (n, %)																																				
60-69	49	2.74	433	49.86	65	4.89	411	47.81	74	4.13	402	48.43	63	3.15	410	50.36	73	6.15	440	45.98	76	6.97	410	45.43	72	4.91	442	47.34	39	3.13	473	49.07	38	3.14	475	49.09
70-79	37	3.97	250	29.06	51	5.11	235	28.02	64	5.64	218	27.32	51	3.20	223	29.75	47	5.35	258	27.38	48	4.98	243	27.84	34	3.20	271	29.45	10	0.87	295	31.81	16	1.38	289	31.28
80 +	39	3.74	101	10.63	51	4.94	87	9.24	46	4.30	93	10.18	34	3.03	93	10.51	54	4.91	105	10.23	33	3.42	112	11.36	44	4.19	115	10.91	4	0.31	155	14.80	9	0.72	150	14.39
Race/Ethnicity (n, %)																																				
Hispanic	29	1.42	145	6.27	44	2.08	129	5.61	39	1.78	134	5.95	52	2.40	109	4.80	38	1.71	152	6.32	34	1.55	136	6.03	39	1.66	151	6.35	10	0.45	180	7.56	20	0.84	170	7.17
Non-Hispanic White	52	7.40	368	71.77	68	10.78	348	68.43	63	8.92	354	70.41	39	4.60	372	75.27	86	12.60	351	65.34	72	11.60	342	66.56	62	8.62	376	69.37	18	2.93	420	75.14	23	3.59	415	74.43
Non-Hispanic Black	24	0.86	200	7.98	40	1.50	182	7.32	60	2.52	159	6.15	47	1.89	165	6.96	23	0.85	217	8.17	35	1.48	198	7.76	25	0.92	215	8.07	21	0.75	218	8.20	13	0.55	227	8.45
Non-Hispanic Asian/Other	20	0.77	71	3.54	15	0.58	74	3.70	22	0.85	66	3.41	10	0.48	80	3.86	27	1.25	83	3.76	16	0.74	89	4.28	24	1.09	86	3.91	4	0.19	105	4.78	7	0.25	102	4.72
Education (n, %)																																				
<12th Grade	68	4.11	200	14.93	73	4.21	192	14.76	87	5.30	175	13.47	90	4.52	154	13.64	66	4.50	244	16.62	49	2.87	240	17.91	65	4.41	245	16.66	20	1.05	289	19.99	25	1.64	284	19.40
Completed High School	25	2.73	172	17.22	37	4.41	156	15.46	53	4.48	140	15.17	31	2.38	158	17.29	36	3.10	174	16.73	43	3.52	155	15.90	41	3.25	169	16.53	15	0.95	195	18.84	17	1.52	193	18.26
>12 Grade	31	3.60	410	57.42	56	6.30	383	54.86	42	4.25	397	57.33	26	2.46	413	59.71	71	8.79	383	50.26	65	8.99	367	50.81	43	4.62	412	54.54	18	2.32	436	56.85	21	2.07	434	57.10
BMI (kg/m2) (n, %)																																				
Underweight (<18.5)	5	0.63	24	2.84	10	0.95	19	2.53	10	0.84	19	2.66	8	0.88	18	2.56	11	0.97	25	2.54	7	0.58	22	2.48	14	1.06	22	2.44	3	0.26	33	3.24	5	0.42	31	3.09
Normal Weight (18.5 to 24.9)	41	3.63	190	20.76	40	3.58	188	20.59	48	3.98	181	20.53	35	1.99	189	22.47	52	5.04	204	20.17	39	3.98	203	20.94	48	4.33	208	20.82	9	0.43	246	24.70	12	0.76	243	24.36
Overweight (25.0 to 29.9)	50	3.63	273	34.80	72	6.48	248	32.10	64	4.34	255	34.25	52	3.13	258	35.05	55	5.26	284	32.33	55	5.81	268	32.47	41	3.01	298	34.49	13	1.10	326	36.43	21	1.69	318	35.82
Obese (30.0+)	29	2.56	297	31.16	45	3.92	278	29.84	62	4.91	258	28.49	53	3.38	261	30.54	56	5.13	290	28.55	56	5.00	272	28.74	47	3.90	300	29.95	28	2.53	318	31.31	25	2.36	322	31.50
Alcohol Use (n, %)																																				
Yes	68	6.09	532	67.00	99	9.71	499	63.52	99	7.96	498	65.58	89	5.49	502	68.38	107	11.41	506	60.47	99	11.00	481	60.82	73	6.48	541	65.48	37	3.32	576	68.66	39	3.74	574	68.20
No	50	4.14	238	22.77	62	5.05	221	21.72	77	5.80	203	20.65	55	3.78	211	22.34	54	4.58	259	23.54	47	4.04	247	24.14	61	5.13	252	22.92	13	0.98	299	27.04	19	1.36	294	26.69
Ever Smoked (n, %)																																				
Yes	63	5.26	409	47.88	79	7.82	389	45.50	91	6.70	375	46.62	81	5.12	372	47.86	97	9.10	408	43.95	78	7.48	399	45.48	74	6.29	432	46.88	29	2.63	476	50.55	35	3.39	471	49.80
No	62	5.19	375	41.67	88	7.12	344	39.56	93	7.37	338	39.30	67	4.26	354	42.76	77	7.31	395	39.64	79	7.89	366	39.15	76	6.01	396	40.82	24	1.69	447	45.13	28	1.85	443	44.97
Physically Active? (n, %)																																				
Yes	39	3.11	289	37.03	50	5.08	275	35.18	42	3.00	284	37.45	36	2.10	282	38.27	52	4.88	290	34.18	43	4.47	279	34.17	43	3.28	299	35.67	15	1.50	327	37.49	16	1.18	325	37.75
No	86	7.34	495	52.52	117	9.85	458	49.89	142	11.08	429	48.48	112	7.28	444	52.35	122	11.53	513	49.41	114	10.90	486	50.46	107	9.02	529	52.03	38	2.81	596	58.20	47	4.05	589	57.01
Diabetes (n, %)																																				
Yes	37	2.44	179	16.05	42	2.91	173	15.66	60	4.18	152	14.36	58	3.20	146	15.17	40	3.42	194	15.00	37	2.65	181	15.37	46	3.78	188	14.59	19	1.87	214	16.47	22	1.87	211	16.48
No	80	7.46	569	69.16	114	11.06	528	65.48	112	9.09	530	67.56	85	5.90	544	71.01	124	12.33	572	64.44	113	12.33	545	64.83	101	8.42	596	68.41	29	1.98	667	74.88	37	2.93	660	73.93
Borderline	8	0.55	36	4.33	11	0.97	32	3.92	12	0.80	31	4.02	5	0.27	36	4.44	10	0.66	37	4.15	7	0.39	39	4.43	3	0.10	44	4.69	5	0.47	42	4.33	4	0.44	43	4.36
Blood Pressure (n, %)																																				
Normal	83	6.54	537	66.10	105	9.72	508	63.00	112	8.69	498	63.72	53	5.28	517	67.56	113	11.32	550	61.06	110	11.29	518	61.26	102	8.25	561	63.96	39	3.47	623	68.75	38	3.58	625	68.64
High	42	3.91	247	23.44	62	5.22	225	22.06	72	5.38	215	22.20	65	4.09	209	23.07	61	5.08	253	22.53	47	4.08	247	23.37	48	4.05	267	23.74	14	0.85	300	26.93	25	1.65	289	26.12
Myocardial Infarction (n, %)																																				
Yes	20	2.17	58	7.96	22	3.08	55	7.09	20	2.06	56	8.13	17	1.38	55	8.57	30	2.79	52	7.19	18	1.89	53	6.94	21	2.44	61	7.51	9	1.15	73	8.82	9	1.15	73	8.81
No	105	8.28	726	81.58	145	11.86	678	77.97	164	12.01	657	77.79	131	8.00	671	82.06	144	13.62	751	76.40	139	13.48	712	77.69	129	9.86	767	80.19	44	3.17	850	86.86	54	4.08	841	85.96
Stroke (n, %)																																				
Yes	11	0.58	46	4.69	17	1.68	40	3.63	21	1.69	34	3.57	16	1.01	34	3.95	20	1.82	51	4.31	14	1.88	50	3.99	23	2.02	48	4.09	8	1.01	62	5.08	5	0.89	66	5.23
No	114	9.90	736	84.83	150	13.30	691	81.39	161	12.17	679	82.57	132	8.39	691	86.65	154	14.62	750	79.25	143	13.53	713	80.60	126	10.27	779	83.61	45	3.32	859	90.59	58	4.36	846	89.53
Coronary Heart Disease (n, %)																																				
Yes	20	2.19	59	7.16	28	3.14	51	6.27	21	1.93	58	7.53	15	1.13	58	7.95	28	2.71	59	6.63	18	1.74	62	7.19	18	1.48	69	7.83	4	0.53	83	8.80	8	0.58	79	8.74
No	103	8.25	720	82.40	137	11.80	677	78.78	161	12.14	650	78.39	131	7.98	665	82.93	144	13.69	739	76.97	137	13.39	698	77.68	129	10.77	755	79.92	49	3.81	833	86.86	55	4.67	828	86.01
Head Trauma (n, %)																																				
Yes	17	2.04	94	14.45	19	2.63	91	13.84	13	1.50	94	14.96	10	1.01	95	15.32	36	4.47	78	11.52	30	3.38	71	12.09	29	3.23	85	12.72	8	1.06	106	14.90	8	1.12	106	14.83
No	107	8.39	690	75.13	147	12.28	642	71.25	170	12.55	619	71.00	138	8.37	631	75.30	137	11.91	725	72.10	127	11.99	693	72.54	120	9.04	743	75.01	45	3.26	816	80.78	55	4.11	807	79.94
Used Birth Control (n, %)																																				
Yes	13	2.88	243	62.17	27	5.31	228	59.79	45	6.77	209	58.25	22	3.14	230	62.90	35	8.17	226	55.73	46	11.33	202	53.73	31	5.57	230	58.33	16	3.43	245	60.54	25	4.73	235	59.14
No	35	5.80	141	29.15	43	7.35	131	27.55	48	8.31	124	26.67	42	6.60	118	27.35	45	7.08	143	29.02	34	5.91	136	29.03	52	7.85	136	28.25	13	1.62	174	34.41	8	1.01	180	35.11
Used Female Hormones (n, %)																																				
Yes	9	2.05	169	51.32	18	3.69	159	49.50	24	4.37	153	48.89	15	2.05	162	52.23	24	5.17	156	47.03	24	6.60	144	46.07	23	3.94	157	48.25	10	2.50	170	49.74	14	2.56	166	49.67
No	36	6.24	248	40.39	49	8.70	198	38.11	68	10.63	176	36.12	48	7.59	183	38.14	53	9.27	210	38.54	53	9.93	191	37.40	56	8.77	207	39.04	19	2.57	243	45.18	19	3.21	243	44.56

Associations Between Exposures to Metalloestrogens and Cognitive Test Scores

Exposures to the Cd, Mn, As, and four cognitive scores (immediate and delayed recall, animal fluency, and DSST score) are summarized in tables 1.2 to 1.21. The cognitive test scores have been used as a surrogate indicator of brain health to assess cognitive decline and the possible development of mild cognitive impairment, dementia, and/or AD elderly patients as part of neuropsychological testing.

Immediate Recall Scores and Exposure to Metalloestrogens: Tables 1.2 to 1.5 present the GMs and GSEs of urinary Cd, Mn, and As levels among subjects with immediate recall scores. Table 1.2 presents GMs and GSEs of subjects who have measurable metalloestrogens levels over the LOD by immediate recall score. Cd was significantly higher in subjects with immediate recall scores ≤ 13 compared to subjects who scored ≥ 14 ($p < 0.05$). Table 1.3 presents age-specific GMs levels by age groups 60-69, 70-79, and 80+. No significant results were observed. Table 1.4 presents gender-specific GM levels. In females, the As GM levels were significantly higher in the ≤ 13 group compared to the ≥ 14. Table 1.5 presents race-specific GM levels among Hispanics, Non-Hispanic Whites, Non-Hispanic Blacks, and Asian/Other. Among all racial groups, no significant results were found.

Table 1.6 presents estimated ORs and 95% CI for immediate recall scores and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. In the unadjusted model, significant associations between lower immediate recall scores and Cd were observed in both males [OR=2.146, 95% CI: 1.109-4.153] and females [OR=2.142, 95% CI: 1.098-4.180] and between lower immediate recall scores and As in females only [OR=2.507, 95%

CI: 1.170-5.372]. In model adjusted for age, education, and race/ethnicity, significant association between lower immediate recall scores and Cd were observed in females [OR=2.033, 95% CI: 1.002-4.126] and between lower immediate recall scores and As in females [OR=2.569, 95% CI: 1.103-5.987]. No significant associations were observed in our second adjusted model.

Table 1.2 Geometric Mean Urinary Metalloestrogen Levels by Immediate Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14		
	GM	GSE	N	GM	GSE	N
Cadmium - Cd	**0.3839 ***	**0.02505**	**169**	0.3298	0.01175	1189
Manganese - Mn	0.2143	0.02799	82	0.1974	0.0108	524
Arsenic - As	9.5711	1.5239	124	9.6814	0.7998	778

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.3 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Immediate Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14		
	GM	GSE	N	GM	GSE	N
Cadmium - Cd	0.3572	0.04305	68	0.3106	0.01884	653
Manganese - Mn	0.2146	0.08907	29	0.1941	0.01622	278
Arsenic - As	8.5617	1.6511	49	8.759	0.692	429
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14		
	GM	GSE	N	GM	GSE	N
Cadmium - Cd	0.366	0.04247	50	0.3462	0.02387	378
Manganese - Mn	0.2187	0.04978	22	0.2009	0.02169	172
Arsenic - As	8.0382	1.8811	37	10.7656	1.4646	249
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14		
	GM	GSE	N	GM	GSE	N
Cadmium - Cd	0.4259	0.04196	51	0.381	0.03484	158
Manganese - Mn	0.2101	0.01604	31	0.2028	0.02544	74
Arsenic - As	12.5417	2.4947	38	11.5491	1.6923	100

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.4 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Immediate Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14			Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium - Cd	0.3182	0.03194	105	0.2669	0.0124	584	0.5057	0.05948	64	0.4008	0.01818	605
Manganese - Mn	0.1727	0.0171	42	0.1409	0.01338	226	0.2651	0.05621	40	0.2547	0.0221	298
Arsenic - As	6.9297	1.3437	75	9.2689	0.735	382	**15.0262 ***	**2.7989**	**49**	10.0662	1.0643	396

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.5 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Immediate Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14			Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium - Cd	0.4278	0.04806	37	0.333	0.02753	223	0.3524	0.02767	69	0.3208	0.01402	575
Manganese - Mn	0.1568	0.01751	17	0.1646	0.01525	105	0.2086	0.02603	31	0.2064	0.01373	250
Arsenic - As	9.3056	1.6131	29	9.2517	1.0461	145	8.48	1.8758	52	9.3807	0.9495	363
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14			Immediate Recall Score ≤ 13			Immediate Recall Score ≥ 14		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium - Cd	0.3789	0.04938	37	0.3359	0.0185	285	0.6829	0.111	26	0.5541	0.05086	105
Manganese - Mn	0.3352	0.2217	18	0.1504	0.008246	117	0.2296	0.03706	16	0.1925	0.02882	52
Arsenic - As	9.2215	1.8467	23	8.0595	0.754	199	33.7027	4.3825	20	29.7997	4.8305	71

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.6 - ORs and 95% CI for Urinary Metalloestrogen Levels by Immediate Recall Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogen	≤13 / ≥14	Unadjusted Odds Ratio [1]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #1 [2]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	38/312	1.00		38/311	1.00		36/303	1.00	
≥ 50th percentile	70/280	**2.146 ***	**1.109-4.153**	68/280	1.524	0.723-3.211	62/279	1.303	0.382-4.444
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	27/312	1.00		27/312	1.00		25/299	1.00	
≥ 50th percentile	38/301	**2.142 ***	**1.098-4.180**	38/300	**2.033 ***	**1.002-4.126**	36/289	2.318	0.857-6.271
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	58/290	1.00		58/289	1.00		52/286	1.00	
≥ 50th percentile	50/302	0.945	0.438-2.041	48/302	0.968	0.408-2.296	46/296	0.961	0.387-2.387
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	28/310	1.00		28/309	1.00		26/298	1.00	
≥ 50th percentile	37/303	0.825	0.397-1.714	37/303	0.838	0.412-1.704	35/290	0.714	0.318-1.600
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	39/192	1.00		38/192	1.00		34/191	1.00	
≥ 50th percentile	36/195	0.628	0.306-1.289	36/194	0.488	0.235-1.014	36/189	0.509	0.248-1.045
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	15/208	1.00		15/208	1.00		15/199	1.00	
≥ 50th percentile	35/189	**2.507 ***	**1.170-5.372**	35/188	**2.569 ***	**1.103-5.987**	33/182	2.499	0.962-6.489

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Delayed Recall Scores and Exposure to Metalloestrogens: Tables 1.7 to 1.11 present the GMs and GSEs of urinary metalloestrogen levels among subjects with delayed recall scores. Table 1.7 presents crude GM levels of metalloestrogens for of subjects 60 years of age and older who have delayed recall cognitive test scores and urinary metalloestrogen levels above the LOD. No significant differences were observed. Table 1.8 presents age-specific GMs among the age groups 60-69, 70-79, and 80+. In the 70-79-year age group, the GM level for As was found to be significantly higher in the delayed recall score ≤ 4 compared to the delayed recall ≥ 3 group ($p<0.05$). Table 1.9 presents gender-specific GMs among males and females. In males, GM levels of Cd were found to be significantly higher in the delayed recall score ≤ 3 compared to the delayed recall ≥ 4 group ($p<0.05$).

Table 1.10 presents race-specific GMs. Among Hispanics, GM levels for As were found to be higher in the delayed recall score group ≤ 3 compared to the delayed recall score ≥ 4 group ($p<0.05$). The GM level for Mn was found to be significantly higher in the delayed recall score ≥ 4 group compared to the delayed recall score group ≤ 3 ($p<0.05$).

