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AN ABSTRACT OF THE DISSERTATION OF

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Title: Polycyclic Aromatic Hydrocarbons (PAH) Exposure Trends, and Evidence of Adverse Health Outcomes in Infants and Children from Prenatal/Early-Life PAH Exposure.

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Molly L. Kile

Polycyclic aromatic hydrocarbons (PAHs) are complex mixtures that form when organic matter is burned. Humans are primarily exposed to PAHs via air pollution from incomplete combustion of fossil fuels and biomass, such a motor vehicle exhaust, cigarette smoke, wood smoke, or industrial emissions; or via ingestion of PAHs bound to particles in household dust, or from grilled or smoked food. Chronic PAH exposure is linked to many adverse health outcomes, including cancer, cardiovascular disease, and respiratory illness. Concern regarding the adverse health effects of PAHs prompted public health surveillance and regulatory measures to monitor and control PAH exposure. Recent air monitoring studies in the U.S. showed PAH levels in ambient air have decreased since the 1990s, but few studies have utilized biomarkers as a measure of internal dose to evaluate if decreased PAHs in ambient air equates to decreased human exposure. Recent toxicological studies in animals, and epidemiologic studies in humans, revealed that PAHs can cross the placenta, and there is a growing epidemiological evidence that prenatal and early-life PAH exposure is linked with adverse human development outcomes, such as low birth weight in infants, and lower IQ scores in children. However, there are few studies that have attempted to address these conflicting results by summarizing the available evidence. The overarching goal of this dissertation is to summarize the global weight of evidence regarding prenatal and early-life PAH exposure on infant/child health, and to evaluate the effectiveness of U.S. environmental health policies in reducing PAH exposure. The first study of this dissertation provides evidence that, while U.S. policies, such as the U.S. Clean Air Act Amendments (1990, as amended), have been successful in reducing ambient PAH concentration, exposure of two semi-volatile PAHs, Naphthalene, and Pyrene, increased in non-smokers from 2001-2014. This

study also provides evidence that, compared to Non-Hispanic Whites, a persistent disparity exists in PAH exposure for Non-Hispanic Blacks and Mexican Americans, suggesting these ethnic groups have not benefited to the same extent from U.S. policies to reduce PAH exposures. The second study is a systematic review and meta-analysis that evaluated prenatal PAH exposure on selected birth outcomes in infants. The results of this study indicate there is sufficient human evidence that prenatal PAH exposure adversely affects birth length, head circumference, and ponderal index. The third study is a systematic reviews and meta-analysis that evaluated prenatal and early-life PAH exposure on neurodevelopment outcomes in children. The results of this study indicate there is sufficient human evidence that prenatal and early-life PAH exposure adversely affects cognitive function, motor function, and behavioral outcomes in children.

These results provide evidence that prenatal and early-life PAH exposure can influence human development, and that, while evidence that U.S. public health efforts to reduce ambient PAH exposure have been successful, the internal dose of Naphthalene and Pyrene have increased over time, especially in minority populations. A persistent disparity exists in PAH exposure for Non-Hispanic Blacks and Mexican Americans, suggesting these groups have not benefited to the same extent from U.S. policies to reduce PAH exposures. Our research also suggests that environmental sources of PAHs have changed over time. Overall, these results will guide future research and inform regulatory guidelines to help further identify sources of PAH exposure and reduce exposure, particularly during pregnancy.

Polycyclic Aromatic Hydrocarbons (PAH) Exposure Trends, and Evidence of Adverse Health Effects in Infants and Children from Prenatal/Early-Life PAH Exposure

by
Barbara A. Hudson-Hanley

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I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Barbara A. Hudson-Hanley, Author

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Barbara Hudson-Hanley, MPH

CONTRIBUTION OF AUTHORS

Barbara Hudson-Hanley conceptualized the study design and research questions, collected analyzed the data, interpreted the results, and drafted the manuscripts.

Dr. Molly Kile helped conceptualized the study design and research questions, supervised all analysis, assisted with the interpretation of findings, and provided critical review and feedback on of the manuscripts.

Dr. Adam Branscum supervised statistical analysis, provided technical assistance, assisted with interpretation of findings, and reviewed and provided feedback on the manuscripts.

Dr. Ellen Smit provided feedback on analytical approach, assisted with the interpretation of the findings, and reviewed and provided feedback on the manuscripts.

Dr Perry Hystad reviewed and provided feedback on the manuscripts.

Dr. David Bernell provided guidance on U.S. environmental and energy policy, and oversight for completing a PhD minor degree in Political Science, with a focus in Environmental Policy.