Table 1.11 presents estimated ORs and 95% CI for delayed recall scores and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and $\geq$ 50th percentile. In the unadjusted model, among males, a significant association between Cd GM levels and lower delayed recall test scores was found [OR=2.588, 95% CI: 1.343-4.9890].

In the adjusted model #1, among males, a significant association was found between Cd GM levels and lower delayed recall test scores [OR=2.070, 95% CI: 1.055-4060]. No significant associations were found in our final adjusted models.

Table 1.7 Geometric Mean Urinary Metalloestrogen Levels by Delayed Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N
Cadmium	0.366	0.02894	241	0.3282	0.01265	1106
Manganese	0.1772	0.01855	117	0.2015	0.01037	483
Arsenic	9.5258	1.5281	166	9.6271	0.7876	727

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.8 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Delayed Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3006	0.04553	94	0.3133	0.01918	619
Manganese	0.207	0.03832	49	0.1937	0.01678	255
Arsenic	10.1671	2.7511	65	8.5695	0.6482	407
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3588	0.0309	73	0.3459	0.02489	354
Manganese	0.1585	0.03226	30	0.2083	0.02398	163
Arsenic	6.352	1.386	51	**11.37 ***	**1.684**	**234**
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4586	0.06833	74	0.3567	0.03288	133
Manganese	0.1711	0.02048	38	0.2206	0.02557	65
Arsenic	13.627	2.5889	50	10.5588	1.4187	86

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.9 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Delayed Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Males					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N
Cadmium	**0.3131 ***	**0.02213**	**142**	0.2638	0.01183	543
Manganese	0.1415	0.01572	67	0.1446	0.01439	198
Arsenic	7.3954	1.3287	97	9.2942	0.7997	356
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Females					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4519	0.07882	99	0.4007	0.01993	563
Manganese	0.2372	0.03562	50	0.2551	0.02281	285
Arsenic	13.6099	2.7464	69	9.9297	1.0512	371

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.10 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Delayed Recall Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogens	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4			Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3603	0.04223	63	0.3403	0.02554	196	0.3658	0.04311	101	0.3161	0.01417	538
Manganese	0.1297	0.01224	36	**0.1807 ***	**0.01909**	**85**	0.1725	0.02077	46	0.2103	0.01312	232
Arsenic	**10.8211 ***	**1.6028**	**44**	8.7522	0.9843	129	9.2727	2.0764	68	9.2182	0.9256	343
Metalloestrogens	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4			Delayed Recall Score ≤ 3			Delayed Recall Score ≥ 4		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3223	0.03307	59	0.3439	0.01894	261	0.5919	0.1442	18	0.5685	0.05876	111
Manganese	0.3631	0.2185	22	0.144	0.009342	112	0.2046	0.03657	13	0.2	0.02938	54
Arsenic	6.5296	0.8656	39	8.5349	0.8946	181	25.5786	4.3194	15	31.1416	4.9994	74

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.11 - ORs and 95% CI for Urinary Metalloestrogen Levels by Immediate Recall Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogens	≤3 / ≥4	Unadjusted Odds Ratio [1]	95% CI	≤3 / ≥4	Adjusted Odds Ratio #1 [2]	95% CI	≤3 / ≥4	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	63/284	1.00		63/284	1.00		61/276	1.00	
≥ 50th percentile	80/269	**2.588 ** **	**1.343-4.989**	78/268	**2.070 ***	**1.055-4.060**	71/268	2.025	0.852-4.816
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	50/285	1.00		50/285	1.00		50/272	1.00	
≥ 50th percentile	50/286	1.336	0.505-3.533	50/285	1.294	0.473-3.544	50/274	1.404	0.469-4.205
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	72/276	1.00		72/275	1.00		65/273	1.00	
≥ 50th percentile	71/277	1.151	0.500-2.649	69/277	1.253	0.584-2.689	67/271	1.227	0.546-2.754
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	43/292	1.00		43/292	1.00		43/279	1.00	
≥ 50th percentile	57/279	1.109	0.599-2.053	57/278	1.245	0.602-2.572	57/267	1.085	0.539-2.182
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	56/173	1.00		55/173	1.00		50/173	1.00	
≥ 50th percentile	44/188	0.575	0.259-1.279	41/187	0.502	0.193-1.301	41/182	0.597	0.227-1.570
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	29/192	1.00		29/191	1.00		29/184	1.00	
≥ 50th percentile	41/180	1.474	0.696-3.126	41/180	1.504	0.638-3.545	41/172	1.334	0.478-3.720

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Animal Fluency Scores and Exposure to Metalloestrogens: Tables 1.12 to 1.16 present the GMs and GSEs of urinary metalloestrogen levels among subjects with animal fluency scores. Table 1.12 presents crude GM levels of metalloestrogens for of subjects 60 years of age and older who have animal fluency cognitive test scores and urinary metalloestrogen levels above the LOD. No significant differences were

observed. Table 1.13 presents age-specific GMs for the ag groups 60-69, 70-79, and 80+. No significant results were observed. Table 1.14 presents gender-specific GMs. No significant results were observed. Table 1.15 presents race-specific GMs across the following groups: Hispanic, Non-Hispanic White, Non-Hispanic Black, and Asian/Other. For all racial groups, no significant results were observed.

Table 1.16 presents estimated ORs and 95% CI for animal fluency scores and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. In the unadjusted model, among males, a significant association between Cd GM levels and lower delayed recall test scores was found [OR=1.971, 95% CI: 1.063-3.654].

Table 1.12 Geometric Mean Urinary Metalloestrogen Levels by Animal Fluency Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3741	0.02301	280	0.3289	0.01218	1060
Manganese	0.2207	0.02332	119	0.1954	0.01067	479
Arsenic	9.1819	1.0455	183	9.8017	0.8204	707

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.13 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Animal Fluency Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3293	0.0604	109	0.3126	0.0188	602
Manganese	0.2165	0.0593	42	0.1932	0.01682	260
Arsenic	6.8857	1.5352	73	8.9844	0.6944	399
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3786	0.03529	99	0.3426	0.02621	322
Manganese	0.2147	0.02339	45	0.1991	0.02333	147
Arsenic	10.2052	1.4183	64	10.4908	1.5071	217
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4181	0.0498	72	0.3774	0.03672	136
Manganese	0.2318	0.04016	32	0.1949	0.01966	72
Arsenic	10.4656	1.6548	46	12.3576	2.2087	91

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.14 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Animal Fluency Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3009	0.034	138	0.2675	0.01187	545	0.4573	0.04291	142	0.4029	0.02067	515
Manganese	0.1647	0.01375	50	0.1426	0.01338	216	0.2661	0.04246	69	0.2528	0.02208	263
Arsenic	7.6807	1.2851	88	9.1355	0.7256	364	10.7057	1.204	95	10.4888	1.1573	343

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table1.15 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Animal Fluency Cut-off Score for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.4236	0.05284	58	0.328	0.02682	200	0.3546	0.02884	102	0.32	0.01472	538
Manganese	0.1734	0.02582	29	0.1602	0.01311	93	0.2278	0.02688	35	0.2028	0.01359	242
Arsenic	8.8717	1.6535	39	9.3797	1.0026	134	8.4117	1.5886	62	9.4515	0.958	350
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12			Animal Fluency Score ≤ 11			Animal Fluency Score ≥ 12		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3712	0.04361	91	0.3315	0.02451	223	0.5692	0.07856	29	0.5697	0.04965	99
Manganese	0.246	0.08075	37	0.1515	0.0135	97	0.2212	0.0408	18	0.1941	0.02797	47
Arsenic	8.5702	1.2119	60	8.1649	0.825	157	30.0025	3.6506	22	30.7608	5.4181	66

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.16 - ORs and 95% CI for Urinary Metalloestrogen Levels by Animal Fluency Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogen	≤11 / ≥12	Unadjusted Odds Ratio [1]	95% CI	≤11 / ≥12	Adjusted Odds Ratio #1 [2]	95% CI	≤11 / ≥12	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	50/297	1.00		50/295	1.00		46/291	1.00	
≥ 50th percentile	89/258	**1.971 ***	**1.063-3.654**	86/260	1.354	0.713-2.570	81/256	1.505	0.653-3.467
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	56/277	1.00		56/277	1.00		56/264	1.00	
≥ 50th percentile	87/246	1.416	0.745-2.692	87/245	1.353	0.640-2.860	80/239	1.552	0.801-3.007
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	68/276	1.00		67/276	1.00		62/272	1.00	
≥ 50th percentile	71/279	1.144	0.635-2.061	69/279	1.305	0.676-2.519	65/275	1.155	0.473-2.822
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	65/267	1.00		65/266	1.00		65/255	1.00	
≥ 50th percentile	78/256	1.046	0.599-1.826	78/256	1.382	0.797-2.395	71/248	1.173	0.600-2.291
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	49/179	1.00		48/179	1.00		44/178	1.00	
≥ 50th percentile	40/189	0.622	0.357-1.084	39/189	0.483	0.255-0.915	38/185	0.473	0.222-1.009
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	42/178	1.00		42/177	1.00		40/171	1.00	
≥ 50th percentile	53/167	1.142	0.673-1.938	53/167	1.149	0.659-2.002	51/161	1.064	0.559-2.026

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and Metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Digit Symbol Substitution Test (DSST) Scores and Exposure to Metalloestrogens:

Tables 1.17 to 1.21 present the GMs and GSEs of urinary metalloestrogen levels among subjects with DSST scores. Table 1.17 presents crude GMs levels of metalloestrogens for subjects 60 years of age and older who have digit symbol substitution scores and urinary metalloestrogen levels above the LOD. The crude GM mean levels for Cd was found to be higher in those with a DSST score ≤ 27 compared to those with a DSST score ≥ 28 ($p<0.05$). Table 1.18 presents age-specific GMs by the age groups 60-69, 70-79, and 80+. For Mn in the 80+ year age group, the GM was significantly higher in

those with a DSST score ≥ 28 compared to those with a DSST score ≤ 27 ($p<0.05$). Table 1.19 presents gender-specific GMs by male and female. No significant results were found. Table 1.20 presents race-specific GMs. No results among race-specific GMs were found to be significant.

Table 1.21 presents estimated ORs and 95% CI for DSST scores and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. In the unadjusted model, among males, a significant association between Cd GM levels and lower DSST test scores was found [OR=2.409, 95% CI: 1.389-4.180].

Table 1.17 Geometric Mean Urinary Metalloestrogen Levels by Digit Symbol Substitution (DSST) Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N
Cadmium	**0.3999 ***	**0.03538**	**228**	0.3266	0.01216	1078
Manganese	0.2586	0.09081	96	0.1905	0.009645	487
Arsenic	9.2296	1.0124	146	9.7471	0.8301	721

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.18 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Digit Symbol Substitution (DSST) Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N
Cadmium	0.2948	0.05346	97	0.3141	0.01876	610
Manganese	0.3322	0.1704	36	0.1848	0.01342	264
Arsenic	7.8106	0.9468	62	8.7712	0.6832	407
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4675	0.07755	80	0.3323	0.02279	327
Manganese	0.3648	0.2775	33	0.1853	0.01651	153
Arsenic	7.4643	1.1419	51	10.8336	1.4845	222
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4676	0.05307	51	0.3759	0.03593	141
Manganese	0.1376	0.02027	27	**0.2341 ***	**0.02303**	**70**
Arsenic	13.8106	3.2215	33	11.9443	1.7993	92

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.19 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Digit Symbol Substitution (DSST) Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	DSST Score ≤ 27			DSST Score ≥ 28			DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3335	0.0406	128	0.2646	0.01071	542	0.479	0.06297	100	0.4003	0.02061	536
Manganese	0.1985	0.09845	50	0.1389	0.009681	214	0.3234	0.1597	46	0.2434	0.01664	273
Arsenic	7.3128	0.6141	81	9.1743	0.8028	364	11.4456	2.2146	65	10.3237	1.1136	357

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.20 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Digit Symbol Substitution (DSST) Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	DSST Score ≤ 27			DSST Score ≥ 28			DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3817	0.05502	82	0.3345	0.02398	160	0.4167	0.07094	63	0.3166	0.01412	568
Manganese	0.1468	0.02376	35	0.1653	0.0167	76	0.4278	0.2363	26	0.1954	0.01166	251
Arsenic	9.5891	1.479	52	8.9243	1.1056	109	9.0462	1.8241	39	9.3658	0.9609	367
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	DSST Score ≤ 27			DSST Score ≥ 28			DSST Score ≤ 27			DSST Score ≥ 28		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3551	0.03703	69	0.3328	0.01853	234	0.5458	0.1045	14	0.5651	0.04797	116
Manganese	0.1323	0.01385	30	0.1517	0.0102	99	0.1467	0.02046	5	0.199	0.02579	61
Arsenic	6.9908	1.0097	45	8.4954	0.8396	165	26.4609	6.4777	10	29.7625	4.3838	80

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.21 - ORs and 95% CI for Urinary Metalloestrogen Levels by Digit Symbol Substitution (DSST) Cut-off Scores for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogen	≤27 / ≥28	Unadjusted Odds Ratio [1]	95% CI	≤27 / ≥28	Adjusted Odds Ratio #1 [2]	95% CI	≤27 / ≥28	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	48/292	1.00		48/292	1.00		48/284	1.00	
≥ 50th percentile	83/258	**2.409 ** **	**1.389-4.180**	82/258	1.676	0.874-3.217	78/254	1.243	0.397-3.890
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	52/270	1.00		52/270	1.00		48/263	1.00	
≥ 50th percentile	48/275	1.569	0.655-3.757	48/274	1.674	0.690-4.066	48/267	1.390	0.373-5.186
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	77/264	1.00		76/264	1.00		70/261	1.00	
≥ 50th percentile	54/286	0.630	0.285-1.392	54/286	0.729	0.366-1.454	56/277	0.721	0.256-2.029
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	52/270	1.00		52/269	1.00		51/260	1.00	
≥ 50th percentile	48/275	0.838	0.412-1.704	48/275	1.022	0.512-2.042	43/270	0.824	0.367-1.851
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	45/180	1.00		45/179	1.00		43/176	1.00	
≥ 50th percentile	37/188	0.731	0.372-1.436	36/189	0.456	0.245-0.846	36/184	0.416	0.213-0.810
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	32/180	1.00		32/179	1.00		30/175	1.00	
≥ 50th percentile	34/178	1.186	0.559-2.516	34/178	1.237	0.549-2.785	32/173	1.497	0.745-3.011

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Associations Between Exposures to Metalloestrogens and Memory Function

Exposures to the metalloestrogens Cd, Mn, and As and three memory function indicators: 1) During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse? 2) During the past 7 days, how often have you had trouble remembering where you put things? 3) Are you limited in any way because of difficulty remembering or because you experience periods of confusion?) are summarized in tables 1.22 to 1.36. Memory function have been included as a surrogate indicator of brain health as declining memory function can indicate the development of mild cognitive impairment, dementia, AD, or other memory-related neurodegenerative disease.

Worsening memory past 12 months and Exposure to Metalloestrogens: Table 1.22 presents the crude GMs for subjects over the age of 60 years of age who responded Y/N to the question "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" and have urinary metalloestrogen levels above the LOD. No significant results were found. Table 1.23 presents age-specific GM levels for the age groups 60-69, 70-79, and 80+. In the 60-69-year age group, Cd GM levels were higher in those who answered "yes" versus those who answered "no". Among the 70 to 79-year age group, As GM mean levels were found to be significantly different in those that answered "no" compared to those that answered "yes" ($p<0.05$). Table 1.24 shows gender-specific GM among males and females. For males, As GM levels are significantly higher among those who answered "no" versus those who answered "no" ($p<0.05$). Table 1.25 shows.

race-specific GM among Hispanics, Non-Hispanic White, Non-Hispanic Black, and Asian/Other. No significant findings were observed.

Table 1.26 presents estimated ORs and 95% CI for Yes/No responses to the question "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. Significant associations were found for Cd among women in the ≥ 50th percentile versus < LOD to 50th percentile (reference), where those who had experience confusion or memory loss over the past 12 months was associated with Cadmium levels in the unadjusted model [OR=2.463, 95% CI: 1.572-3.8610, model adjusted for age, education, and race/ethnicity [OR=2.517, 95% CI: 1.483-4.272] and the model adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status [OR=2.175, 95% CI: 1.207-3.921].

Table 1.22 Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3916	0.0325	257	0.3307	0.01173	1187
Manganese	0.1758	0.01473	124	0.2037	0.01154	530
Arsenic	8.2517	1.0081	171	9.9903	0.7947	799

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.23 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N " During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4161	0.05847	111	0.3083	0.01982	650
Manganese	0.1851	0.03617	55	0.1958	0.01916	270
Arsenic	7.2239	1.0657	72	9.0248	0.6698	437
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3417	0.03614	69	0.3546	0.02321	382
Manganese	0.1516	0.0245	29	0.212	0.02643	176
Arsenic	6.5234	0.871	46	**11.3961 ***	**1.573**	**258**
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4168	0.04176	77	0.3767	0.02928	155
Manganese	0.1897	0.03105	40	0.2147	0.02026	84
Arsenic	12.5252	2.5776	53	11.0389	1.4565	104

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.24 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N " During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3121	0.02582	133	0.2711	0.0132	605	0.5151	0.07551	124	0.3965	0.01356	582
Manganese	0.1257	0.01279	57	0.149	0.0137	232	0.236	0.02956	67	0.2562	0.02386	298
Arsenic	7.0807	0.9018	86	**9.4469 ***	**0.781**	**410**	9.702	1.5331	85	10.5178	1.058	389

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.25 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Y/N " During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.4229	0.05634	58	0.3366	0.02325	223	0.3767	0.03927	131	0.3179	0.01366	535
Manganese	0.1367	0.01069	30	0.1642	0.01565	104	0.1835	0.01888	60	0.2126	0.01551	233
Arsenic	8.7211	1.2465	38	9.4049	1.0928	152	7.3995	1.0411	84	9.6281	0.9728	348
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.373	0.07252	32	0.3377	0.01727	309	0.557	0.08301	36	0.6049	0.04703	120
Manganese	0.1387	0.02782	13	0.17	0.01892	131	0.1882	0.02433	21	0.2025	0.02621	62
Arsenic	8.2309	1.6858	22	8.1028	0.7087	216	22.4454	5.2137	27	32.8095	4.8363	83

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.26 - ORs and 95% CI for Urinary Metalloestrogen Levels by Y/N "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" for Subjects >= 60 years of age, NHANES 2011-2014									
Metalloestrogen	Yes / No	Unadjusted Odds Ratio [1]	95% CI	Yes / No	Adjusted Odds Ratio #1 [2]	95% CI	Yes / No	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	58/317	1.00		56/317	1.00		51/302	1.00	
≥ 50th percentile	77/299	1.741	0.883-3.433	77/298	1.901	0.969-3.731	71/282	1.515	0.690-3.331
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	48/309	1.00		48/309	1.00		45/291	1.00	
≥ 50th percentile	76/282	**2.463 *****	**1.572-3.861**	76/281	**2.517 ****	**1.483-4.272**	71/265	**2.175 ***	**1.207-3.921**
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	57/317	1.00		57/316	1.00		52/302	1.00	
≥ 50th percentile	78/299	1.866	0.728-4.784	76/299	1.912	0.817-4.474	70/282	1.973	0.886-4.391
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	57/300	1.00		57/299	1.00		52/284	1.00	
≥ 50th percentile	67/291	1.374	0.703-2.685	67/291	1.175	0.588-2.348	64/272	1.523	0.713-3.252
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	50/200	1.00		49/200	1.00		44/191	1.00	
≥ 50th percentile	38/213	0.539	0.263-1.105	38/212	0.483	0.222-1.050	36/199	0.579	0.278-1.205
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	43/195	1.00		43/194	1.00		40/183	1.00	
≥ 50th percentile	43/195	0.793	0.445-1.414	43/195	0.622	0.340-1.140	40/184	0.544	0.232-1.273
NHANES sampling weight applied before calculating the geometric mean.									
The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001									
[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.									

Trouble remembering past 7 days and Exposure to Metalloestrogens: Table 1.27 presents crude GM levels of metalloestrogens for subjects 60 years of age and older who have responded to the yes/no question, "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" and have urinary metalloestrogen levels above the LOD. No significant findings were observed. Table 1.28 presents age-specific GMs by the age groups 60-69, 70-79, and 80+ years of age. No significant findings were observed. Table 1.29 presents gender-specific GM levels. In males and females, no significant findings were observed. Table 1.30 presents race-specific geometric means. Cd GM levels were higher in those that answered "yes" versus "no" among Hispanics, Non-Hispanic Whites, and Asian/Other. Cd and Mn GM levels were significantly higher in those that answered "no" among Non-Hispanic Blacks ($p<0.05$).

Table 1.31 presents ORs and 95% CI for those with Yes/No responses to the question "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. No significant associations were found with our analysis of ORs.

Table 1.27 Geometric Mean Urinary Metalloestrogen Levels Y/N "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3568	0.03751	236	0.3387	0.01003	1132
Manganese	0.2371	0.04713	112	0.1958	0.01149	496
Arsenic	8.8395	1.0114	156	9.6986	0.7345	759

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.28 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3905	0.07554	113	0.3112	0.01672	608
Manganese	0.2008	0.04588	50	0.1974	0.01972	250
Arsenic	7.5115	1.1202	75	8.9598	0.6502	407
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3115	0.03834	73	0.3617	0.02363	359
Manganese	0.3175	0.1534	38	0.1854	0.01467	159
Arsenic	8.2705	0.9664	48	10.7178	1.4782	242
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3582	0.03303	50	0.4065	0.02983	165
Manganese	0.196	0.01915	24	0.2159	0.0213	87
Arsenic	13.5074	3.164	33	10.401	1.4049	110

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.29 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.2872	0.03351	109	0.278	0.01237	599	0.4249	0.05984	127	0.4134	0.01703	533
Manganese	0.1393	0.0193	47	0.1482	0.01391	224	0.3334	0.09685	65	0.2434	0.01785	272
Arsenic	7.6583	1.2608	70	9.0999	0.701	404	9.8272	1.3695	86	10.3382	1.0499	355

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.30 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.4055	0.03021	48	0.3357	0.02963	204	0.3443	0.04775	112	0.3266	0.01149	524
Manganese	0.1395	0.02234	26	0.1647	0.01718	93	0.2728	0.0661	53	0.2006	0.01459	220
Arsenic	10.184	2.3493	34	8.9909	0.933	136	8.1171	1.1886	71	9.2188	0.8607	338
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.2827	0.02211	52	**0.3517 ***	**0.0197**	**278**	0.7948	0.1396	24	0.5701	0.05043	126
Manganese	0.1073	0.02575	16	**0.1822 ***	**0.0211**	**122**	0.2053	0.02623	17	0.1981	0.02566	61
Arsenic	7.3151	1.4456	35	8.2592	0.7266	196	35.9647	7.3555	16	31.3738	4.2059	89

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.31 - ORs and 95% CI for Urinary Metalloestrogen Levels by Y/N "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogen	Yes / No	Unadjusted Odds Ratio [1]	95% CI	Yes / No	Adjusted Odds Ratio #1 [2]	95% CI	Yes / No	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	50/311	1.00		50/309	1.00		45/293	1.00	
≥ 50th percentile	61/299	1.316	0.571-3.034	61/298	1.097	0.426-2.824	54/286	1.061	0.420-2.681
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	66/269	1.00		64/269	1.00		57/256	1.00	
≥ 50th percentile	61/273	1.087	0.617-1.918	63/272	1.104	0.594-2.050	59/255	1.080	0.475-2.457
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	55/303	1.00		55/302	1.00		51/288	1.00	
≥ 50th percentile	56/307	0.855	0.330-2.215	56/305	0.895	0.340-2.359	48/291	0.620	0.257-1.495
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	65/271	1.00		65/270	1.00		60/253	1.00	
≥ 50th percentile	62/271	1.357	0.650-2.834	62/271	1.407	0.668-2.965	56/258	1.282	0.625-2.628
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	37/202	1.00		37/201	1.00		33/192	1.00	
≥ 50th percentile	34/206	0.737	0.346-1.569	34/205	0.738	0.366-1.488	32/193	0.815	0.340-1.950
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	42/179	1.00		43/178	1.00		38/169	1.00	
≥ 50th percentile	44/178	0.947	0.572-1.568	43/178	0.735	0.395-1.367	41/167	0.804	0.410-1.575

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Limitations Due to Difficulty Remembering or Confusion and Exposure to Metalloestrogens: Table 1.32 presents crude GM means for subjects who responded to the yes/no question "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" and who have measurable

metalloestrogen urinary levels above the LOD. In the analysis, no significant associations were found. Table 1.33 presents age-specific geometric means divided amongst three age groups. Among all age groups, no significant associations were found. Table 1.34 presents gender-specific GM levels. Amongst males, Cd and Mn GM levels were higher amongst those who answered “yes” compared to those who answered “no”. There were no significant findings in our analysis of gender-specific GM levels. Table 1.35 presents race-specific GMs by racial group. Cd GM levels were higher in those who answered “yes” compared to those who answered “no” amongst all racial groups. There were no significant findings among racial groups. Table 1.36 presents ORs and 95% CI for those with Yes/No responses to the question "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. In the unadjusted model, a significant association was found answering “yes” to being limited because difficulty remembering or because of periods of confusion and Cd, among females in the ≥ 50th percentile group [OR=1.952, 95% CI: 1.126-3.384]. The adjusted models were found not to be significant. Among males in the ≥ 50th percentile and Cd a significant association was observed [OR=2.075, 95% CI=1.029-4.185] in the first adjusted model controlling for age, education, and race/ethnicity. The second adjusted model was found to be not significant.

Table 1.32 Geometric Mean Urinary Metalloestrogen Levels by Y/N "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3993	0.03364	217	0.3325	0.01176	1229
Manganese	0.2234	0.0431	106	0.195	0.007832	548
Arsenic	9.9504	1.3274	148	9.6526	0.7632	823

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.33 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3775	0.06417	106	0.3145	0.01879	657
Manganese	0.3214	0.136	47	0.1844	0.01341	278
Arsenic	9.3726	1.7523	71	8.7476	0.6515	439
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3622	0.04967	50	0.3515	0.02173	401
Manganese	0.1676	0.04507	21	0.2047	0.02122	184
Arsenic	8.7666	1.9198	34	10.6219	1.4041	270
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4589	0.06375	61	0.366	0.03203	171
Manganese	0.1891	0.0325	38	0.2145	0.01997	86
Arsenic	11.7613	2.6919	43	11.4034	1.4413	114

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.34 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3227	0.04037	89	0.2732	0.01181	651	0.4748	0.05024	128	0.4036	0.01925	528
Manganese	0.1886	0.07547	38	0.139	0.009702	251	0.2502	0.03475	68	0.2531	0.02169	297
Arsenic	8.9348	1.3318	60	9.0086	0.7082	437	10.7949	1.7682	88	10.3254	1.0542	386

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.35 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3839	0.04416	59	0.3466	0.02651	222	0.3775	0.04405	92	0.321	0.01409	576
Manganese	0.1447	0.01979	30	0.1612	0.01221	104	0.2364	0.05618	46	0.2035	0.01078	247
Arsenic	9.4822	1.1434	39	9.1964	1.1371	151	8.6561	1.5424	61	9.312	0.9191	372
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3675	0.05186	32	0.3381	0.01684	309	0.726	0.1112	34	0.5625	0.04587	122
Manganese	0.4235	0.3938	13	0.1523	0.007981	131	0.1873	0.02783	17	0.2014	0.02415	66
Arsenic	12.4755	3.8178	24	7.7405	0.5951	214	26.4076	8.6919	24	30.8778	3.8751	86

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and phthalate levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.36 - ORs and 95% CI for Urinary Metalloestrogen Levels by Y/N "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogen	Yes / No	Unadjusted Odds Ratio [1]	95% CI	Yes / No	Adjusted Odds Ratio #1 [2]	95% CI	Yes / No	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	34/344	1.00		31/344	1.00		26/328	1.00	
≥ 50th percentile	56/320	1.966	0.971-3.980	56/319	**2.075 ***	**1.029-4.185**	45/309	1.531	0.500-4.691
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	49/308	1.00		49/308	1.00		47/289	1.00	
≥ 50th percentile	81/277	**1.952 ***	**1.126-3.384**	81/276	1.766	0.991-3.150	72/264	1.618	0.773-3.387
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	43/333	1.00		43/332	1.00		36/320	1.00	
≥ 50th percentile	46/331	1.589	0.532-4.748	44/331	1.651	0.604-4.511	35/317	1.607	0.558-4.630
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	65/292	1.00		65/291	1.00		61/275	1.00	
≥ 50th percentile	65/293	0.836	0.370-1.888	65/293	0.727	0.347-1.521	58/278	0.642	0.275-1.497
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	34/217	1.00		33/217	1.00		25/210	1.00	
≥ 50th percentile	27/224	0.814	0.449-1.474	27/223	0.862	0.448-1.656	24/212	0.989	0.488-2.008
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	42/196	1.00		42/195	1.00		37/186	1.00	
≥ 50th percentile	47/191	0.818	0.479-1.395	47/191	0.646	0.348-1.201	45/179	0.594	0.280-1.258

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Associations Between Exposures to Metalloestrogens and Taste/Smell Function

Exposures to the metalloestrogens Cd, Mn, and As, and two indicators of taste/smell function: 1) Do you sometimes smell an unpleasant, bad, or burning odor when nothing is there (phantosmia), and 2) During the past 12 months have you had a taste or other sensation in your mouth that does not go away? Taste and smell indicators have been included as a surrogate indicator of brain health as taste and

smell dysfunction is a possible pre-clinical indicator in the development of AD and other memory-related neurodegenerative diseases.

Smell Dysfunction and Exposure to Metalloestrogens: Table 1.37 presents crude GM means for subjects who responded to the yes/no "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" and who have measurable metalloestrogen urinary levels above the LOD. Crude As GM levels were found to be significantly higher in those who responded “no”, compared to those who responded “yes” ($p<0.05$). Table 1.38 presents age-specific GMs by the age groups 60-69, 70-79, and 80+. Cd GM levels were significantly higher among those who responded “yes” compared to those who responded “no” in significantly higher in the 80+ age group ($p<0.01$). Table 1.39 presents gender-specific GMs. Among males, Mn GM levels were significantly higher among those who responded “yes” compared to those who responded “no” ($p<0.01$). Among females, Mn and As GM levels, were significantly higher for those who responded “no” compared to those who responded “yes” (Mn, $p<0.05$; As, $p<0.01$).

Table 1.40 presents race-specific GMs. Among Non-Hispanic Whites, As GM levels were found to be significantly higher in those that responded “no” compared to those who responded “yes” ($p<0.01$). Among Asian/Others, the Cd GM level was significantly higher among those who responded “yes” compared to those who responded “no” ($p<0.001$). The As GM level was found to be higher among those who responded “no” compared to those who responded “yes” ($p<0.05$).

Table 1.41 presents ORs and 95% CI for those with Yes/No responses to the question "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?"

and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. In the second adjusted model for males in the ≥ 50th percentile group, Cd and experiencing a phantom odor were found to be significantly associated when controlling for age, education, race/ethnicity, alcohol use, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status [OR=10.770, 95% CI: 2.826-41.047). We removed diabetes status from the final model since it contributed to a quasi-separation of data, making the model validity questionable.

Table 1.37 Geometric Mean Urinary Metalloestrogen Levels by Y/N "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3579	0.04639	67	0.3393	0.0114	1376
Manganese	0.188	0.0195	38	0.1974	0.00958	613
Arsenic	6.6513	1.0879	53	**9.8535 ***	**0.7633**	**916**

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.38 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3729	0.0549	52	0.3169	0.01929	708
Manganese	0.1891	0.02418	30	0.1915	0.01659	292
Arsenic	6.2777	1.2596	39	8.9926	0.6798	469
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.2864	0.09536	11	0.3542	0.02177	440
Manganese	0.1775	0.03617	6	0.2018	0.02004	199
Arsenic	8.0468	1.9187	10	10.4974	1.2967	294
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	**0.4082 ****	**0.06266**	**4**	0.3892	0.02754	228
Manganese	0.2049	0.008173	2	0.2061	0.0157	122
Arsenic	6.9858	2.1654	4	11.6256	1.4704	153

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.39 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.2924	0.02978	27	0.2776	0.01239	712	0.4132	0.08311	40	0.4129	0.01711	664
Manganese	**0.2258 ****	**0.02295**	**8**	0.1425	0.01176	280	0.1794	0.02282	30	**0.2559 ***	**0.01982**	**333**
Arsenic	6.1009	1.5527	22	9.1335	0.6863	474	7.0641	1.0455	31	**10.5977 ****	**1.0416**	**442**

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.40 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3974	0.06979	12	0.3521	0.02662	269	0.3489	0.05893	25	0.3258	0.01328	643
Manganese	0.1267	0.01616	9	0.1598	0.01324	125	0.2161	0.02325	16	0.2067	0.01246	277
Arsenic	9.6007	2.3016	10	9.2347	1.1386	180	5.4105	1.1653	18	**9.4339 ****	**0.9076**	**415**
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.3059	0.05116	26	0.3469	0.02099	313	**0.9093 *****	**0.02821**	**4**	0.5849	0.04487	151
Manganese	0.1358	0.04909	11	0.1538	0.009915	131	0.1461	0.01225	2	**0.1994 ***	**0.02169**	**80**
Arsenic	8.9313	2.5935	21	8.0142	0.711	216	20.9802	9.6899	4	30.4782	3.9991	105

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.41 Geometric Mean Urinary Metalloestrogen Levels by Y/N "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogen	Yes / No	Unadjusted Odds Ratio [1]	95% CI	Yes / No	Adjusted Odds Ratio #1 [2]	95% CI	Yes / No	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	12/363	1.00		12/363	1.00		11/343	1.00	
≥ 50th percentile	18/359	3.219	0.674-15.383	18/356	3.826	0.039-2.086	18/335	**10.770 *****	**2.826-41.047**
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	19/337	1.00		19/337	1.00		18/317	1.00	
≥ 50th percentile	21/336	1.036	0.358-2.997	21/235	1.083	0.100-1.709	19/316	1.135	0.415-3.108
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	13/363	1.00		13/362	1.00		13/343	1.00	
≥ 50th percentile	17/359	1.505	0.236-9.590	17/357	1.540	0.301-7.887	16/335	1.415	0.424-4.722
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	19/337	1.00		19/337	1.00		17/317	1.00	
≥ 50th percentile	21/336	1.038	0.353-3.052	21/335	1.044	0.317-3.441	20/316	1.869	0.582-6.000
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	13/237	1.00		13/236	1.00		12/223	1.00	
≥ 50th percentile	9/242	0.634	0.152-2.644	9/241	0.697	0.162-3.002	9/226	0.703	0.280-1.764
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	18/219	1.00		18/219	1.00		16/207	1.00	
≥ 50th percentile	13/225	0.497	0.235-1.051	13/224	0.551	0.230-1.320	13/210	0.742	0.274-2.007

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Taste Dysfunction and Exposure to Metalloestrogens: Table 1.42 presents crude GM means for subjects who responded to the yes/no question "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" and who have measurable metalloestrogen urinary levels above the LOD. No significant increases were observed.

Table 1.43 presents age-specific GMs for the age groups 60-69, 70-79, and 80+. In the 79-79-year age group, the GM for As are higher in among subjects who answered "no" compared to those that answered "yes" ($p<0.05$). Table 1.44 presents gender-specific GMs. Among males, the GM for Cd was significantly higher among those that answered "yes" compared to those that answered "no" ($p<0.01$). Among females, the GM for Mn were found to be significantly higher among those who answered "no" compared to those that answered "yes" ($p<0.01$). Table 1.45 presents race-specific GMs. No significant results were observed among racial groups.