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LIST OF ABBREVIATIONS AND ACRONYMS

95%CI	95% Confidence Interval
ACE	Acenaphthene
ACY	Acenaphthylene
ADHD-DSM-IV	Attention Deficit/Hyperactivity Disorder section of the DSM-IV
aGM	adjusted Geometric Mean
AhR	Aryl Hydrocarbon Receptor
ANT	Anthracene
ANT	Attentional Network Test
ATSDR	Agency for Toxic Substances and Disease Registry
β	Regression beta coefficient
BaA	Benzo[a]anthracene
BaP	Benzo[a]pyrene
BbF	Benzo[b]fluorene
BG	Bender Visual Motor Gestalt Test
BghiP	Benzo[g,h,i]perylene
BITSEA	Brief Infant-Toddler Social and Emotional Assessment
BjF	Benzo[j]pyrene
BkF	Benzo[k]pyrene
BL	Birth Length (cm)
BMI	Body Mass Index
BSID-II	Bayley Scales of Infant Development, 2nd Edition
BSID-III	Bayley Scales of Infant Development, 3rd Edition
BW	Birth Weight (g)
CBCL	Child Behavior Checklist
CDC	U.S. Centers for Disease Control and Prevention
CHR	Chrysene
CI	Cephalization Index (gm/g)
cm	Centimeters
CMA	Comprehensive Meta-Analysis software
Cohen's *d*	Standardized mean difference
CPRS-R	Conners Parent Rating Scale-Revised
DahA	Dibenz[a,h]anthracene
DESR	Deficient Emotional Regulation, part of the CBCL
df	Degrees of Freedom
DNA	Deoxyribonucleic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Translated
FGR<85%	Fetal Growth Restriction that is below 85% of normal
FID	Flame-Ionization Detection
FLA	Fluoranthene
FLU	Fluorene
g	Gram

LIST OF ABBREVIATIONS AND ACRONYMS (Continued)

GC	Gas Chromatography
GDS	Gesell Development Schedules
GM	Geometric Mean
HC	Head Circumference (cm)
HPLC	High Pressure Liquid Chromatography
Hx-PC	Maternal History of Pregnancy Complications
I2	I-squared; analogous to a signal-to-noise ratio that estimates the proportion of observed variation (s2 + T2) explained by the variance of true effects (T2)
IcdP	Indo[c,d]pyrene
IQ	Intelligence Quotient
IQR	Inter-Quartile Range
IUGR	Intra-Uterine Growth Restriction (fetal weight < 10th percentile; and abdominal circumference < 25th percentile for gestational age)
k	Number of primary studies included in a meta-analysis
Kg	Kilogram
ksub	Number of exposure-outcome sub-studies in a meta-analysis
L	Liter
LBW	Low Birth Weight (<2,500 g)
LOD	Limit of Detection
MA	Mexican American
MEC	Mobile Exam Center
mg	Milligram
mL	Milliliter
MS	Mass Spectrometry
NAP	Naphthalene
NBNA	Neonatal Behavioral Neurological Assessment
NCHS	U.S. National Center for Health Statistics
NEPSY-II	A Developmental Neuropsychological Assessment, 2nd Edition
ng	Nanogram
NHANES	National Health and Nutrition Examination Survey
NHB	Non-Hispanic Black
NHW	Non-Hispanic White
NIEHS	U.S. National Institute of Environmental Health Sciences
NPL	U.S. National Priorities List
NRC	U.S. National Research Council
NTP	U.S. National Toxicology Program
OR	Odds Ratio
OSU	Oregon State University
p	*p*-value
PAH	Polycyclic Aromatic Hydrocarbon
PAH16	16 PAHs prioritized by the U.S. EPA
PHE, PHEN	Phenanthrene

LIST OF ABBREVIATIONS AND ACRONYMS (Continued)

PI	Ponderal Index (g/cm3)
PIR	Poverty-to-Income Ratio
POM	Polycyclic Organic Material
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTB	Preterm Birth (< 37 weeks gestation)
PYR	Pyrene
Q	Cochrane's Q, a statistic to measure between-study variation in a meta-analysis
r	Pearson's correlation coefficient
R2	R-squared; the proportion of variation explained by a statistical model
RCPM	Raven Colored Progressive Matrices
REML	Restricted Maximum Likelihood
RfD	Reference Dose
RoB	Risk of Bias
s2	s-squared; an index of variance of observed effects
SCQ	Social Communication Questionnaire
SDQ	Strengths and Difficulties Questionnaire
SES	Socio-Economic Status
SGA	Small for Gestational Age
T	Tau
T2	Tau-squared; an index of the variance of true effects in a meta-analysis
TRAP	Traffic-Related Air Pollution
U.S.	United States
uFLU	Urinary biomarker of Fluorene metabolism
ug	Microgram
uNAP	Urinary biomarker of Naphthalene metabolism
uPAH	Urinary biomarkers of PAH metabolism
uPHEN	Urinary biomarker of Phenanthrene metabolism
uPYR	Urinary biomarker of Pyrene metabolism
US EPA	United States Environmental Protection Agency
W	Weight
WHO	World Health Organization
WISC-IV	Weschler Intelligence Scale for Children-4th Edition
WISC-R	Weschler Intelligence Scale for Children-Revised
WJ-III	Woodcock-Johnson Tests of Achievement, 3rd Edition
WoE	Weight of Evidence
WPPSI-R	Weschler Preschool and Primary Scale of Intelligence
Y/N	Yes/No

Polycyclic Aromatic Hydrocarbons (PAH) Exposure Trends, and Evidence of Adverse Health Outcomes in Infants and Children from Prenatal/Early-Life PAH Exposure

Chapter 1 – INTRODUCTION

1.1 Theoretical Framework of Environmental Epidemiology

Environmental epidemiology, also referred to as environmental health, is the branch of public health that focuses on environmental exposures leading to adverse health effects in a population, and seeks to understand the causal relationship between these factors and human health [1]. The World Health Organization defines environmental health (p.18), as "the theory and practice of assessing and controlling factors in the environment that can potentially affect the health of present and future generations" [2]. Evaluating and controlling harmful exposures in a work setting is referred to as occupational health.

The fundamental assumption of all public health disciplines is that human disease does not happen by chance, and that identifying and controlling exposure to the cause of disease can reduce occurrence [3]. Therefore, the primary goal of public health is to prevent exposures at a level associated with adverse human health. Vaccines, prenatal care, and well-baby checks are clinical examples of primary public health prevention. In environmental epidemiology, primary prevention methods are the policies and procedures, based on scientific research, to reduce the dose, frequency, and duration of harmful exposures, such as noise, radiation, and toxic chemicals.

A recent report from WHO estimated that 23% of all deaths, and 26% of deaths in children under five years of age, are due to exposure to environmental factors that are preventable [4]. Harmful exposures tend to occur disproportionately in a population, with some groups more likely to be exposed than others [5]. In general, people living in low-income countries have the highest risk to harmful exposures, and thus, the greatest risk of disease [4]. The developing fetus, infants, and children are considered vulnerable subgroups [6,7]. Fetal development is a critical window of susceptibility to environmental stressors due to rapid cellular growth (division, migration and differentiation), and an underdeveloped detoxification metabolism and immune system [7–9]. Infants and young children are also more vulnerable to harmful environmental exposures, compared to adults, due to differences in inhalation rate and volume, metabolism, body weight, hand-to-mouth behavior, and other

factors [7,10,11]. Other vulnerable subgroups include racial/ethnic minorities [12–14], and those at a lower socio-economic status (SES) [15–17], who tend to live in sub-standard housing and/or near sources of environmental pollution, compared to the dominant racial/ethnic group, or those with more financial means [18–23]. In addition, workers, especially general labor engaged in hazardous occupations, such as transportation [24,25], manufacturing [26–29], food preparation and service [19,30,31], agriculture [32–35], and waste management [36,37], are more likely to encounter harmful exposures at elevated concentrations, duration, and frequency, relative to the general population.

Environmental (and occupational) epidemiologists seek to prevent adverse human health effects by quantifying exposures to environmental stressors in the places where humans live and work, to understand the causal relationship these stressors have on human health, and to recommend policies and procedures to reduce or eliminate exposure to stressors associated with adverse health effects [1]. This effort is not without its challenges. Not every harmful exposure leads to an adverse health condition [1]. Genetic variation in a population adds more complexity, as not every person who receives a relatively similar exposure will develop a similar health outcome, due to many factors, including detoxification metabolism differences based on genotype [6,38–42]. Quantifying an association between an environmental exposure and a human health effect is made even more difficult when the exposure occurs *in utero*. Humans are exposed to a wide range of environmental stressors daily, including chemical mixtures that can have synergistic adverse health effects [43–45], such as polycyclic aromatic hydrocarbons (PAHs), which are environmentally ubiquitous chemical mixtures associated with human disease.

1.2 Polycyclic Aromatic Hydrocarbons (PAHs) – An Overview

Polycyclic aromatic hydrocarbons (PAHs) are a complex mixture of organic compounds commonly found in the environment primarily from anthropogenic sources of combustion [46,47]. The United States Environmental Protection Agency (US EPA) defines PAHs as compounds with more than one aryl ring with a boiling point >100°C [48]. PAHs are generally found in the environment as either unsubstituted rings (parent PAHs), or as derivatives in which the rings are substituted with hydroxyl groups [46], nitrogen [49], sulfur [50], alkyl groups [51], quinones [50], or halogens [52]. A small number of PAHs are used to make

pharmaceuticals, dyes, plastics and pesticides [46,47]. Parent PAHs consisting of 2 to 4 fused benzene rings, such as Naphthalene (NAP), Acenaphthylene (ACY), Acenaphthene (ACE), Fluorene (FLU), Phenanthrene (PHEN), Anthracene (ANT), Fluoranthene (FLA), Pyrene (PYR), Benz[a]anthracene (BaA), and Chrysene (CHR), are low molecular weight (LMW) semi-volatile compounds predominantly detected in the vapor-phase and thus, more likely to be directly inhaled [47,53,54]. PAHs with five or more rings, such as Benzo[b, j, or k] fluoranthene (Bb/j/kF), Benzo[a]pyrene (BaP), Dibenz[a,h]anthracene (DahA), Benzo[ghi]perylene (BghiP), or Indeno[1,2,3-cd]pyrene (IcdP), are high molecular weight (HMW), less volatile PAHs that tend to adhere to particulate matter [55].

1.2.1 Sources of PAHs and Mechanisms of Formation

PAHs form from natural events (i.e., volcanic eruptions, crude oil seepage, forest fires and biological processes) and from anthropogenic activities, such as burning wood [56], and fossil fuels [7], industrial processes[48], smoking[57–60], certain types of food preparation and cooking methods [61–64], and waste incineration [46,47]. There are three major classes of PAHs. *Pyrogenic* PAHs form relatively quickly as a by-product of combustion of organic matter (the largest contributing source of environmental PAHs) [46,47,65,66]. *Petrogenic* PAHs form relatively slowly, as in the case of crude oil or coal formation, and enter the environment in several ways, including crude oil spills, underground tank leaks and from fugitive emissions or effluents of petroleum products used in transportation [47,65,66]. *Biological* PAHs form from plant and bacterial synthesis and vegetative decay (smallest contributing environmental source of PAHs) [47,65]. PAH mixture composition varies with the source and conditions of formation and environmental release, such as the temperature and oxygen level during combustion [46]. For example, soot (i.e., black carbon) is formed from the incomplete combustion of organic material, and is a mixture of PAHs, particulate matter (PM), and other combustion by-products [67].