Table 1.46 presents ORs and 95% CI for those with Yes/No responses to the question "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" and metalloestrogens stratified by gender with two groups: < LOD to 50th percentile (reference) and ≥ 50th percentile. For males in the ≥ 50th percentile group, Cd was found to be significantly associated with taste issues in the first adjusted model controlling for age, education, race/ethnicity [OR=4.444, 95% CI: 1.564-12.630], and the second adjusted model controlling for age, education, race/ethnicity, alcohol use, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status [OR=3.751, 95% CI: 1.103-12.763]. We removed diabetes status from the final

model since it contributed to a quasi-separation of data, making the model validity questionable.

Table 1.42 Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.4332	0.0528	91	0.3352	0.01164	1354
Manganese	0.1722	0.01624	45	0.2002	0.009317	608
Arsenic	7.6795	1.2809	62	9.8023	0.7702	908

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.43 Age-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 60-69					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3994	0.05737	55	0.315	0.01875	707
Manganese	0.16	0.01746	32	0.1977	0.01679	292
Arsenic	7.6542	1.8706	38	8.8675	0.6761	471
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 70-79					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.5432	0.1454	24	0.3457	0.02076	427
Manganese	0.1788	0.04444	6	0.2019	0.02024	199
Arsenic	7.0141	0.7715	15	**10.588 ***	**1.3343**	**289**
Metalloestrogen	Geometric Mean (ug/ml) (GSE, N), Age 80 +					
	Yes			No		
	GM	GSE	N	GM	GSE	N
Cadmium	0.3911	0.08895	12	0.3894	0.02822	220
Manganese	0.2505	0.06654	7	0.2044	0.015	117
Arsenic	9.117	3.3521	9	11.637	1.4675	148

NHANES sampling weight applied before calculating the geometric mean.
The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.
*p<0.05, **p<0.01 ***p<0.001

Table 1.44 Gender-Specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ug/ml) (GSE, N)						Geometric Mean (ug/ml) (GSE, N)					
	Males						Females					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	**0.4285 ** **	**0.07048**	**39**	0.2727	0.0117	701	0.4367	0.07316	52	0.4103	0.01848	653
Manganese	0.1915	0.06236	10	0.1436	0.01172	279	0.1699	0.01784	35	**0.2627 ** **	**0.0199**	**329**
Arsenic	8.2886	2.3636	26	9.0337	0.6802	471	7.2922	1.3284	36	10.6049	1.05	437

NHANES sampling weight applied before calculating the geometric mean.
The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.
*p<0.05, **p<0.01 ***p<0.001

Table 1.45 Race-specific Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014, over the LOD

Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Hispanic						Geometric Mean (ng/ml) (GSE, N), Non-Hispanic White					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.4094	0.08975	30	0.348	0.02671	251	0.4425	0.07468	32	0.3221	0.01426	636
Manganese	0.1252	0.01799	19	0.1625	0.0133	115	0.2037	0.02269	17	0.2073	0.01209	276
Arsenic	10.1299	2.0136	20	9.1571	1.1248	170	6.4749	1.3872	22	9.3922	0.9167	411
Metalloestrogen	Geometric Mean (ng/ml) (GSE, N), Non-Hispanic Black						Geometric Mean (ng/ml) (GSE, N), Asian/Other					
	Yes			No			Yes			No		
	GM	GSE	N	GM	GSE	N	GM	GSE	N	GM	GSE	N
Cadmium	0.345	0.08018	20	0.3404	0.01799	321	0.7206	0.1684	9	0.5826	0.04734	146
Manganese	0.07289	0.01199	4	0.1739	0.0203	140	0.1949	0.02197	5	0.2009	0.02247	77
Arsenic	7.2645	2.7402	13	8.1729	0.7111	225	35.2148	16.9838	7	29.2516	4.2144	102

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels below the LOD were taken into account using the appropriate domain statement in SAS.

*p<0.05, **p<0.01 ***p<0.001

Table 1.46 Geometric Mean Urinary Metalloestrogen Levels by Y/N "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Subjects >= 60 years of age, NHANES 2011-2014

Metalloestrogen	Yes / No	Unadjusted Odds Ratio [1]	95% CI	Yes / No	Adjusted Odds Ratio #1 [2]	95% CI	Yes / No	Adjusted Odds Ratio #2 [3]	95% CI
Cd - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	15/362	1.00		13/362	1.00		11/343	1.00	
≥ 50th percentile	26/350	1.871	0.547-6.404	28/347	**4.444 ****	**1.564-12.630**	27/327	**3.751 ***	**1.103-12.763**
Cd - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	23/334	1.00		23/333	1.00		22/314	1.00	
≥ 50th percentile	29/328	1.214	0.483-3.051	29/328	1.257	0.521-3.033	28/307	1.786	0.679-4.696
Mn - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	19/357	1.00		19/356	1.00		19/337	1.00	
≥ 50th percentile	22/355	2.458	0.691-8.735	22/353	2.478	0.800-7.675	19/333	1.532	0.511-4.587
Mn - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	32/324	1.00		32/323	1.00		30/305	1.00	
≥ 50th percentile	20/338	0.657	0.244-1.767	20/338	0.670	0.230-1.954	20/316	0.855	0.356-2.056
As - Above/Below 50th Percentile - Males									
< LOD to 50th percentile (reference)	15/236	1.00		15/235	1.00		15/220	1.00	
≥ 50th percentile	12/239	0.832	0.245-2.828	12/238	0.877	0.236-3.257	9/227	0.790	0.194-3.223
As - Above/Below 50th Percentile - Females									
< LOD to 50th percentile (reference)	24/213	1.00		24/213	1.00		24/199	1.00	
≥ 50th percentile	12/226	0.396	0.137-1.145	12/225	0.410	0.141-1.195	10/213	0.428	0.099-1.851

NHANES sampling weight applied before calculating the geometric mean.

The EEDs were creatinine-adjusted then log transformed prior to analyses. Extreme creatinine values (<30 mg/dL and >300 mg/dL) and metalloestrogen levels were into account using the appropriate domain statement in SAS. *p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

DISCUSSION

This study takes a novel approach in the assessment of exposure to metalloestrogens in the development of cognitive dysfunction and possible neurodegenerative disease using surrogate indicators of brain health. The study examined an older geriatric-aged population of US adults 60 years of age and older. We first assessed the bioburden of the urinary metalloestrogens, Cd, Mn, and As, by

calculating and comparing the GMs of each EEDCs versus each surrogate indicator of brain health, looking at age, gender, and race and subsequently used ORs and 95% CI to determine the risk of developing cognitive dysfunction.

Major Findings: Overall, we observed a higher bioburden of Cd in the GMs of subjects who scored lower on the four cognitive tests, who answered "yes" to having memory function issues on the four memory function surrogates and had taste/smell deficits on our taste/smell function surrogates (Tables 1.2, 1.7, 1.12, 1.17, 1.22, 1.27, 1.32, 1.37, and 1.47). In our analyses of GMs by age, gender, and race, we accounted for subjects that have extreme creatinine measurements and examined subjects who had Cd, Mn, and As levels over the LOD. A higher bioburden of Cd was observed according to gender (Tables 1.3, 1.9, 1.14, 1.19, 1.24, 1.29, 1.34, 1.39, 1.33, 1.48 and 1.49). This trend was higher in females, but the significant differences were observed in males (Tables 1.48 and 1.49). No meaningful trends were observed by age and race, although it was observed metalloestrogen bioburden increased with age. A higher bioburden of Mn was found in those who scored lower on cognitive tests, while bioburden trends for As were inconclusive (Tables, 1.2, 1.7, 1.12, and 1.17).

In our logistic regression models, when controlling for all, known and suspected covariates of AD, Cd levels in females were found to be significantly associated with worsening memory over the past 12 months (Table 1.26). Cd levels in females were also associated with adverse taste and smell functioning when controlling for all known and suspected covariates of AD (Table 1.41 and 1.46). Caution must be taken in interpreting the results of taste and smell dysfunction

because of the large confidence interval and smaller number of causes with the covariates of the model.

The findings with cadmium and adverse brain function are consistent with other studies. A recent meta-analysis found higher Cd bioburden in AD patients [84]. Another study using NHANES survey data from 1988-1994 and 1999-2006, linked AD mortality with elevated Cd levels [85]. Higher circulating Cd levels were also associated with reduce attention and perception scores in a cross-sectional study of US adults [86] and in a cohort of rural elderly Chinese person, increased serum cadmium was associated with lower composite cognitive scores [5]. Mn, although not significant, was still found in higher levels among those who experience memory issues and/or scored lower on cognitive exams. Since metalloestrogens can affect sensitive populations differently, can bioaccumulate, and may exhibit non-monotonic dose responses [87], this may provide some basis for Mn to have higher bioburdens in subjects with memory issues.

Table 1.47 - Summary Table of EEDCs overall signficance of GMs by Surrogate of Brain Health Indicators (* p<0.05, ** p<0.01, *** p<0.001)	Immediate Recall Score (n=940)		Delayed Recall Score (n=930)		Animal Fluency Score (n=931)		Digit Symbol Substitution Test Score (n=891)		Past 12 months, memory getting worse? (n=1,025)		Past 7 days, trouble remembering? (n=971)		Limited due to difficulty remembering or confusion? (n=1,024)		Phantom Odor? (n=1,024)		Sensation in mouth that does not go away? (n=1024)	
	≤13	≥14	≤3	≥4	≤11	≥12	≤27	≥28	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Cadmium	*						*											
Manganese																		
Arsenic																*		

Table 1.48 - Summary Table of EEDCs overall signficance of GMs by Surrogate of Brain Health Indicators in males (* p<0.05, ** p<0.01, *** p<0.001)	Immediate Recall Score (n=940)		Delayed Recall Score (n=930)		Animal Fluency Score (n=931)		Digit Symbol Substitution Test Score (n=891)		Past 12 months, memory getting worse? (n=1,025)		Past 7 days, trouble remembering? (n=971)		Limited due to difficulty remembering or confusion? (n=1,024)		Phantom Odor? (n=1,024)		Sensation in mouth that does not go away? (n=1024)	
	≤13	≥14	≤3	≥4	≤11	≥12	≤27	≥28	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Cadmium			*														**	
Manganese															**			
Arsenic										*								

Table 1.49 - Summary Table of EEDCs overall signficance of GMs by Surrogate of Brain Health Indicators in females (* p<0.05, ** p<0.01, *** p<0.001)	Immediate Recall Score (n=940)		Delayed Recall Score (n=930)		Animal Fluency Score (n=931)		Digit Symbol Substitution Test Score (n=891)		Past 12 months, memory getting worse? (n=1,025)		Past 7 days, trouble remembering? (n=971)		Limited due to difficulty remembering or confusion? (n=1,024)		Phantom Odor? (n=1,024)		Sensation in mouth that does not go away? (n=1024)	
	≤13	≥14	≤3	≥4	≤11	≥12	≤27	≥28	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Cadmium																		
Manganese																*		**
Arsenic	*															**		

Biological Mechanisms and Brain Health: Our results show the effects of Cd exposure and its role in cognitive dysfunction. Numerous biological effects and mechanisms can result in cognitive dysfunction. Cadmium, arsenic, and manganese have been found to all have estrogenic activity and affinity for estrogen receptors [27] and have been found to interact with estrogen-responsive genes implicated in various neurodegenerative disorders [28] Heavy metals have also been demonstrated to affect and cross the blood brain barrier [29–31].

Cell models have shown cadmium to have adverse effects on brain health. In a one study hippocampal CA1 neurons, Cd was demonstrated to affect synaptic transmission and short-term neural plasticity [88]. Another studied that used PC12 and SH-SY5Y neuronal cells, cadmium induced cell death and apoptosis [89,90].

Animal models have shown cadmium to affect brain health. In a zebrafish model, cadmium inhibited neurogenesis in embryonic development [91]. Cadmium has been shown to induce apoptosis rat cerebellum cortical neurons by disrupting calcium homeostasis [92] and also has been shown to induce apoptosis in vitro in through damage of mitochondria in rat oligodendrocytes [93]. Cadmium has also been shown to interact with beta amyloid peptides which is implicated in the development of AD [94].

Animal studies in rats have shown arsenic exposure to affect synaptic plasticity, by affecting the expression of NDMA receptors [95,96] and downregulating the PTEN-Akt-Creb signaling pathway and damaging cerebral neurons [97]. In one cell study, arsenic

was found to cause enhanced oxidative stress and cell death in cultured neuronal cells, when administered with dopamine [98]. In a study using a cholingeric neuronal cell line overexpressing amyloid precursor protein (APP) and exposing it to sodium arsenite and its' metabolite, dimethylarsenic acid, it was found to affect cleavage of APP and increase its' production [99].

Evidence also suggests manganese having a role in neurotoxicity. Chronic manganese exposure has been shown to promote the build-up of the metal in the basal ganglia, white matter, and cortical structures of the brain [100]. Animal studies have shown manganese has also been shown to cause an inhibitory effect on NMDA receptors [101]. Manganese appears to interfere with dopaminergic synaptic transmission, by possibly impairing presynaptic dopamine release. A study using a monkey model showed manganese exposure caused neurotoxicity by inhibiting dopamine neurotransmission [102].

Furthermore, genes that have been implicated in the development of neurodegenerative disease such as AD which are also estrogen-responsive are also pathway for Cd, Mn, and As to exert their effects on the aging brain. Genes that are estrogen-responsive, metalloestrogen-responsive, and interfere with mitochondrial energetics, and implicated in AD include ENO1 [28]. Additionally, a recent search of the Comparative Toxicogenomic Database (CTD) reveals that from 88 genes implicated in AD, 39 of those genes are estrogen and Cd-responsive, 30 are estrogen and As-responsive, and 23 are estrogen and Mn-responsive [103]. These indicate other targets where metalloestrogens can exert their effects in the AD and neurodegenerative disease

pathways. The results from our study can originate from any of the biological mechanisms that have been referenced.

Strengths and Limitations: There are strengths and limitations to our study. The largest limitations are the cross-sectional design of our study. The data is self-reported which makes inference difficult and prone to misclassification bias. Our outcome variables are surrogates rather than actual clinical endpoints, which limits our ability to say that our outcome will lead to neurodegenerative disease. The cut-off scores of our cognitive exams were based on previous studies, however, performance on those exams are heavily dependent on education, so there is a possibility that poor performance might be a function of lack of education. For our taste/smell indicators, the senses heavily affected by numerous confounders, some of which were not feasible in study due to making the sample smaller, or the confounder not being available. Strengths of our study include the novelty of such an analysis to be conducted on an older population. We had relatively large sample sizes available for our analyzes. The generalizability of our study to the US population and the large amount of chemical measurements available gives the study the ability to examine different aspects of chemical exposure.

CONCLUSION

Based on our findings, Cd, and possibly Mn play a role in the development of neurodegenerative conditions in an older population. With an ever-increasing aging population, the study provides some insight in how metalloestrogen exposure can affect this sensitive population.

Further research is need, particularly human epidemiological studies examining older populations, to shed more light into the development of neurodegenerative disease and exposures to metalloestrogens.

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CHAPTER VII

MANUSCRIPT IV

EXPOSURE TO ORAL CONTRACEPTIVES AND HORMONE REPLACEMENT THERAPY AND ASSOCIATIONS WITH BRAIN HEALTH: NHANES 2011-2014

ABSTRACT

BACKGROUND: The role of estrogenic endocrine disrupting chemicals (EEDCs) and their role in the development of neurodegenerative disease is of great public health concern, due to increasing exposures to these chemicals and increasingly aging population. Evidence suggests EEDCs exposure plays a role in the development of neurodegenerative disease, although epidemiological evidence is lacking in this area. Oral contraceptives (OC) and hormonal replacement therapy (HRT) are known estrogenic endocrine disrupting chemicals (EEDCs), have a strong affinity for estrogen receptors with proven estrogenic activity, and are almost functionally similar to estrogen, which affects estrogen and its protective effects on brain health.

OBJECTIVE: The objective of this study is to investigate the relationship between surrogate brain health indicators and to past OC and HRT use among the older individuals of the United States (US) population.

METHODS: In this study, we analyzed participants from the Center for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) in the survey cycles 2011-2012 and 2013-2014. The participants were 60 years of age and older who had answered medical questions concerning oral contraceptive and hormonal replacement therapy use. Other data pertaining to

covariates and demographics were also obtained. The two medical questions analyzed were: 1) “Have you ever taken birth control pills for any reason?” and 2) “Have you ever used female hormones such as estrogen and progesterone?”. These responses were analyzed versus various brain health indicators available in the form of test scores and questionnaires, available in the NHANES datasets. The brain health indicators test scores were the following: immediate recall test scores; delayed recall test scores; animal fluency test scores; digit symbol substitution test scores. The brain health indicator questions were as follows: worsening memory over the past 12 months; trouble remembering over the past week; difficulty remembering or because you experience periods of confusion. The following smell and taste questions were also included as brain health indicators due to their potential as pre-clinical indicators of cognitive impairment: phantom odor (phantosmia) and persistent taste in mouth over the past 12 months. Chi-square test of independence was used to test the associations between the medical questions (Y/N) versus the brain health indicators. Logistic regression was then used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Three logistic regression models were presented in our study with all of them stratified by gender: unadjusted; age, race, education; age, race, education, body mass index (BMI), smoking status, blood pressure, diabetes status, alcohol use, coronary heart disease status, heart attack status, stroke status, head injury status, and physical activity status.

RESULTS: We observed a the existence of a relationship between past OC and HRT use and the following surrogates of brain function: immediate recall scores; delayed recall scores; animal flluency scores; DSST scores, and limitations due to difficulty

remembering or confusion. In our logisitic regression models, when controlling for all known and suspected covariates of cognitive dysfunction and AD in our second adjusted model, we found past OC use to lower the risk of developing cognitive dysfunction and the possible development of AD. Specifically, we found past OC use to be associated with better immediate recall, delayed recall, animal fluency and DSST scores. We also found past HRT use to lower the risk fo developing cognitive dysfunction and the possible development of AD. Specifically, we found past HRT use to be associated with better immediate recall, animal fluency, and DSST scores. Past HRT use was also associated with less occurrences of limitations due to periods of difficulty remembering or periods of confusion.

Conclusion: Our study takes a novel approach to assessing cognitive dysfunction neurodegenerative disease and exposures to past OC and HRT use. It appears there is a link between exposure to past OC and HRT use and adverse brain health. Further research is needed with the use of clinical endpoints to further establish the relationship between neurodegenerative disease and phthalate/BPA exposure.

Exposure to Oral Contraceptives and Hormone Replacement Therapy and Associations with Brain Health: NHANES 2011-2012

INTRODUCTION

The role of exposure to EEDCs and neurodegenerative disease development is of great public health concern as stated by the World Health Organization (WHO) [1], due to cognitive health and neurodegenerative disease emerging as great public health concerns due to an increasingly aging population [2]. Exposures to EEDCs have been linked to neurodegenerative diseases and other adverse brain health conditions, such as Alzheimer's disease (AD). In this study, we examine the associations of past OC and HRT use and their associations with brain health in an older US population.

Pharmaceutical drugs are also considered to be estrogenic endocrine disrupting chemicals [3]. A particularly powerful example are the health effects brought about by the use of diethylstilbestrol a potent estrogen mimic whose use brought about immediate and long-term health effects to the mothers who took the drug [4]. Both had indications as a hormone replacement therapy (HRT) and oral contraceptive (OC).

Oral contraceptives containing specifically containing ethinyl estradiol are considered EEDCs due to its ability to mimic estrogen and influence the reproductive cycle. OC use has been shown to reduce the amount of available endogenous estrogen in the body [5]. OCs has varying effects brain structure, function, and cognition [6]. Most recent studies have shown varying effects; however, the studies do not differentiate between the various types of contraceptives, making it difficult to find out if the

contraceptives used contained ethinyl estradiol and inconsistencies are found in the reporting of the type of OC used (Beltz et al, 2015).

A cross-sectional study by Beltz et al.[7] examined OC effects on spatial and verbal abilities found OC users to perform better on spatial ability and verbal tests. Another cross-sectional study by Egan and Gleason [8] found OC users to have better performance on cognitive exams compared to non-users. Griksiene and Ruksenas[5] found OC to negatively affect cognition. A review by Warren et al. [9] suggest an overall positive effect with OC use and verbal memory.

Hormone replacement therapy, or HRT, has been shown to be associated with the onset of neurodegenerative disease, although evidence points to a timeframe dependent response, depending on when the therapy is initiated. As summarized in Maki and Henderson[10], initial observation studies and analyses with women indicated the use of HRT's containing estrogen to be associated with a reduced risk of Alzheimer's disease. Studies suggest that the timing of HRT use during parts of the menopausal stage may dictate whether beneficial adverse effects are observed [10,11]. Several analytical studies, however, showed associations between the use of HRT and neurodegenerative disease. In the Women's Health Initiative Memory Study (WHIMS), a randomized, double-blind, placebo-controlled clinical trial, it was found that an HRT treatment of estrogen plus progestin increased the risk for dementia in postmenopausal women and did not prevent cognitive impairment [12]. In another study from the same trial, it was found that estrogen only HRT did not reduce the incidence of dementia, or cognitive impairment, and increased the risk for both [13].

An ancillary to the WHIMS study, the Women's Health Initiative Study of Cognitive Aging, or WHISCA, further supports HRT's association with neurodegenerative disease, however, results are varied. One finding from Resnick et al [14] from the WHISCA study found that a combination of conjugated equine estrogen with medroxyprogesterone acetate (estrogen + progestin) appeared to negatively impact verbal memory, but positively affect figural memory among postmenopausal women, free of probable dementia, and compared to controls. Another finding from Resnick et al [15] showed estrogen alone, as conjugated equine estrogen, did not improve cognitive functioning and lowered certain cognitive functions in women with prior hysterectomy. Other studies have indicated that no visible improvement has been observed in using estrogen only treatments for cognitive function [16–19].

New studies and reviews give mixed results. A cohort study conducted by Shao et al, [20] showed increased Alzheimer's disease risk amongst women who used HRT more than five years after menopause, but observed a decreased risk of AD if used within five years of menopause. Another recent meta-analysis showed no observable associated between postmenopausal HRT use and AD and dementia [21]. While another study found that an increased risk in the type of hormonal therapy used and PD risk [22].

OBJECTIVE

There is limited information regarding exposures to OC and HRT use the development of cognitive dysfunction and neurodegenerative disease in older populations. In this study we examine the relationship between OC and HRT use with surrogate brain health indicators, from the CDC's NHANES 2011-2012 and 2013-

2014 data cycles. The objectives of the study are as follows: 1) to assess past OC and HRT use and any relationships in older adults in the US, 60 years of age and above with the surrogates of brain health indicators in the US population, 2) assess the association between phthalate and BPA levels and surrogate brain health indicators in older adults in the US, to find the risk of poor cognitive function and development of mild cognitive impairment, dementia, and AD.

METHODS

Study Design and Population: NHANES is a continuous cross-sectional data collection utilizing a complex multi-stage sampling design that creates a survey representative of the non-institutionalized population of the United States [23,24]. The survey has been conducted since 1999 and consists of an at-home questionnaires followed by a standardized physical examination and specimen collection conducted in mobile examination centers (MEC) [23,24]. Eligibility is determined using preset selection probabilities for the desired demographic subdomains [24]. A household screener is performed before to determine if any household members are eligible for the interview and examination [24]. The interview collects demographic, health, nutrition, and household information, while the physical examination includes physical measurements, dental examination, and the collection of blood and urine specimens for laboratory testing [24]. Prior to any to interviews and examinations, informed consent was obtained and all procedures were approved by the CDC Institutional Review Board [25]

In our study, we merged the NHANES 2011-2012 and 2013-2014 data cycles. All our analyses were limited to individuals 60 years of age and older who have recorded

responses to cognitive test scores and/or memory and taste/smell questions and have responses to questions concerning oral contraceptive and hormonal therapy use.

Inclusion/Exclusion Criteria

Inclusion criteria:

13. Females, 60 years of age and older
14. History of OC and/or HRT use.
15. Complete responses to identified outcome variables.

Exclusion criteria:

13. All males
14. Females, 59 years of age and younger
16. Unavailable History of OC and/or HRT use.
15. Complete responses to identified outcome variables.

Oral Contraceptive Use Assessment and Measurements

Oral contraceptive use was recorded by the question yes/no question, "Have you ever taken birth control pills for any reason?". Female participants aged 12 years and older were eligible [26,27]. These questions were administered in the mobile examination center (MEC) by trainer interviewers [26,27]. A total of 1670 female subjects over the age of 60, provided a response, with 952 participants responding "yes" and 718 participants responding "no".

Hormonal Replacement Therapy Use Assessment and Measurements

Oral contraceptive use was recorded by the question yes/no question, "Have you ever used female hormones such as estrogen and progesterone?". Female participants aged 12 years and older were eligible [26,27]. These questions were

administered in the mobile examination center (MEC) by trainer interviewers [26,27]. A total of 1662 female subjects over the age of 60, provided a response, with 628 participants responding "yes" and "1034" participants responding "no".

Assessment of Surrogate Brain Health Indicators – Cognitive Scores

CERAD Word Learning Subtest – Immediate Recall and Delayed Recall: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word assesses both immediate and delayed learning [28,29]. The delayed and immediate recall tests available in NHANES assess the ability to process new verbal information [28,29]. The tests are part of the neuropsychological assessment for the entire CERAD testing protocol, which was initially created to standardize AD assessment and diagnosis [30]. The tests in the neuropsychological assessment itself were chose because of their ability to assess cognitive functions inherent in AD [30]. The assessments have the ability to differentiate those of adequate cognitive status versus those who have mild cognitive impairment or dementia [30–33]. Although developed for use in the assessment of AD, the CERAD assessments have shown utility in use for Parkinson's disease [33] and frontotemporal lobar degeneration [34].

Immediate Recall: For immediate recall, , the subjects are asked to read aloud a sequence of 10 unrelated words as they are presented to them and immediately after, they are asked to recall as many words as possible [28,29]. This is done in three trials with the order of the words differing in each trial. [28,29]. Each trial has a maximum score of 10, with a maximum overall score of 30 [28,29,31].

In our study, we included individuals 60 years of age and older who completed all immediate recall word list trials identified as: CFDCST1, CFDCST2,

and CFDCST3 in the 2011-2012 and 2013-2014 NHANES data cycles. Those who did not have three trials completed were not included in the immediate recall analysis. We summed the total of the three trials and created a new variable with cut-off scores named IMMEDIATERECALL. A cut-off score of ≤ 13 and ≥ 14 was used as it is the standard in other assessments [31,35]. A total of 3,149 subjects from the 2011-2012 and 2013-2014 responded with complete immediate recall trials. We then accounted for those who provided responses to OC and HRT use. After, our OC/immediate recall study population consisted of 1576 subjects, 193 subjects ≤ 13 and 1383 subjects ≥ 14. Our HRT/immediate recall study population consisted 1567 subjects, with 189 subjects ≤ 13 and 1378 subjects ≥ 14.

Delayed Recall: For delayed recall, the subject is asked to repeat the sequence of 10 unrelated words after the other cognitive tests are completed, which is typical 8 to 10 minutes after the start of the word learning trials [28,29]. The maximum score is 10 for delayed recall [28,29].

In our study, we included subjects 60 years of age and older who completed the delayed recall trial, identified as CFDCSR, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with the cut-off scores named DELAYEDRECALL. A cut-off score of ≤ 13 and ≥ 14 was used as it is the standard in other assessments [31,35,36]. A total of 3,126 subjects from the 2011-2012 and 2013-2014 responded with a complete delayed recall trial. We then accounted for those who provided responses to OC and HRT use. After, our OC/delayed recall study population consisted of 1568 subjects, 218 subjects ≤ 3 and 1350 subjects ≥ 4. Our

HRT/immediate recall study population consisted of 1560 subjects with 213 subjects ≤ 3 and 1347 subjects ≥ 4.

Animal Fluency: The animal fluency test is used to determine categorical verbal fluency, which is part of executive function and can differentiate between with normal cognition versus those with MCI and more severe cognitive impairment [28,29]. Since the test uses animal names, it does not require cultural consideration or formal education experience [28,29]. In the test, subjects are asked to name as many animals in a one minute span, with a maximum range of 40 words in the NHANES 2011-2014 data set. [28,29]. A sample test is given to each subject before the actual test [28,29].

In our study, we included subjects 60 years of age and older who completed the animal fluency trial, identified as CFDAST, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with cut-off scores named VERBALFLUENCY. cut-off score of ≤ 11 and ≥ 12 was used as it is the standard in other assessments [31,35–37]. A total of 3,110 subjects from the 2011-2012 and 2013-2014 responded with a complete animal fluency trial. We then accounted for those who provided responses to OC and HRT use. After, our OC/Animal Fluency study population consisted of 1565 subjects, 321 subjects ≤ 321 and 1244 subjects ≥ 12. Our HRT/Animal Fluency study population consisted of 1557 subjects with 318 subjects ≤ 11 and 1239 subjects ≥ 12.

Digit Symbol Substitution Test: The Digit Symbol Substitution Test (DSST) is part of the Wechsler Adult Intelligence Scale (WAIS III) [28,29,38]. The test measures processing speed, sustained attention, and working memory [28,29,38]. The subtests have shown utility in the identification of dementia and other neurodegenerative disorders

[39–41]. The test is given in paper form, with a key that has 9 numbers paired to different symbols. The subject has 2 minutes to match each symbol to 133 boxes with a number associated to it, with the score as the total correct matches with a maximum score of 105 in the 2011-2014 NHANES dataset. [28,29]. A sample test is given to each subject before the actual test [28,29].

In our study, we included subjects 60 years of age and older who completed the DSST trial, identified as CFDDS, for the 2011-2012 and 2013-2014 NHANES data cycles. After we created a new variable with cut-off scores named DSST, cut-off score of ≤ 27 and ≥ 28 was used as it is the standard in other assessments [42–44]. A total of 3,104 subjects from the 2011-2012 and 2013-2014 responded with a complete delayed recall trial. We then accounted for those who provided responses to OC and HRT use. After, our OC/DSST study population consisted of 1511 subjects, 227 subjects ≤ 27 and 1284 subjects ≥ 28. Our HRT/DSST study population consisted of 1505 subjects with 226 subjects ≤ 27 and 1279 subjects ≥ 28.

Assessment of Surrogate Brain Health Indicators – Memory Function

During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the yes=0/no=1 question," During the past 12 months, {have you/has she/has he} experienced confusion or memory loss that is happening more often or is getting worse?" [45]. Memory issues, such as confusion and memory loss often precede the development of dementia and neurodegeneration[2,46], which makes this question a potential surrogate for the development of memory issues. 3,628 subjects responded

to this question in the 2011-2012 and 2013-2014 survey cycle. We then accounted for those who provided responses to OC and HRT use. After, our OC/MCQ084 study population consisted of 1669 subjects, 274 subjects responded “yes” and 1395 subjects responded “no”. Our HRT/MCQ084 study population consisted of 1661 subjects with 272 subjects responded “yes” and 1389 subjects responded “no”.

During the past 7 days, how often have you had trouble remembering where you put things?: In our study we included subjects 60 years of age and older who had phthalate and BPA samples taken and responded to the question,” During the past 7 days, how often {have you/has SP} had trouble remembering where {you/he/she} put things, like {your/his/her} keys or {your/his/her} wallet?” [45]. Memory issues, such as confusion and memory loss often precede the development of dementia and neurodegeneration[2,46], which makes this question a potential surrogate for the development of memory issues. 3,448 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

The question is multi-leveled, where 1,993 subjects answered “Never” =0, 809 subjects answered “About once” =1, 544 subjects answered “Two or three times” =2, 175 subjects answered “Nearly every day” =3, and 102 subjects answered “Several times a day” =4. We created a new variable named MCQ380_WK, which combines responses coded as 0/Never and 1/About once into a variable =2 coded as “no” and 2/Two or three times, 3/Nearly every day and 4/Several times a day into a variable =1 coded as “yes”

We then accounted for those who provided responses to OC and HRT use. After, our OC/MCQ380_WK study population consisted of 1576 subjects, 335 subjects

responded “yes” and 1241 subjects responded “no”. Our HRT/MCQ380_WK study population consisted of 1568 subjects with 332 subjects responded “yes” and 1236 subjects responded “no”.

Are you limited in any way because of difficulty remembering or because you experience periods of confusion?: In our study we included subjects 60 years of age and older who had responses to OC and/or HRT use and responded to the question,” {Are you/Is SP} limited in any way because of difficulty remembering or because {you/s/he} experience{s} periods of confusion?” [45]. Limitations in physical movement due to difficulty remembering and confusion can indicate the development of cognition issues [47]. 3,629 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for those who provided responses to OC and HRT use. After, our OC/PFQ057 study population consisted of 1670 subjects, 259 subjects responded “yes” and 1411 subjects responded “no”. Our HRT/PFQ057 study population consisted of 1662 subjects with 254 subjects responded “yes” and 1408 subjects responded “no”.

Assessment of Surrogate Brain Health Indicators – Taste and Smell Function

It has been observed that neurodegenerative disease has been shown to be preceded by smell and taste disorders [48–51]. The causes of these disorders have been linked to genetic alterations [48], overexpression of key proteins[49], and direct effect of some environmental chemicals on the olfactory mucosa [52], which can have associations with exposure to EEDCs [48,49,51,52]. However, issues with olfaction can

also be caused by upper respiratory tract infections, sino-nasal disease, head trauma, idiopathic causes, surgery of the nasal area, and congenital loss of smell [53].

The two most common and prevalent neurodegenerative diseases, AD and PD have been shown to be preceded by smell disorders [54–59]. These disorders manifest themselves when evidence of pathological changes in the olfactory system are evident [59]. These are characterized by the build-up of pathological proteins, which cause the death of olfactory cells [59]. Several human epidemiological studies have also alluded to the utility of using sensory biomarkers as an early detection for neurodegenerative diseases [60–63]

Do you sometimes smell and unpleasant, bad, or burning odor when nothing is there?: In our study we included subjects 60 years of age and older who had OC and/or HRT responses and responded to the question," {Do you/Does SP} sometimes smell an unpleasant, bad or burning odor when nothing is there?" [45]. 3,617 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.
We then accounted for those who provided responses to OC and HRT use. After, our OC/CSQ040 study population consisted of 1664 subjects, 123 subjects responded "yes" and 1541 subjects responded "no". Our HRT/CSQ040 study population consisted of 1655 subjects with 123 subjects responded "yes" and 1532 subjects responded "no".

During the past 12 months have you had a taste or other sensation in your mouth that does not go away?: In our study we included subjects 60 years of age and older who provided responses to OC/HRT use and responded to the question," During the past 12 months {have you/has SP} had a taste or other sensation in

{your/his/her} mouth that does not go away?"[45]. 3,623 subjects responded to this question in the 2011-2012 and 2013-2014 survey cycle.

We then accounted for those who provided responses to OC and HRT use. After, our OC/CSQ110 study population consisted of 1667 subjects, 134 subjects responded "yes" and 1533 subjects responded "no". Our HRT/CSQ110 study population consisted of 1658 subjects with 134 subjects responded "yes" and 1524 subjects responded "no".

Covariates

In our study we included a number of covariates, based off a review of literature and well-known risk factors for neurodegenerative diseases, if they were available in the NHANES datasets.

The demographic variables are as follows: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade) [45].

Modifiable health variables and risk factors are as follows: ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [45].

Statistical Analysis

Statistical analysis was performed using SAS software [64]. The 2011-2012 and 2013-2014 survey cycles were merged and a four-year sampling weight was

calculated to account for the complex sampling design in order to calculate correct statistical estimates and standard errors when calculating means, geometric means, and other statistics [65].