1.2.2 PAHs in the Environment

In general, PAHs are stable, lipophilic (i.e., lipid soluble) compounds [68]. The lipophilicity of PAHs increases with the complexity of the compound; parent PAHs are generally not soluble in water [69,70]. As the molecular weight of parent PAHs increase, so does the octanol/water partition coefficient (K_{ow}), a measure of a chemical's ability to

dissolve in either water or organic solvents. As K_{ow} increases, water solubility decreases [70]. Substituted PAHs tend to have a higher water solubility than parent PAHs [71]. Primary fate and transport of PAHs in the environment is by photochemical transformation, adsorption onto PM, and by air dispersion and deposition into terrestrial and aquatic environments, where PAHs can accumulate in soil [72], sediments [73], food sources such as grains or aquatic organisms [46,47,74–79], and sources of drinking water [80–82]. PAHs decay faster from PM in atmospheric conditions that are humid, warm and sunny [83], and are found in higher concentration in the air, terrestrial, and aquatic environments near urban areas, where most sources of anthropogenic PAHs are generated, relative to rural areas [47,78,84,85].

1.2.3 Sources of Human Exposure to PAHs

Human exposure to PAHs usually occurs to PAH mixtures rather than individual PAH congeners. Because PAHs are lipid-soluble and exist in the environment in both the gas-phase and solid-phase, they can be absorbed through the skin, the respiratory tract, and the gastrointestinal tract. Routes of PAH exposure include inhalation and ingestion of vapor-phase PAHs in air, or solid-phase PAHs adsorbed onto PM, such as air pollution, cigarette smoke, or house dust [46,47,86]. Humans are also exposed to PAHs through food consumption (including breast milk) [46,87,88], occupational settings [89–91], and via placental transfer [88,92]. In addition, humans can be exposed to PAHs through the use of personal care products, such as coal tar-based ointments, used to treat skin conditions [93].

1.2.3.1 PAHs in Ambient Air

In the atmosphere, two-, three-, and four-ringed PAHs tend to partition in gas-phase, while five-, and six-ringed PAHs tend to partition in the solid-phase [84,74,94,95]. The molecular weight of PAHs is inverse to their vapor pressure. Low molecular weight PAHs, such as Naphthalene (NAP) with 2 fused rings, have the lowest vapor pressure, and Benzo[a]pyrene (BaP), a high molecular weight PAH with 5 rings, has the highest vapor pressure of the PAHs measured. LMW PAHs are more prevalent in ambient air, with NAP accounting for 82% of PAHs detected in U.S. (2011) [84]. In 1995, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, a Division of the U.S. Centers for Disease Control and Prevention, or CDC) estimated background levels of PAHs in U.S. ambient air at 0.02 - 1.2 ng/m^3 in rural areas, and 0.15 - 19.3 ng/m^3 in urban areas [46].

Padula, et al., measured both PAHs and PM in the Los Angeles County basin for approximately 9 months, and detected a median ambient PAH concentration of 3.6 ng/m^3, with an interquartile range (IQR) of 1.6 – 12.4 ng/m^3 [96]. The authors found that ambient PAHs concentrations positively correlated with ambient $PM_{2.5}$, PM_{10} (PM with a diameter of < 2.5, and <10 microns, respectively), and traffic density within 300 meters of a residence, with Pearson's correlation coefficients (*r*) of 0.53, 0.38, and 0.30, respectively [96]. These results, along with similar findings by Bostrőm, et al., (2002), and Rehwagen, et al., (2005), suggest that PAHs are present at higher concentrations in fine PM (e.g., $\leq PM_{2.5}$) compared to larger particles (e.g. $\geq PM_{10}$) [69,97,96]. Ambient PAH concentrations fluctuate by season, with residential heating as the main source of airborne PAHs in winter [98], and engine fuel consumption (motor vehicles & non-road engines) as the main source of airborne PAHs in summer [98,99]. Forest fires and non-U.S. sources of airborne PAHs, such as ship traffic offshore, and fossil-fuel based energy generation in Asia, can also increase summer levels of ambient PAHs levels [100,101]. PAHs are strongly correlated with traffic related air pollution (TRAP) [102]. LMW PAHs are more abundant in diesel fuel, while HMW PAHs are more abundant in gasoline [103].

1.2.3.2 PAHs in Indoor Air

PAHs are a common indoor pollutant and in general, most people, and especially children, spend a majority of their time indoors [75,104,105]. Indoor PAH concentrations tend to be higher than ambient levels, but depend on several factors, including the time of year[106–108], smoking in the home [83,106], furnishing materials [109,110], cooking fuel [111], ventilation while cooking [112,113], burning candles or incense [114], and the home heating source [107]. For example, a PAH exposure trend study in New York children by Jung, et al., (2014) found that, in spite of local policies to decrease TRAP that also led to decreased ambient PAH concentrations, urinary metabolites of Pyrene (PYR), a four-ringed PAH, actually increased in children during the heating season [115], suggesting policies to control PAH exposure in ambient air do not necessarily effect indoor air exposure. Gustafson, et al., (2008) found the median indoor benzo[a]pyrene (BaP) concentration in Swedish homes with wood combustion appliances was 0.52 ng/m^3, five times higher than the World Health Organization (WHO) guideline of 0.1 ng/m^3 (based on lifetime exposure to BaP and a 1/100,000 cancer risk) [108].

The ratio of indoor to outdoor PAH concentration also depends on molecular weight, as reported by Li, et al., (2005), who estimated the ratio of indoor to outdoor airborne PAHs in ten Chicago homes of non-smokers was between 0.5-1.0 (median values, units in ng/m^3 cancelled out in the ratio), controlling for season, age of home, and proximity to industry [116]. Indoor concentrations of PAHs increased with age of the home, while outdoor PAHs increased with proximity to major roads or sources of industrial pollution [116]. The authors also found that LMW PAHs were higher in indoor air, while HMW PAHs were higher in ambient air [116], which aligned with findings reported by Naumova, et al., (2002), and Choi, et al., (2008) who both measured personal, indoor, and outdoor PAHs in four U.S. cities and found higher LMW PAH concentration in indoor air, and higher HMW PAHs in outdoor air [106,107]. Naumova, et al., reported mean indoor PAH concentration range from June 1999 to May 2000 in three cities, Los Angeles, CA: 16-220 ng/m^3; Houston, TX: 21-310 ng/m^3; and Elizabeth, NJ: 22-350 ng/m^3 [106], values much higher than the ATSDR background estimate in ambient air.

In a review of 35 studies (1,545 samples), representing eight U.S. states and 13 countries, Ma and Harrad (2015) reported an average indoor PAH concentration of 1,124 ± 449 ng/m^3 [75]. Ma and Harrad did not include NAP in the average estimate because one-third of the studies used polyurethane foam (PUF) filters as sorbents, whereas NAP has an affinity for resin rather than PUF [75]. However, the authors reported that NAP accounted for approximately 50% of PAHs detected in indoor air samples [75]. The average indoor PAH concentration (1986-2009) in the eight U.S. states reported in Ma and Harrad, was 112 ± 30 ng/m^3, which is approximately 6 - 93 times greater than the high range ambient background level estimated by the ATSDR in 1995, indicating that indoor PAH concentrations can be much higher than ambient levels, and because of time-activity patterns, more likely to be inhaled. In a study of 375 Canadian pregnant women (97% non-smokers), Wheeler, et al., (2014) found a positive correlation between NAP detected in personal air sampling and in indoor air (Spearman's correlation coefficient, r = 0.83 to 0.91; $p < 0.001$), and between prenatal NAP urinary biomarkers and both personal air (r = 0.40; p = 0.003), and indoor air NAP concentrations (r = 0.46; p =0.0004) [117].

1.2.3.3 Occupational Exposures to PAHs

Occupational PAH exposure can occur in jobs involving food preparation [118], construction activities (i.e., roofing tar and asphalt application)[119], fossil fuel production and processing [26,120,121], transportation services (i.e., fuel filling, repair stations, toll-booths, traffic management) [25,122], fire-fighting [123], metal foundries or coke production [124], and waste incineration [125]. In 1989, the U.S. Occupational Safety and Health Administration (OSHA) established a permissible exposure limit (PEL), an enforceable exposure limit, at 0.2 mg/m^3, for the benzene-soluble fraction of coal tar pitch volatiles, and 5 mg/m^3 for mineral oil mist, both of which contain several PAH compounds, based on a 8-hour work day or a 40-hour work week, time-weighted average [126,127].

1.2.3.4 PAHs in Water

Due to their lipophilicity, parent PAHs are not considered a significant water contaminant. However, some substituted PAHs have the higher water solubility [70]. Presence of PAHs in water tends to come from soil leaching or from run-off [70]. Several U.S. studies have reported values of PAHs in drinking-water in the range 0.1–61.6 ng/l, although most of the values fell between 1 and 10 ng/l [70]. In 1995, the ATSDR estimated background levels of PAHs in drinking water were estimated at 4 – 24 ng/L[46]. The US EPA established a drinking water maximum contaminant level of 100-400 ng/L for PAHs known or suspected to cause cancer [128]. The European Union and WHO international standard is 200 ng/L [46].

1.2.3.5 PAHs in Food

For persons without occupational exposure, predominant routes of PAH exposure are generally from consuming foods containing PAHs [129]. Grilling, frying, or other heat-processing leads to PAH formation in meat and other foods, such as grains, tubers, coffee and teas [93,130–132]. Raw fruits and vegetables generally contain low levels of PAHs, but can be contaminated by airborne particle deposition or via contaminated soil [93] or water[133].

As lipophilic compounds, PAHs have been detected in breast milk. A review by Somogyi and Beck (1993) reported that a 1984 national survey by the Federal Republic of Germany detected a BaP concentration range of 5-15 ng/kg breast milk [134]. Pulkrabova, et al., (2016), found the range of PAHs in breast milk from women in the Czech Republic was

0.71 – 378 ng/g lipid weight, with LMW PAHS the most abundant PAHs detected, and with seasonal fluctuations (concentrations higher in winter) [135]. A review of ten studies by Drwal, et al., (2019) reported detection of 16 PAHs in breast milk, with Anthracene (ANT) NAP, and PYR having the highest concentrations, 67.9, 45, and 23.7 ng/g lipid, respectively [136].