For OC AND HRT variables, a value of "1" indicates a "yes" response and "2" indicates a "no" response. We used the SAS Survey procedures to account for the complex sampling design of the NHANES data sets [66].

We used PROC SURVEYFREQ was used to obtain descriptive statistics for the different populations we were examining in our study which accounts for the complex survey design of the NHANES data sets [66]. Descriptive statistics were organized based on the following categories per variable: gender (male, female), age (60-69, 7-79, 80+), Race/Ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Other), Family Income (Under 24k, 25k to 54,999k, 55k to 74,999k, over 75k), Education (<12th grade, completed high school, >12th grade), ever smoked (yes, no), blood pressure (normal/high), diabetes (yes, no, borderline), coronary heart disease (yes, no), stroke (yes, no), heart attack (yes, no), head trauma (yes, no), alcohol use (yes, no), ever use birth control (yes, no), every use hormonal replacement therapy (yes, no) [45].

We also used PROC SURVEYFREQ to perform chi-square test of independence to examine associations between OC/HRT use and our select surrogate of brain health indicators.

We used PROC SURVEYREG and guidance provided by the SAS institute to directly to determine the geometric mean of the EEDC to test if they were significant between the responses of our outcome variables [66,67]. The standard errors were

calculated using the Taylor Series linearization method, which is the default method in the survey procedures to calculate standard error [66]. Geometric means (GM), geometric standard errors (GSE), and number of subjects were reported for the results of the outcome variables for all subjects that had EEDCs over the LOD. We looked at geometric means between the outcome variables (yes vs. no, low test score vs. high test score), and also performed age-specific, gender-specific, and race/ethnicity-specific geometric means between the responses to the outcome variable. Due to the smaller range of ages in our dataset, 60 years and older, we calculated age-specific rates in lieu of age-standardized rates.

We used PROC SURVEYLOGISTIC to find the unadjusted and adjusted odds ratios (ORs) and the 95% confidence intervals (CI) to examine the association between our outcome variables and exposures to phthalates and BPA [66]. Analysis was done per EEDC per outcome variable. We presented three logistic regression models which were stratified by gender and presented the EEDC as a continuous variable as well as a ranked variable < LOD to 50^{th} percentile (reference) and $\geq 50^{th}$ percentile: unadjusted, adjusted for known risk factors, age, education, race/ethnicity, adjusted for known and suspected risk factors, age, education, race/ethnicity, smoking, blood pressure history, history of coronary heart disease, stroke, heart attack, diabetes status, head trauma, and alcohol use. We did not include income use as variables as they significantly reduced the size of the population.

RESULTS

Descriptive statistics for the Surrogates of Brain Health Indicators and Covariates: Descriptive statistics of the study populations are described in table 1.1 and 1.1a for each of our 9 outcomes with their respective covariates for OC and HRT use respectively.

Table 1.1 - Descriptive Statistics -- Surrogate brain health indicators and covariates for OC use	Immediate Recall (n=1576)				Delayed Recall (n=1568)				Animal Fluency (n=1565)				Digit Symbol Substitution Test (n=1511)				Past 12 months, memory getting worse? (n=1669)				Past 7 days, trouble remembering? (n=1576)				Limited due to difficulty remembering or confusion? (n=1670)				Do you sometimes smell an unpleasant, bad or burning odor when nothing is there? (n=1664)				Past 12 months, have you had a taste or sensation in your mouth that does not go away? (n=1667)			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	≤ 13		≥ 14		≤ 3		≥ 4		≤ 11		≥ 12		≤ 27		≥ 28		Yes		No		Yes		No		Yes		No		Yes		No		Yes		No	
Total Population	193	9.83	1383	90.17	218	11.88	1350	88.12	321	13.72	1244	86.28	227	9.00	1284	91.00	274	14.47	1395	85.53	335	20.76	1241	79.24	259	11.88	1411	88.12	123	6.42	1541	93.58	134	6.38	1533	93.62
Age (years)																																				
60-69	58	2.31	768	50.53	71	3.40	753	49.62	120	3.81	699	48.88	79	2.31	736	51.74	124	6.55	736	45.37	160	10.33	659	42.25	115	4.70	746	47.25	77	3.91	782	48.07	82	3.66	778	48.30
70-79	60	3.11	411	26.55	66	3.69	400	25.82	116	5.41	352	24.37	81	3.17	366	26.37	65	3.29	429	26.14	94	5.56	376	24.00	52	2.24	442	27.18	30	1.75	462	27.64	26	1.23	468	28.20
80 +	75	4.41	204	13.09	81	4.79	197	12.67	85	4.50	193	13.03	67	3.52	182	12.90	85	4.62	230	14.01	81	4.87	206	12.99	92	4.95	223	13.68	16	0.76	297	17.87	26	1.49	287	17.12
Race/Ethnicity																																				
Hispanic	53	1.46	254	6.12	54	1.46	251	6.11	77	1.92	229	5.67	86	2.25	195	4.84	68	1.67	252	5.99	64	1.57	223	5.63	74	1.73	246	5.92	33	0.81	285	6.82	53	1.20	266	6.44
Non-Hispanic White	79	6.67	682	71.19	97	8.46	661	69.42	97	7.65	658	70.19	60	4.40	686	74.38	126	10.63	663	66.29	161	16.07	591	61.25	102	7.74	688	69.19	47	4.48	742	72.51	47	4.23	743	72.73
Non-Hispanic Black	39	1.06	319	8.29	51	1.41	306	7.97	108	3.00	248	6.38	64	1.88	279	7.25	45	1.15	336	8.38	73	2.00	292	7.57	49	1.26	332	8.27	34	0.85	345	8.66	25	0.64	355	8.89
Non-Hispanic Asian/Other	22	0.65	128	4.56	16	0.56	132	4.62	39	1.15	109	4.04	17	0.46	124	4.52	35	1.02	144	4.87	37	1.12	135	4.79	34	1.15	145	4.74	9	0.28	169	5.59	9	0.32	169	5.55
Education																																				
<12th Grade	89	3.24	327	13.95	90	3.49	322	13.63	145	5.15	268	12.06	144	4.70	230	11.42	105	3.94	366	14.73	104	4.71	330	13.55	127	4.38	344	14.28	55	2.17	413	16.46	67	2.32	402	16.32
Completed High School	43	2.52	327	21.53	53	2.99	316	21.15	80	3.56	289	20.47	44	2.15	317	22.07	54	2.55	335	21.37	80	4.79	290	19.28	49	2.23	340	21.68	25	1.38	363	22.50	24	1.22	365	22.69
>12 Grade	61	4.08	728	54.68	75	5.41	711	53.34	96	5.02	686	53.75	39	2.15	736	57.51	113	7.90	693	49.52	149	11.18	620	46.49	81	5.18	726	52.25	43	2.87	762	54.62	43	2.85	763	54.59
BMI (kg/m2)																																				
Underweight (<18.5)	13	0.80	44	2.76	18	0.99	39	2.58	19	0.94	38	2.64	17	0.82	34	2.55	16	0.73	50	3.03	11	0.77	45	2.55	23	0.95	43	2.82	3	0.14	62	3.62	8	0.38	57	3.37
Normal Weight (18.5 to 24.9)	58	3.09	343	23.57	59	3.61	338	26.55	79	3.69	316	22.89	47	1.91	337	24.45	88	4.73	346	22.25	91	6.24	311	20.46	82	4.05	352	22.92	27	1.31	405	25.66	30	1.13	402	25.82
Overweight (25.0 to 29.9)	60	3.20	400	27.67	68	3.73	388	27.07	96	4.26	367	26.84	70	3.08	375	28.25	69	3.55	418	27.36	95	5.80	366	25.23	65	3.02	422	27.87	30	1.39	457	29.55	35	1.93	452	28.97
Obese (30.0+)	62	2.75	596	36.16	73	3.56	585	35.53	127	4.83	523	33.91	93	3.19	538	35.75	101	5.46	581	32.89	138	7.94	519	31.00	89	3.87	594	34.51	63	3.59	617	34.75	61	2.94	622	35.46
Alcohol Use																																				
Yes	71	4.07	753	56.85	84	5.52	738	55.41	129	5.91	692	55.20	82	3.48	725	58.42	130	7.85	713	51.81	175	12.96	623	47.21	108	5.58	736	54.10	65	3.80	778	55.94	61	3.43	782	56.26
No	122	5.77	630	33.32	134	6.37	612	32.70	192	7.81	552	31.08	145	5.51	559	32.58	142	6.58	682	33.77	160	7.81	616	32.02	149	6.26	675	34.06	58	2.62	761	37.64	73	2.96	749	37.35
Ever Smoked																																				
Yes	60	3.34	538	37.97	65	4.00	532	37.35	110	5.16	484	36.13	71	3.04	505	38.24	113	6.47	508	34.39	129	8.52	453	32.22	94	4.57	527	36.27	60	3.43	560	37.47	49	2.63	571	38.22
No	133	6.50	843	52.19	153	7.89	816	50.75	211	8.57	758	50.14	156	5.96	778	52.76	161	8.01	885	51.13	206	12.25	786	47.01	165	7.32	882	51.83	63	2.99	979	56.11	85	3.76	960	55.40
Physically Active?																																				
Yes	54	2.98	528	37.38	60	3.68	519	36.67	69	2.90	509	37.54	59	1.96	506	38.81	63	3.42	536	36.29	118	7.74	461	32.69	52	2.46	547	37.23	31	2.02	568	37.73	33	1.84	565	37.85
No	139	6.86	855	52.78	158	8.20	831	51.45	252	10.82	735	48.74	168	7.04	778	52.19	211	11.05	859	49.24	217	13.02	780	46.55	207	9.42	864	50.89	92	4.40	973	55.85	101	4.54	968	55.77
Diabetes																																				
Yes	46	2.09	297	15.51	55	2.80	287	14.85	91	3.18	251	14.49	79	3.08	245	14.31	85	3.73	287	14.07	78	3.85	265	13.42	86	3.76	286	14.03	40	2.02	331	15.78	40	1.54	331	16.24
No	135	7.26	1025	71.05	150	8.49	1005	69.89	215	9.91	936	68.37	142	5.75	975	72.77	180	10.44	1041	67.67	246	16.46	914	62.23	165	7.82	1057	70.30	75	3.89	1142	74.22	88	4.43	1132	73.71
Borderline	12	0.49	60	3.61	13	0.60	57	3.37	14	0.62	57	3.45	6	0.17	63	3.92	8	0.27	67	3.81	11	0.45	61	3.59	7	0.28	68	3.81	8	0.51	67	3.58	6	0.41	69	3.67
Blood Pressure																																				
Normal	106	4.79	933	63.46	127	6.78	908	61.63	193	7.92	840	60.25	127	4.91	869	63.51	175	9.68	919	58.12	219	13.91	825	54.65	161	6.75	934	61.07	84	4.48	1006	63.30	82	3.57	1012	64.27
High	87	5.04	450	26.71	91	5.11	442	26.48	128	5.80	404	26.03	100	4.09	415	27.49	99	4.79	476	27.41	116	6.85	416	24.60	98	5.13	477	27.05	39	1.94	535	30.28	52	2.82	521	29.35
Myocardial Infarction																																				
Yes	17	0.87	83	5.49	12	0.89	88	5.49	23	1.02	74	5.22	20	0.92	72	5.22	24	1.23	82	5.12	23	1.21	74	5.01	27	1.62	79	4.72	17	0.84	89	5.52	9	0.47	97	5.88
No	176	8.97	1298	84.67	206	11.00	1260	82.62	298	12.70	1168	81.06	206	8.06	1211	85.80	250	13.24	1311	80.41	312	19.56	1165	74.22	232	10.27	1330	83.39	106	5.58	1450	88.06	125	5.92	1434	87.73
Stroke																																				
Yes	23	1.13	94	5.40	23	1.20	93	5.23	42	2.07	74	4.45	35	1.53	74	4.94	34	1.60	99	5.43	38	2.29	84	4.43	44	1.92	89	5.10	15	0.73	117	6.28	16	0.84	117	6.19
No	170	8.72	1285	84.75	195	10.71	1253	82.86	276	11.51	1169	81.96	192	7.48	1207	86.05	239	12.87	1293	80.11	296	18.47	1154	74.81	214	9.97	1319	83.01	108	5.70	1420	87.29	118	5.56	1412	87.42
Coronary Heart Disease																																				
Yes	17	0.93	89	5.77	20	1.12	86	5.61	29	1.21	75	5.41	23	1.13	76	5.33	33	1.57	84	5.34	29	1.53	78	5.19	37	1.97	80	4.94	14	0.65	103	6.26	13	0.69	104	6.21
No	175	8.91	1286	84.39	196	10.72	1257	82.54	289	12.46	1163	80.92	200	7.64	1203	85.89	241	12.99	1302	80.11	301	19.07	1160	74.21	220	9.73	1324	83.37	107	5.73	1431	87.36	119	5.68	1422	87.41
Head Trauma																																				
Yes	20	1.04	139	10.67	15	0.85	143	10.85	21	0.96	136	10.73	15	0.72	132	10.80	32	1.53	132	9.93	39	2.26	110	8.85	37	1.70	127	9.76	20	1.41	143	10.04	13	0.86	151	10.60
No	173	8.82	1241	79.47	203	11.06	1204	77.24	300	12.80	1105	75.51	212	8.30	1149	80.18	242	12.97	1260	75.56	295	18.46	1129	70.43	222	10.21	1281	78.33	103	5.02	1395	83.52	121	5.54	1379	83.00
Ever Used Female Hormones																																				
Yes	37	2.69	582	46.48	50	3.86	566	45.22	75	3.81	541	45.35	43	1.86	563	47.49	90	6.20	536	41.38	120	9.81	476	38.13	62	3.42	565	44.19	40	2.66	586	45.00	44	2.85	583	44.77
No	151	6.90	795	43.92	163	7.82	779	43.10	242	9.71	697	41.13	182	7.09	715	43.55	180	7.98	852	44.44	211	10.72	758	41.34	191	8.14	841	44.26	83	3.80	944	48.55	90	3.57	939	48.81