In 1995, the ATSDR estimated background levels of PAHs in the typical U.S. diet were estimated to be less than 2ug/kg of food consumed, assuming adult exposure.[46] There currently is no regulatory threshold for PAHs in food in the U.S., but the European Union established regulatory thresholds for BaP in specific food stuffs, from 1.0 – 5.0 ug/kg wet weight , the lowest threshold set for infant formula, baby foods, and foods for medical purposes [137].

1.2.3.6 PAHs in House Dust

In a study characterizing PAH exposures by measuring PAHs in the house dust of 14 urban and 10 rural homes, Chuang, et al., (1995) reported the predominance of 4- and 5-ringed PAHs, with NAP the least abundant PAH detected [138]. The concentration range for seven carcinogenic PAHs of 13 – 160 ppm, and 10 – 300 ppm, in the non-heating, and heating season, respectively [138]. The authors estimated the difference in PAH exposure between adults and children under five years old, as well as the difference in the percentage of PAH exposure from route of exposure.[139] In both rural (1.54 ng/kg body weight/day) and urban settings (5.64 ng/kg/day), the average potential daily dose of carcinogenic PAHs in children under 5 years of age was over twice that estimated for adults, (0.52 and 2.67 ng/kg/day for rural and urban settings, respectively) for all sources of exposure.[139] In addition, children were more likely to be exposed via inhalation (73% of total PAH exposure) and less likely to be exposed from ingestion (26%), compared to adults (61% and 38% for inhalation and ingestion, respectively), indicating children may be more susceptible to dust-borne PAH exposure than adults.

1.2.3.7 PAHs in Fetal Tissue, Placental Tissue, and Cord Blood

Research shows that an individual's PAH exposure begins in the womb because PAHs can cross placenta and exposed the developing fetus, although most of the scientific evidence is based on animal studies [46]. In human epidemiologic studies, PAHs have been detected in fetal tissue, placental tissue, and umbilical cord blood. Hatch, et al., (1990) found

PAH-DNA adducts (described in the PAH Toxicity section) in 27% of livers and 42% of lung tissue samples from 15 spontaneously aborted fetuses of non-smoking women in New York [140]. Gladen, et al., (2000) reported a median PAH concentration (n = 200) of 7.36 ng/g placental tissue (dry weight) in Ukraine [141]. More recently, a review of ten studies (including Gladen, et al.) by Drwal, et al., (2019) reported the mean concentrations of 16 PAHs measured in placental tissue, and umbilical cord blood, with NAP, ANT, and PYR having the highest concentrations in placental tissue (34.5, 9.9, and 4.3 ng/g, respectively), and Fluoranthene (FLA), NAP, ANT, and PYR with the highest concentrations in umbilical cord blood (50.6, 50.0, 37.0, and 12.4, respectively) [136]. These results indicate that the developing fetus may not be protected from the adverse effects of PAH exposure by placental detoxification mechanisms.

1.2.4 PAHs: Human Metabolism, Excretion, and Biomarkers of Exposure

The measurement of parent PAHs and/or their metabolites in body fluids or tissues provides a way to assess an individual's internal dose [142]. Once inside the human body, PAHs are metabolized by enzymes that increase water solubility and facilitate excretion [143]. PAH metabolism is complex and occurs primarily in the liver, and to a lesser extent, in other tissues [46,144]. PAH elimination occurs via urine and feces, although urinary metabolites of PAH exposure (uPAHs) are the more common biomarker of PAH exposure. Some parent PAHs can produce more than one measurable urinary metabolite, and some parent PAHs are excreted unmetabolized [130,145,146]. The median half-life of uPAH detection is approximately 2-35 hours, depending on the PAH species, route of exposure and individual factors such as age, sex, body mass index (BMI), lifestyle (smoking, location of residence, etc.), and general health [121,130,143,148]. The relatively short half-life of uPAHs means that detection reflects only recent exposure. However, because PAHs are widely dispersed in the environment, a certain amount of constant PAH exposure can be assumed, with varying concentration levels over time and place. Inhaled LMW PAHs tend to be eliminated within a few days, but elimination of inhaled HMW PAHs absorbed onto particles can take several weeks due to particle retention in the respiratory tract , allowing for the accumulation of HMW PAHs over time [149]. It is important to note that detection of uPAH metabolites does not imply the presence of an adverse health effect [93].

Whether inhaled, ingested, or absorbed through the skin, PAHs and their metabolites are distributed by the blood to the tissues [46]. While PAH concentration in blood, including umbilical cord blood, is also used to assess PAH exposure, the kinetics of PAHs in human blood is not well characterized. One study that assessed the toxicokinetics of intravenously introduced pyrene tagged with a radioisotope ([^{14}C]PYR) observed a half-life in male Sprague-Hawley rat blood of approximately 4 hours (n = 24) [150]. Another study measured a BaP metabolite in the blood of male Sprague-Hawley rats and observed a mean half-life of 6.2 hours (n = 24) [151]. This limited evidence suggests that PAHs have a relatively short half-life in blood and can only indicate recent exposure, similar to urinary biomarkers. PAHs readily pass through cellular membranes due to their lipophilicity [46], and another biomarker of PAH exposure is PAH-DNA adducts, which are explained in more detail in the next section on PAH toxicity.