Table 1.1a - Descriptive Statistics -- Surrogate brain health indicators and covariates for HRT use	Immediate Recall (n=1567)				Delayed Recall (n=1560)				Animal Fluency (n=1557)				Digit Symbol Substitution Test (n=1505)				Past 12 months, memory getting worse? (n=1661)				Past 7 days, trouble remembering? (n=1568)				Limited due to difficulty remembering or confusion? (n=1662)				Do you sometimes smell an unpleasant, bad or burning odor when nothing is there? (n=1665)				Past 12 months, have you had a taste or sensation in your mouth that does not go away? (n=1658)			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	≤ 13		≥ 14		≤ 3		≥ 4		≤ 11		≥ 12		≤ 27		≥ 28		Yes		No		Yes		No		Yes		No		Yes		No		Yes		No	
Total Population	193	9.83	1383	90.17	218	11.88	1350	88.12	321	13.72	1244	86.28	227	9.00	1284	91.00	274	14.47	1395	85.53	335	20.76	1241	79.24	259	11.88	1411	88.12	123	6.42	1541	93.58	134	6.38	1533	93.62
Age (years)																																				
60-69	58	2.31	768	50.53	71	3.40	753	49.62	120	3.81	699	48.88	79	2.31	736	51.74	124	6.55	736	45.37	160	10.33	659	42.25	115	4.70	746	47.25	77	3.91	782	48.07	82	3.66	778	48.30
70-79	60	3.11	411	26.55	66	3.69	400	25.82	116	5.41	352	24.37	81	3.17	366	26.37	65	3.29	429	26.14	94	5.56	376	24.00	52	2.24	442	27.18	30	1.75	462	27.64	26	1.23	468	28.20
80 +	75	4.41	204	13.09	81	4.79	197	12.67	85	4.50	193	13.03	67	3.52	182	12.90	85	4.62	230	14.01	81	4.87	206	12.99	92	4.95	223	13.68	16	0.76	297	17.87	26	1.49	287	17.12
Race/Ethnicity																																				
Hispanic	53	1.46	254	6.12	54	1.46	251	6.11	77	1.92	229	5.67	86	2.25	195	4.84	68	1.67	252	5.99	64	1.57	223	5.63	74	1.73	246	5.92	33	0.81	285	6.82	53	1.20	266	6.44
Non-Hispanic White	79	6.67	682	71.19	97	8.46	661	69.42	97	7.65	658	70.19	60	4.40	686	74.38	126	10.63	663	66.29	161	16.07	591	61.25	102	7.74	688	69.19	47	4.48	742	72.51	47	4.23	743	72.73
Non-Hispanic Black	39	1.06	319	8.29	51	1.41	306	7.97	108	3.00	248	6.38	64	1.88	279	7.25	45	1.15	336	8.38	73	2.00	292	7.57	49	1.26	332	8.27	34	0.85	345	8.66	25	0.64	355	8.89
Non-Hispanic Asian/Other	22	0.65	128	4.56	16	0.56	132	4.62	39	1.15	109	4.04	17	0.46	124	4.52	35	1.02	144	4.87	37	1.12	135	4.79	34	1.15	145	4.74	9	0.28	169	5.59	9	0.32	169	5.55
Education																																				
<12th Grade	89	3.24	327	13.95	90	3.49	322	13.63	145	5.15	268	12.06	144	4.70	230	11.42	105	3.94	366	14.73	104	4.71	330	13.55	127	4.38	344	14.28	55	2.17	413	16.46	67	2.32	402	16.32
Completed High School	43	2.52	327	21.53	53	2.99	316	21.15	80	3.56	289	20.47	44	2.15	317	22.07	54	2.55	335	21.37	80	4.79	290	19.28	49	2.23	340	21.68	25	1.38	363	22.50	24	1.22	365	22.69
>12 Grade	61	4.08	728	54.68	75	5.41	711	53.34	96	5.02	686	53.75	39	2.15	736	57.51	113	7.90	693	49.52	149	11.18	620	46.49	81	5.18	726	52.25	43	2.87	762	54.62	43	2.85	763	54.59
BMI (kg/m2)																																				
Underweight (<18.5)	13	0.80	44	2.76	18	0.99	39	2.58	19	0.94	38	2.64	17	0.82	34	2.55	16	0.73	50	3.03	11	0.77	45	2.55	23	0.95	43	2.82	3	0.14	62	3.62	8	0.38	57	3.37
Normal Weight (18.5 to 24.9)	58	3.09	343	23.57	59	3.61	338	26.55	79	3.69	316	22.89	47	1.91	337	24.45	88	4.73	346	22.25	91	6.24	311	20.46	82	4.05	352	22.92	27	1.31	405	25.66	30	1.13	402	25.82
Overweight (25.0 to 29.9)	60	3.20	400	27.67	68	3.73	388	27.07	96	4.26	367	26.84	70	3.08	375	28.25	69	3.55	418	27.36	95	5.80	366	25.23	65	3.02	422	27.87	30	1.39	457	29.55	35	1.93	452	28.97
Obese (30.0+)	62	2.75	596	36.16	73	3.56	585	35.53	127	4.83	523	33.91	93	3.19	538	35.75	101	5.46	581	32.89	138	7.94	519	31.00	89	3.87	594	34.51	63	3.59	617	34.75	61	2.94	622	35.46
Alcohol Use																																				
Yes	71	4.07	753	56.85	84	5.52	738	55.41	129	5.91	692	55.20	82	3.48	725	58.42	130	7.85	713	51.81	175	12.96	623	47.21	108	5.58	736	54.10	65	3.80	778	55.94	61	3.43	782	56.26
No	122	5.77	630	33.32	134	6.37	612	32.70	192	7.81	552	31.08	145	5.51	559	32.58	142	6.58	682	33.77	160	7.81	616	32.02	149	6.26	675	34.06	58	2.62	761	37.64	73	2.96	749	37.35
Ever Smoked																																				
Yes	60	3.34	538	37.97	65	4.00	532	37.35	110	5.16	484	36.13	71	3.04	505	38.24	113	6.47	508	34.39	129	8.52	453	32.22	94	4.57	527	36.27	60	3.43	560	37.47	49	2.63	571	38.22
No	133	6.50	843	52.19	153	7.89	816	50.75	211	8.57	758	50.14	156	5.96	778	52.76	161	8.01	885	51.13	206	12.25	786	47.01	165	7.32	882	51.83	63	2.99	979	56.11	85	3.76	960	55.40
Physically Active?																																				
Yes	54	2.98	528	37.38	60	3.68	519	36.67	69	2.90	509	37.54	59	1.96	506	38.81	63	3.42	536	36.29	118	7.74	461	32.69	52	2.46	547	37.23	31	2.02	568	37.73	33	1.84	565	37.85
No	139	6.86	855	52.78	158	8.20	831	51.45	252	10.82	735	48.74	168	7.04	778	52.19	211	11.05	859	49.24	217	13.02	780	46.55	207	9.42	864	50.89	92	4.40	973	55.85	101	4.54	968	55.77
Diabetes																																				
Yes	46	2.09	297	15.51	55	2.80	287	14.85	91	3.18	251	14.49	79	3.08	245	14.31	85	3.73	287	14.07	78	3.85	265	13.42	86	3.76	286	14.03	40	2.02	331	15.78	40	1.54	331	16.24
No	135	7.26	1025	71.05	150	8.49	1005	69.89	215	9.91	936	68.37	142	5.75	975	72.77	180	10.44	1041	67.67	246	16.46	914	62.23	165	7.82	1057	70.30	75	3.89	1142	74.22	88	4.43	1132	73.71
Borderline	12	0.49	60	3.61	13	0.60	57	3.37	14	0.62	57	3.45	6	0.17	63	3.92	8	0.27	67	3.81	11	0.45	61	3.59	7	0.28	68	3.81	8	0.51	67	3.58	6	0.41	69	3.67
Blood Pressure																																				
Normal	106	4.79	933	63.46	127	6.78	908	61.63	193	7.92	840	60.25	127	4.91	869	63.51	175	9.68	919	58.12	219	13.91	825	54.65	161	6.75	934	61.07	84	4.48	1006	63.30	82	3.57	1012	64.27
High	87	5.04	450	26.71	91	5.11	442	26.48	128	5.80	404	26.03	100	4.09	415	27.49	99	4.79	476	27.41	116	6.85	416	24.60	98	5.13	477	27.05	39	1.94	535	30.28	52	2.82	521	29.35
Myocardial Infarction																																				
Yes	17	0.87	83	5.49	12	0.89	88	5.49	23	1.02	74	5.22	20	0.92	72	5.22	24	1.23	82	5.12	23	1.21	74	5.01	27	1.62	79	4.72	17	0.84	89	5.52	9	0.47	97	5.88
No	176	8.97	1298	84.67	206	11.00	1260	82.62	298	12.70	1168	81.06	206	8.06	1211	85.80	250	13.24	1311	80.41	312	19.56	1165	74.22	232	10.27	1330	83.39	106	5.58	1450	88.06	125	5.92	1434	87.73
Stroke																																				
Yes	23	1.13	94	5.40	23	1.20	93	5.23	42	2.07	74	4.45	35	1.53	74	4.94	34	1.60	99	5.43	38	2.29	84	4.43	44	1.92	89	5.10	15	0.73	117	6.28	16	0.84	117	6.19
No	170	8.72	1285	84.75	195	10.71	1253	82.86	276	11.51	1169	81.96	192	7.48	1207	86.05	239	12.87	1293	80.11	296	18.47	1154	74.81	214	9.97	1319	83.01	108	5.70	1420	87.29	118	5.56	1412	87.42
Coronary Heart Disease																																				
Yes	17	0.93	89	5.77	20	1.12	86	5.61	29	1.21	75	5.41	23	1.13	76	5.33	33	1.57	84	5.34	29	1.53	78	5.19	37	1.97	80	4.94	14	0.65	103	6.26	13	0.69	104	6.21
No	175	8.91	1286	84.39	196	10.72	1257	82.54	289	12.46	1163	80.92	200	7.64	1203	85.89	241	12.99	1302	80.11	301	19.07	1160	74.21	220	9.73	1324	83.37	107	5.73	1431	87.36	119	5.68	1422	87.41
Head Trauma																																				
Yes	20	1.04	139	10.67	15	0.85	143	10.85	21	0.96	136	10.73	15	0.72	132	10.80	32	1.53	132	9.93	39	2.26	110	8.85	37	1.70	127	9.76	20	1.41	143	10.04	13	0.86	151	10.60
No	173	8.82	1241	79.47	203	11.06	1204	77.24	300	12.80	1105	75.51	212	8.30	1149	80.18	242	12.97	1260	75.56	295	18.46	1129	70.43	222	10.21	1281	78.33	103	5.02	1395	83.52	121	5.54	1379	83.00
Ever Used Female Hormones																																				
Yes	37	2.69	582	46.48	50	3.86	566	45.22	75	3.81	541	45.35	43	1.86	563	47.49	90	6.20	536	41.38	120	9.81	476	38.13	62	3.42	565	44.19	40	2.66	586	45.00	44	2.85	583	44.77
No	151	6.90	795	43.92	163	7.82	779	43.10	242	9.71	697	41.13	182	7.09	715	43.55	180	7.98	852	44.44	211	10.72	758	41.34	191	8.14	841	44.26	83	3.80	944	48.55	90	3.57	939	48.81

Associations Between Exposures to Past OC and HRT use and Cognitive Test Scores

Exposures OC and HRT and four cognitive scores (immediate and delayed recall, animal fluency, and DSST score) are summarized in tables 1.2 to 1.13. The cognitive test scores have been used as a surrogate indicator of brain health to assess cognitive decline and the possible development of mild cognitive impairment, dementia, and/or AD elderly patients as part of neuropsychological testing.

Immediate Recall Scores and Exposure to OC and HRT: Tables 1.2 and 1.3 present chi-square results for immediate recall scores and OC use and HRT use. We observed a significant relationship exists between OC use and HRT use with respect to immediate recall scores.

Chi Square Results		
Table 1.2 Immediate Recall Cut-off Scores	OC use?	
	Yes	No
≤ 13	63 (3.35%)	130 (6.48%)
≥ 14	865 (60.83%)	518 (29.34%)
$\chi 2$ (df=1, N=1576) F=72.45, p<0.0001)		
The relationship is significant.		

Chi Square Results		
Table 1.3 Immediate Recall Cut-off Scores	HRT use?	
	Yes	No
≤ 13	37 (2.69%)	152 (6.91%)
≥ 14	583 (46.60%)	795 (43.81%)
$\chi 2$ (df=1, N=1567) F=35.55, p<0.0001)		
The relationship is significant.		

Table 1.4 presents the ORs and 95% CIs for OC and HRT use and immediate recall scores. In immediate recall scores and OC use, it was observed that OC use was associated with lower odds of a low immediate recall score in the unadjusted model, adjusted model #1, and adjusted model #2.

In immediate recall scores and HRT use it was observed that HRT use was also associated with lower odds of a low immediate recall score in the adjusted model, adjusted model #1, and adjusted model #2.

Table 1.4 - ORs and 95% CI for OC and HRT Use Levels by Immediate Recall Cut-off Scores for Female Subjects >= 60 years of age, NHANES 2011-2014									
EEDC	≤13 / ≥14	Unadjusted Odds Ratio [1]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #1 [2]	95% CI	≤13 / ≥14	Adjusted Odds Ratio #2 [3]	95% CI
OC use	193/1383	0.249 ***	0.175-0.356	193/1382	0.487 ***	0.343-0.692	192/1364	0.521 **	0.358-0.760
HRT use	189/1378	0.366 ***	0.252-0.530	189/1377	0.507 **	0.332-0.773	187/1359	0.517 **	0.340-0.785
*p<0.05, **p<0.01 ***p<0.001									
[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.									

Delayed Recall Scores and Exposure to OC and HRT: Tables 1.5 and 1.6 present chi-square results for delayed recall scores and OC use and HRT use. We observed a significant relationship exists between OC use and HRT use with respect to delayed recall scores.

Chi Square Results		
Table 1.5 Delayed Recall Cut-off Scores	OC use?	
	Yes	No
≤ 3	82 (4.71%)	136 (7.18%)
≥ 4	842 (59.46%)	506 (28.66%)
$\chi 2$ (df=1, N=1568) F=30.53, p<0.0001)		
The relationship is significant.		

Chi Square Results		
Table 1.6 Delayed Recall Cut-off Scores	HRT use?	
	Yes	No
≤ 3	50 (3.85%)	163 (7.80%)
≥ 4	567 (45.34%)	780 (43.01%)
$\chi 2$ (df=1, N=1560) F=13.56, p<0.0008)		
The relationship is significant.		

Table 1.7 presents the ORs and 95% CIs for OC and HRT use and delayed recall scores. In delayed recall scores and OC use, it was observed that OC use was associated with lower odds of a low delayed recall score in the unadjusted model, adjusted model #1, and adjusted model #2.

In immediate recall scores and HRT use it was observed that HRT use was also associated with lower odds of a low delayed recall score in the adjusted model and adjusted model #1.

Table 1.7 - ORs and 95% CI for OC and HRT Use Levels by Delayed Recall Cut-off Scores for Female Subjects >= 60 years of age, NHANES 2011-2014									
EEDC	≤3 / ≥4	Unadjusted Odds Ratio [1]	95% CI	≤3 / ≥4	Adjusted Odds Ratio #1 [2]	95% CI	≤3 / ≥4	Adjusted Odds Ratio #2 [3]	95% CI
OC use	218/1350	0.316 ***	0.202-0.495	218/1349	0.538 *	0.323-0.895	216/1332	0.560 *	0.323-0.971
HRT use	213/1347	0.468 ***	0.306-0.717	213/1346	0.609 *	0.389-0.954	211/1328	0.621	0.383-1.007
*p<0.05, **p<0.01 ***p<0.001									
[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.									

Animal Fluency Scores and Exposure to OC and HRT: Tables 1.8 and 1.9 present chi-square results for animal fluency scores and OC use and HRT use. We observed a significant relationship exists between OC use and HRT use with respect to animal fluency scores.

Chi Square Results		
Table 1.8 Animal Fluency Cut-off Scores	OC use?	
	Yes	No
≤ 11	141 (5.71%)	180 (8.01%)
≥ 12	780 (58.40%)	464 (27.88%)
$\chi 2$ (df=1, N=1565) F=39.92, p<0.0001)		
The relationship is significant.		

Chi Square Results		
Table 1.9 Animal Fluency Cut-off Scores	HRT use?	
	Yes	No
≤ 11	75 (3.80%)	243 (9.71%)
≥ 12	542 (45.46%)	697 (41.03%)
$\chi 2$ (df=1, N=1557) F=58.18, p<0.0001)		
The relationship is significant.		

Table 1.10 presents the ORs and 95% CIs for OC and HRT use and animal fluency scores. In animal fluency scores and OC use, it was observed that OC use was associated with lower odds of a low animal fluency score in the unadjusted model, adjusted model #1, and adjusted model #2. In animal fluency scores and HRT use it

was observed that HRT use was also associated with lower odds of a low animal fluency score in the adjusted model, adjusted model #1, and adjusted model #2.

Table 1.10 - ORs and 95% CI for OC and HRT Use Levels by Animal Fluency Cut-off Scores for Female Subjects >= 60 years of age, NHANES 2011-2014									
EEDC	≤11 / ≥12	Unadjusted Odds Ratio [1]	95% CI	≤11 / ≥12	Adjusted Odds Ratio #1 [2]	95% CI	≤11 / ≥12	Adjusted Odds Ratio #2 [3]	95% CI
OC use	321/1244	0.340 ***	0.238-0.487	321/1243	0.606 *	0.385-0.952	314/1231	0.595 *	0.369-0.958
HRT use	318/1239	0.353 ***	0.266-0.468	318/1238	0.533 ***	0.375-0.758	310/1226	0.523 **	0.362-0.756
*p<0.05, **p<0.01 ***p<0.001									
[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.									

Digit Symbol Substitution Test (DSST) Scores and Exposure to OC and HRT:

Tables 1.11 and 1.12 present chi-square results for DSST scores and OC use and HRT use. We observed a significant relationship exists between OC use and HRT use with respect to DSST scores.

Chi Square Results		
Table 1.11 DSST Cut-off Scores	OC use?	
	Yes	No
≤ 27	83 (2.83%)	144 (6.17%)
≥ 28	834 (62.57%)	450 (28.44%)
$\chi 2$ (df=1, N=1511) F=103.90, p<0.0001)		
The relationship is significant.		

Chi Square Results		
Table 1.12 DSST Cut-off Scores	HRT use?	
	Yes	No
≤ 27	43 (1.86%)	183 (7.10%)
≥ 28	564 (47.61%)	715 (43.44%)
$\chi 2$ (df=1, N=1505) F=32.64, p<0.0001)		
The relationship is significant.		

Table 1.13 presents the ORs and 95% CIs for OC and HRT use and DSST scores. In DSST scores and OC use, it was observed that OC use was associated with lower odds of a low DSST scores in the unadjusted model, adjusted model #1, and adjusted model #2. In DSST scores and HRT use it was observed that HRT use was also associated with lower odds of a low DSST score in the adjusted model, adjusted model #1, and adjusted model #2.

Table 1.13 - ORs and 95% CI for OC and HRT Use Levels by DSST Cut-off Scores for Female Subjects >= 60 years of age, NHANES 2011-2014									
EEDC	≤27 / ≥28	Unadjusted Odds Ratio [1]	95% CI	≤27 / ≥28	Adjusted Odds Ratio #1 [2]	95% CI	≤27 / ≥28	Adjusted Odds Ratio #2 [3]	95% CI
OC use	227/1284	0.208 ***	0.150-0.289	227/1283	0.401 ***	0.262-0.614	222/1271	0.411 ***	0.258-0.656
HRT use	226/1279	0.239 ***	0.143-0.401	226/1278	0.419 **	0.234-0.749	220/1266	0.434 *	0.231-0.813
*p<0.05, **p<0.01 ***p<0.001									
[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.									

Associations Between Exposures to OC and HRT and Memory Function

Exposures to OCs and HRTs and three memory function indicators: 1) During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse? 2) During the past 7 days, how often have you had trouble remembering where you put things? 3) Are you limited in any way because of difficulty remembering or because you experience periods of confusion?) are summarized in tables 1.14 to 1.22. Memory function have been included as a surrogate indicator of brain health as declining memory function can indicate the development of mild cognitive impairment, dementia, AD, or other memory-related neurodegenerative disease.

Worsening memory past 12 months and Exposure to OC and HRT: Tables 1.14 and 1.15 present chi-square results for the Y/N question "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" and OC use and HRT use. We observed a significant relationship does not exists between OC use and HRT use with respect to experiencing confusion or memory loss in the past 12 months, that is happening more often or getting worse.

Chi Square Results		
Table 1.14 During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse?	OC use?	
	Yes	No
Yes	132 (8.03%)	142 (6.43%)
No	819 (54.71%)	576 (30.82%)
$\chi 2$ (df=1, N=1669) F=0.06, p=n.s.)		
The relationship is not significant.		

Chi Square Results		
Table 1.15 During the past 12 months, have you experienced confusion or memory loss that is happening more often or getting worse?	HRT use?	
	Yes	No
Yes	90 (6.18%)	182 (8.00%)
No	537 (41.50%)	852 (44.32%)
$\chi 2$ (df=1, N=1661) F=1.44, p=n.s.)		
The relationship is not signfiicant.		

Table 1.16 presents the ORs and 95% CIs for OC and HRT use and Y/N question "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?". No significant associations were observed.

Table 1.16 - ORs and 95% CI for OC and HRT Use Levels by Y/N "During the past 12 months, you experienced confusion or memory loss that is happening more often or is getting worse?" for Female Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
OC use	274/1395	0.703	0.482-1.026	272/1394	0.983	0.640-1.511	268/1377	0.973	0.634-1.493
HRT use	272/1389	0.825	0.594-1.145	270/1388	1.002	0.715-1.405	265/1371	0.994	0.671-1.472

*p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Trouble remembering past 7 days and Exposure to Metalloestrogens: Tables 1.17 and 1.18 present chi-square results for the Y/N question "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" and OC use and HRT use. We observed a significant relationship does not exists.