It is difficult to determine the extent of PAH exposure from PAH biomarkers outside of a controlled exposure experiment. In a study to determine PAH excretion rates after consuming a measured quantity of smoked salmon, Motorykin, et al., (2015) found the uPAH levels of nine non-smoking adult Native American participants did not reflect the PAH levels in the smoked salmon prior to consumption.[130] However Beyea, et al., (2006), found a decreasing trend in BaP levels in soil, and a decrease in PAH-DNA adducts in study participants, with increasing distance of residence from major roads, industrial sites and pavement [152]. Castano-Vinyals, et al., (2004) found that airborne BaP levels and urinary metabolites of PYR (1-hydroxypyrene) are well correlated, with Pearson's $r = 0.83$ (p=0.04) for BaP levels detected from personal air monitoring, and $r = 0.70$ (p=0.017) for BaP levels detected from stationary air monitors [153], suggesting that inhalation exposure of PAHs may produce better correlation with uPAH biomarkers, compared to ingestion.

1.2.5 PAH Toxicity and Human Health Effects from PAH Exposure

There are hundreds of PAHs and not all are considered hazardous to human health or have been assessed for human health effects [46]. Exposure to some PAHs have been linked to human disease, such as cancer [46,69,154–156], cardiovascular disease [157,158], decreased lung function [159], obesity [160,161], adverse reproductive outcomes [162,163], and adverse developmental effects [10,164]. The British physician, Sir Percivall Pott (1714-1788), first recorded the association between soot exposure and scrotal cancer in boys and young men occupied as

chimney sweeps, but it was not until 1922 that BaP exposure distilled from coal tar was associated with a carcinogenic effect [165,166]. Several PAHs have since been characterized for carcinogenicity, and thus far seven parent PAHs are considered carcinogenic (referred to as *c-PAHs*): BaA, BaP, BbF, BkF, CHR, DahA, and IcdP [46,154]. Some sources also add BjF to the c-PAH list [46,154].

The lipophilic, non-polar nature of parent PAHs can result in passive diffusion across cell membranes into the cytosol, where PAHs can be transported through the nuclear membrane, forming DNA adducts that can lead to genotoxicity [46,154]. PAH-DNA adducts form when certain PAHs, such as BaP, bind to the aryl hydrocarbon receptor (AhR), a cellular ligand-activated transcription factor, and part of the cytosolic core complex that initiates induction of cytochrome P450 enzymes, which have a central role in cellular detoxification [46,154,167]. The PAH-AhR ligand can then be transported across the nuclear membrane, where PAHs may be biotransformed into highly reactive diol epoxides that bind to DNA[168], causing kinks in the DNA strand [156], and potentially altering the genetic sequence during transcription [46,154,156].

The assay to quantify adducts specifically measures BaP-DNA adducts, which is used as a proxy for total PAH-DNA adducts because of a high correlation with other PAH congeners [169]. The estimated half-life of BaP-DNA adducts (henceforth referred to as PAH-DNA adducts) in leukocytes is 10-13 weeks [170], allowing a longer time-span to estimate PAH exposure [46]. Thus, PAH-DNA adducts measured in blood or tissue collected at the end of pregnancy, reflect prenatal PAH exposure from 27-30 weeks gestation (i.e., the beginning of the 3rd trimester). The ATSDR has stated that PAH-DNA adducts can be used as a biomarker to assess human exposure to combustion emissions [46].

1.2.5.1 PAH Exposure and Evidence of Effect on Human Development Outcomes

There are hundreds of scientific papers published on the carcinogenicity of several PAHs [171]. However, cancer is a disease that manifests primarily in adulthood [172]. and there is increasing epidemiological evidence that prenatal and early-life PAH exposure adversely affects human developmental outcomes [162,173–176]. PAH exposure mechanisms that lead to adverse developmental effects in humans have not been broadly studied, and the literature available is mostly experimental data from animal studies [177–180] or human cell cultures [181].

Perera, et al., (2012) describes several hypotheses regarding PAH mode of action on human development [182]. One hypothesis is that PAHs interfere with endocrine processes through AhR interaction [162,183–185]. Carpenter, et al., (2002) posited that PAH binding to the AhR may result in anti-estrogenic activity, disrupting the critically-timed cascade of endocrine processes necessary for normal fetal development [184]. Other hypotheses involve epigenetic alterations affecting gene expression [186], or oxidative stress in placental tissue decreasing available fetal oxygen and nutrition [164].

Because PAHs are environmentally ubiquitous and associated with adverse developmental effects, the developing fetus, infants, and children are especially vulnerable to PAH exposures. Developing organs are more susceptible to the adverse effects of PAH exposure. Dejmek, et al., (2000) noted a positive relationship between intrauterine growth retardation (IUGR) and exposure to airborne PAHs during pregnancy in over 5,000 women/infant dyads in the Czech Republic.[164] For each 10-ng increase of maternal airborne PAH exposure in the first gestational month of pregnancy, the adjusted odds ratio (AOR) of IUGR was 1.22 (95%CI: 1.07-1.39) [164]. IUGR refers to less than normal fetal growth for gestational age and is associated with fetal mortality and morbidity in childhood and later in life [187].