Chi Square Results		
Table 1.17 During the past 7 days, how often have you dad trouble remembering where you put things?	OC use?	
	Yes	No
Yes	188 (13.02%)	147 (7.73%)
No	722 (50.66%)	519 (28.58%)
$\chi 2$ (df=1, N=1576) F=0.79, p=n.s.)		
The relationship is not significant.		

Chi Square Results		
Table 1.18 During the past 7 days, how often have you dad trouble remembering where you put things?	HRT use?	
	Yes	No
Yes	120 (9.79%)	212 (10.71%)
No	477 (38.26%)	759 (41.25%)
$\chi 2$ (df=1, N=1568) F=0.02, p=n.s.)		
The relationship is not significant.		

Table 1.19 presents the ORs and 95% CIs for OC and HRT use and Y/N question "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" No significant associations were observed.

Table 1.19 - ORs and 95% CI for OC and HRT Use Levels by Y/N "During the past 7 days, how often have you had trouble remembering where you put things, like your keys or your wallet?" for Female Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
OC use	335/1241	0.950	0.651-1.389	333/1240	1.134	0.714-1.803	326/1227	1.151	0.737-1.800
HRT use	332/1236	0.986	0.776-1.252	330/1235	1.091	0.824-1.443	323/1221	1.097	0.830-1.449

*p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Limitations Due to Difficulty Remembering or Confusion and Exposure to OC and HRT: Tables 1.20 and 1.21 present chi-square results for the Y/N question "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" and OC use and HRT use. We observed a significant relationship exists between OC use and HRT use with respect to being limited in any way because of difficulty remembering or because you experience periods of confusion.

Chi Square Results		
Table 1.20 Are you limited in any way because of difficulty remembering or because you experience periods of confusion?	OC use?	
	Yes	No
Yes	115 (5.50%)	144 (6.39%)
No	837 (57.26%)	574 (30.85%)
$\chi 2$ (df=1, N=1670) F=13.75, p=0.0008)		
The relationship is significant.		

Chi Square Results		
Table 1.21 Are you limited in any way because of difficulty remembering or because you experience periods of confusion?	HRT use?	
	Yes	No
Yes	62 (3.41%)	192 (8.13%)
No	566 (44.29%)	842 (44.16%)
$\chi 2$ (df=1, N=1662) F=32.06, p=0.0001)		
The relationship is significant.		

Table 1.22 presents the ORs and 95% CIs for OC and HRT use and responses to the Y/N question "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" With regard to OC use, it was observed that OC use was associated with lower odds in the unadjusted model. With regard to HRT use it was observed that HRT use was also associated with lower odds in the adjusted model, adjusted model #1, and adjusted model #2.

Table 1.22 - ORs and 95% CI for OC and HRT Use Levels by Y/N "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" for Female Subjects >= 60 years of age, NHANES 2011-2014

EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
OC use	259/1411	0.464 **	0.300-0.716	257/1410	0.788	0.479-1.295	251/1395	0.809	0.462-1.417
HRT use	254/1408	0.418 ***	0.304-0.575	252/1407	0.555 **	0.396-0.778	246/1391	0.574 **	0.400-0.823

*p<0.05, **p<0.01 ***p<0.001

[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.

Associations Between Exposures to Phthalate and BPA and Taste/Smell Function

Exposures to the metalloestrogens Cd, Mn, and As, and two indicators of taste/smell function:

1) Do you sometimes smell an unpleasant, bad, or burning odor when nothing is there (phantosmia), and 2) During the past 12 months have you had a taste or other sensation in your mouth that does not go away? Taste and smell indicators have been included as a surrogate indicator of brain health as taste and smell dysfunction is a possible pre-clinical indicator in the development of AD and other memory-related neurodegenerative diseases.

Smell Dysfunction and Exposure to OC and HRT: Tables 1.23 and 1.24 present chi-square results for the Y/N question "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" and OC use and HRT use. We observed a significant relationship does not exist.

Chi Square Results		
Table 1.23 Do you sometimes smell and unpleasant, bad, or burning odor when nothing is there?	OC use?	
	Yes	No
Yes	75 (4.19%)	48 (2.23%)
No	877 (58.67%)	664 (34.91)
$\chi 2$ (df=1, N=1664) F=0.23, p=n.s.)		
The relationship is not significant.		

Chi Square Results		
Table 1.24 Do you sometimes smell and unpleasant, bad, or burning odor when nothing is there?	HRT use?	
	Yes	No
Yes	40 (2.65%)	83 (3.79%)
No	587 (45.11%)	945 (48.45%)
$\chi 2$ (df=1, N=1655) F=1.53, p=0.22)		
The relationship is not significant.		

Table 1.25 presents the ORs and 95% CIs for OC and HRT use and responses to the Y/N question "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?". With both OC use and HRT use, we did not observe any significant relationships.

Table 1.25 - ORs and 95% CI for OC and HRT Use Levels by Y/N "Do you sometimes smell an unpleasant, bad or burning odor when nothing is there?" for Female Subjects >= 60 years of age, NHANES 2011-2014									
EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
OC use	123/1541	1.116	0.704-1.770	123/1538	0.902	0.557-1.460	121/1519	0.952	0.556-1.630
HRT use	123/1532	0.751	0.464-1.216	123/1529	0.865	0.514-1.455	121/1509	0.880	0.531-1.457
*p<0.05, **p<0.01 ***p<0.001									
[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.									

Taste Dysfunction and Exposure to OC and HRT: Tables 1.26 and 1.27 present chi-square results for the Y/N question "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" and OC use and HRT use. We observed a significant relationship does not exist.

Chi Square Results		
Table 1.27 During the past 12 months have you had a taste or other sensation in your mouth that does not go away?	HRT use?	
	Yes	No
Yes	44 (2.85%)	90 (3.56%)
No	584 (44.89%)	940 (48.71%)
$\chi 2$ (df=1, N=1658) F=0.35, p=0.55)		
The relationship is not significant.		

Chi Square Results		
Table 1.26 During the past 12 months have you had a taste or other sensation in your mouth that does not go away?	OC use?	
	Yes	No
Yes	75 (3.79%)	59 (2.59%)
No	876 (58.97%)	657 (34.64%)
$\chi 2$ (df=1, N=1667) F=0.42, p=n.s.)		
The relationship is not significant.		

Table 1.28 presents the ORs and 95% CIs for OC and HRT use and responses to the Y/N question "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?". With both OC use and HRT use, we did not observe any significant relationships

Table 1.28 - ORs and 95% CI for OC and HRT Use Levels by Y/N "During the past 12 months have you had a taste or other sensation in your mouth that does not go away?" for Female Subjects >= 60 years of age, NHANES 2011-2014									
EEDC	Yes/No	Unadjusted Odds Ratio [1]	95% CI	Yes/No	Adjusted Odds Ratio #1 [2]	95% CI	Yes/No	Adjusted Odds Ratio #2 [3]	95% CI
OC use	134/1533	0.861	0.538-1.378	134/1530	0.921	0.578-1.468	132/1511	0.947	0.587-1.528
HRT use	134/1524	0.867	0.531-1.417	134/1521	1.081	0.685-1.706	132/1501	1.180	0.748-1.859
*p<0.05, **p<0.01 ***p<0.001									
[1] Unadjusted model. [2] Adjusted for age, education, race/ethnicity. [3] Adjusted for age, education, race/ethnicity, alcohol use, diabetes status, high blood pressure status, coronary heart disease status, heart attack status, stroke status, physical activity status, smoking status, head trauma status.									

DISCUSSION

This study takes a novel approach in the assessment of exposure to OC and HRT in the development of cognitive dysfunction and possible neurodegenerative disease using surrogate indicators of brain health. The study examined an older geriatric-aged population of US adults 60 years of age and older. We first assessed the existence of a relationship between past OC and HRT use by calculating and chi-square test of independence versus each surrogate indicator of brain health, and subsequently used ORs and 95% CI to determine the risk of developing cognitive dysfunction.

Major Findings: Overall, we observed a the existence of a relationship between past OC and HRT use and the following surrogates of brain function: immediate recall scores; delayed recall scores; animal flluency scores; DSST scores, and limitations due to difficulty remembering or confusion (Tables 1.2 to 1.28). In our logisitic regression models, when controlling for all known and suspected covariates of cognitive dysfunction and AD in our second adjusted model, we found past OC use to lower the risk of developing cognitive dysfunction and the possible development of

AD. Specifically, we found past OC use to be associated with better immediate recall, delayed recall, animal fluency and DSST scores.

We also found past HRT use to lower the risk fo developing cognitive dysfunction and the possible development of AD. Specifically, we found past HRT use to be associated with better immediate recall, animal fluency, and DSST scores. Past HRT use was also associated with less occurrences of limitations due to periods of difficulty remembering or periods of confusion. Tables (1.2 to 1.28).

With regards to past OC use, it was not possible to differentiate between OCs containing estrogen and those not containing it, which is an issue with past studies [68]. Past OC use with other studies that suggest its' use can improve cognitive function with regards to cognitive tests [8] and better performance of spatial ability and cognitive tests [68]. The majority of evidence with regard to past HRT use suggests that HRT use may be harmful to brain health. Increased risk of dementia [12,13,16–19].

One of the prevailing hypothesis states the timing of estrogen therapies may dictate its' effectiveness in protecting cognition and function. An increase in estrogen in early to mid-adulthood and early on in menopause suggests a possible protective benefit from the use of OC and HRT [69], which was shown in one study, which showed increased AD risk if HRTs were used more than five years after menopause and a decreased risk if HRTs were used within five years after menopause [20]. From our study, we cannot fully determine the composition of the OC and HRT therapies. It is suggested that the composition, and hence, the estrogen amount and dosage may also dictate the effectiveness, or adversness of the OC and/or HRT therapy.

Biological Mechanisms and Brain Health: OCs and HRTs, although considered to EEDCs because of their ability to mimic estrogen are unique since their main active ingredients may contain derivatives of estrogen, making them highly estrogen-responsive with their high affinity for estrogen receptors [70] which is very similar to biologically available estrogen, with its effects mediated through the known estrogen receptor pathways, ERa , ERß, GPER/GPR30, which are widely expressed in the brain [71]. Estrogen itself has been demonstrated to have roles in neuroprotection as well as exert anti-inflammatory effects on the brain [72–77] and with its' similar bioactivity to biological estrogen, may provide a protective effect to the aging brain.

Although a number genes that are implicated in AD and other neurodegenerative diseases are estrogen-sensitive [71], it is possible that a deficit in naturally circulating estrogen may be one of culprits of neurodegeneration which supports the critical window hypothesis when estrogen production is lowest around menopause [69].

Strengths and Limitations: There are strengths and limitations to our study. The largest limitations the cross-sectional design of our study. The data is self-reported which makes inference difficult and prone to misclassification bias. Our OC and HRT variable does not give us a dosage, or amount. It also does not indicate the length of time, or when the OC/HRT therapy was stated and finished. Our outcome variables are surrogates rather than actual clinical endpoints, which limits our ability to say that our outcome will lead to neurodegenerative disease. The cut-off scores of our cognitive exams were based on previous studies, however, performance on those exams are heavily dependent on education, so there is a possibility that poor

performance might be a function of lack of education. For our taste/smell indicators, the senses heavily affected by numerous confounders, some of which were not feasible in study due to making the sample smaller, or the confounder not being available. Strengths of our study include the novelty of such an analysis to be conducted on an older population. We had relatively large sample sizes available for our analyzes. The generalizability of our study to the US population and the large amount of chemical measurements available gives the study the ability to examine different aspects of chemical exposure.

Conclusion

Based on our findings, OC and HRT use has a beneficial and possible protective effect on cognitive function and might possibly be protective against neurodegenerative disease. Further study is needed, especially to examine time frames and extent of OC and HRT use to establish the most effective points to take it in a female's life. This may add to the therapeutic benefits of these therapies.

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CHAPTER VIII

OVERALL CONCLUSIONS

The goal of this research was to find out if exposures to EEDCs had an adverse effect on brain health, using our surrogates of brain health indicators found in the CDC's NHANES datasets. Our surrogate indicators, cognitive scores that include immediate recall, delayed, recall, animal fluency, and digit symbol substitution scores, have been proven to differentiate between normal cognitive function, cognitive decline, and the development of dementia and AD. They are further supported by their use in a clinical setting. The memory questions that indicated if memory issues were present in a year's time and a week's time have utility in the fact that the first symptom of cognitive decline is memory issues. Taste and smell questions have their utility in taste and smell dysfunction can be an early sub-clinical indicator of cognitive dysfunction.

The EEDCs considered in this study, phthalates, BPA, PCBs, Cd, As, and Mn, all have proven estrogenic activity and can interfere with the protective and therapeutic effect that estrogen has on brain health and function. The epidemiologic evidence, however, is lacking, as most exposure studies have been performed at the cellular, animal, or before, during, and after birth in humans. Our study addresses the gaps present in this study area.

Our first specific aim, assessing exposure to phthalates and bisphenol-A (BPA) using urinary biomarkers from the CDC NHANES 2011-2014 datasets to find associations between phthalate and BPA bioburden and adverse brain health using surrogate indicators of brain health was addressed in manuscript II.

Increased levels of phthalate metabolites were observed in those who had lower cognitive test scores, reported having memory issues, and reported taste and smell deficits compared to those who did not have any observed brain health issues. Females have a greater bioburden of phthalates compared to males. In females, the phthalates ECP, MBP, MOH, MZP, and MIB were observed to have significantly higher bioburdens among two or more of the surrogate brain health indicators. In males, the phthalates ECP, MHH, MOH, and MIB were observed to have significantly higher bioburdens among two or more of the surrogate brain health indicators. BPA did not have any significant results in any of our tests. When controlling for known and suspected covariates of AD in males in our final logistic regression model, COP, ECP, MBP, MC1, MEP, MHH, MOH, and MIB were associated with one or more of the surrogate brain health indicators. When controlling for known and suspected covariates of AD in females in our final logistic regression model, ECP, MBP, MHH, MOH, MZP, and MIB were associated with one or more of the surrogate brain health indicators. BPA did not have any significant results in any of our tests.

Our second specific aim, assessing exposure to the metalloestrogens, cadmium (Cd), arsenic (As), and manganese (Mn) using urinary biomarkers from the CDC NHANES 2011-2014 datasets to find associations between phthalate and BPA bioburden and adverse brain health using surrogate indicators of brain health was addressed in manuscript III. Cd and Mn bioburdens were found to be more evident in individuals who have lower cognitive scores and/or have memory cognition issues. In our logistic regression models, Cd stood out as the

metalloestrogen that plays a larger role in the development of neurodegenerative disease and adverse brain health in an older population. No significant results were observed in our full logistic regression models.

Our third specific aim, assessing exposure to oral contraceptives (OC) and hormonal replacement therapy (HRT) using urinary biomarkers from the CDC NHANES 2011-2014 datasets to find associations between phthalate and BPA bioburden and adverse brain health using surrogate indicators of brain health, was addressed in manuscript IV. We observed the existence of a relationship between past OC and HRT use and the following surrogates of brain function: immediate recall scores; delayed recall scores; animal flluency scores; DSST scores, and limitations due to difficulty remembering or confusion. In our logisitic regression models, when controlling for all known and suspected covariates of cognitive dysfunction and AD in our second adjusted model, we found past OC use to lower the risk of developing cognitive dysfunction and the possible development of AD. Specifically, we found past OC use to be associated with better immediate recall, delayed recall, animal fluency and DSST scores. We also found past HRT use to lower the risk fo developing cognitive dysfunction and the possible development of AD. Specifically, we found past HRT use to be associated with better immediate recall, animal fluency, and DSST scores. Past HRT use was also associated with less occurrences of limitations due to periods of difficulty remembering or periods of confusion.

Our fourth specific aim, to Assess estrogen-responsive genes networks common to the EEDCs, phthalates, BPA, Cd, As, and Mn, NRF1, and neurodegenerative disease using bioinformatics methods, was addressed in manuscript I. From our bioinformatics approach, we identified several novel gene NRF1 gene targets that are both estrogen-responsive and responsive to our selection of EEDCs which are also implicated in the gene networks of several major neurodegenerative diseases.

Our study has several strengths. We had sufficient sample sizes to examine our variables, and our covariates had a large response rate. The generalizability of our study to the US population and the large amount of chemical measurements available gives the study the ability to examine different aspects of chemical exposure.

Our overall study has several limitations. Most of the data is self-reported, which lends itself to misclassification bias, with the chance of incorrectly reported endpoints. Also, the lack of true clinical endpoints allows us to make limited inference pertaining to disease diagnosis. Our OC and HRT variables do not give information on the type of treatment given, so we could not assess if synthetic estrogens were part of the drug formulation. Our cut-off scores were based on previous studies, however, performance on these test is also influenced by education. For our taste/smell indicators, the senses heavily affected by numerous confounders, some of which were not feasible in study due to making the sample smaller, or the confounder not being available.

In summary, our findings suggest that EEDCs do play a role in the development of cognitive dysfunction and the development of neurodegenerative disease in older people. These findings are further supported by our finding of gene targets which play a role in the development of various neurodegenerative diseases.

VITA

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PUBLICATIONS AND PRESENTATIONS

Preciados M, Yoo C, Roy D. Estrogenic Endocrine Disrupting Chemicals Influencing NRF1 Regulated Gene Networks in the Development of Complex Human Brain Diseases. *Int J Mol Sci*. 2016;17(12):2086. doi:10.3390/ijms17122086.

Preciados, Mark, (March, 2017). *Role of Estrogenic Endocrine Disruptors (EEDs)-Genes interactions associated with both estrogen signaling and NRF1 signaling pathways in Alzheimer's Disease (AD).* Poster presented at the Society of Toxicology Meeting, Baltimore, MD, March 2017.