In 90 Polish mother/infant dyads, Perera, et al., (1998) found PAH-DNA adducts in umbilical cord leukocytes of 70 newborns were negatively associated with birth weight [188]. Newborns with PAH-DNA adducts above the median had difference of 147-grams birth weight, compared to newborns with PAH-DNA adducts below the median, after adjustment for confounding factors [189]. Low birth weight is associated with an increase in neurodevelopment problems, including lower cognition, attention and psychomotor functioning in children [190]. In a New York birth cohort of 40 children who underwent neuroimaging scans at 10-12 years of age, Peterson, et al., (2015), found a negative correlation between prenatal PAH exposure and the development of white matter in areas of the brain responsible for executive function, after adjustment for confounding factors [191]. In the same cohort, prenatal PAH exposure was positively associated with developmental delay at 3 years (n=183; OR 2.89; 95%CI: 1.33, 6.25) [88], negatively associated with verbal IQ at 5 years (n=249; β= -4.67; 95%CI: -7.73, -1.61)[192], and positively associated with symptoms of anxiety/depression (n=253; OR 4.59; 95%CI: 1.46, 14.27), after adjustment [182].

Other epidemiological studies found weak or null associations between early-life PAH exposure and developmental outcomes. Perera, et al., (2012) found no association between prenatal PAH exposure, measured via personal air monitors worn by pregnant women, and attention deficit/hyperactivity disorder (ADHD), (n=253; OR 2.30; 95%CI: 0.79, 6.70) [182]. In a cross-sectional study evaluating uPAH concentration in children and parental reporting of their child diagnosed with ADHD, a learning disability or the need for special education services, Abid, et al., (2014) found a positive correlation between uPAH metabolites and assignment to special education in U.S. male children, 6-15 years of age (n=608; OR 2.3; 95%CI: 1.2, 4.1), but not in female children (n=649; OR 1.8; 95%CI: 0.6, 5.4), after adjustment [193].

As stated previously, quantifying the biological effect of an environmental toxicant is difficult when the exposure is a chemical mixture that occurs *in utero* or early-life, and this complexity can lead to conflicting results when studies assess the effect of prenatal PAH exposure in different populations. For example, Wilhelm, et al., (2011) reported a positive association between prenatal NAP, BaP, and Benzo[ghi]perylene (BghiP) exposure and preterm birth (OR, 95%CI: 1.29, 1.14-1.45; 1.13, 1.02-1.25; and 1.34, 1.17-1.52, respectively) in a spatio-temporal study that modeled airborne PAH exposure in Los Angeles County, CA over the entire pregnancy (n = 112,203). Padula et al., (2014) utilized a similar spatio-temporal model to evaluate prenatal PAH exposure in Fresno, CA, and reported increasing odds of preterm birth, and reported a positive association between prenatal PAH exposure and preterm birth at 28-31 weeks preterm, but not at 34-36 weeks, 32-33 weeks, or 20-27 weeks [96]. Willis & Hystad (2018) also utilized a spatio-temporal model to evaluate prenatal exposure to hazardous air pollutants (HAPs) including PAHs in Portland (Oregon), but did not find a significant association between prenatal PAH exposure in ambient air and preterm birth, or small for gestational age [194].

It is clear there are gaps in our understanding regarding the developmental effects from PAH exposure, relative to what is known about cancer. For instance, although LMW PAHs account for more than 90% of the estimated PAH concentration in ambient air (U.S, data, 1990-2014) [84], only BaP has been characterized by the US EPA for adverse effects on fetal development, based primarily on animal studies (discussed in more detail in the *Regulatory Measures* section below) [195]. While there are public health programs in place to

track PAH exposure in the U.S. general population, as well as U.S. policy actions to regulate industrial releases of PAHs into the environment, the primary impetus for these actions has been to mitigate cancer occurrence associated with PAH exposure, and not protecting pregnant women, infants, and children from PAH exposures at concentration levels associated with adverse human developmental outcomes. More research is needed to gain a clear understanding regarding PAH exposure and human development, which could lead to more effective surveillance and control measures to reduce PAH exposure, especially in vulnerable populations.

1.2.6 PAHs: Public Health Concerns, Surveillance, and Policy Actions.

Public health concerns regarding the health effects from PAH exposure prompted the U.S. CDC to add a biomarker profile (urine) for PAH metabolites to the National Health and Nutrition Examination Survey (NHANES), to better understand the extent of PAH exposure in the U.S. population. NHANES uses a complex, multistage probability cluster design to generate a nationally-representative cross-sectional sample of the non-institutionalized civilian population, to assess the health and nutrition status of adults and children living in the U.S [196]. Since 1999, the CDC has administered NHANES as a biennial survey from up to 15 different U.S counties per year (each 2-year NHANES cycle, $n \approx 10{,}000$) [197]. The multi-stage survey design randomly chooses counties, then segments of counties, then households, and finally a study participant within the household to take part in several questionnaires and a physical exam [198]. Under-represented populations are oversampled [196]. Parents take part in the questionnaires when children are randomly selected to be the study participant [198]. NHANES processes, protocols and design are reviewed and approved by the Ethics Review Board of the National Center for Health Statistics [196]. Parental permission is obtained for minors <18 years of age, and consent is obtained for all adults [199].

Approximately one-third of NHANES exam participants also provide biospecimen samples for analysis of nutrients, health indicators and environmental pollutants [196]. In the 1999-2000 cycle, only one PAH, 3-fluoranthene, was included in the uPAH biomarker analysis. Starting in 2001-2002, 3-fluoranthene was dropped and urinary metabolites of NAP, FLU, PHEN, and PYR were added the uPAH analysis panel [196]. In 2013-2014, metabolites of phenanthrene were combined into a single measurement [196].

The US EPA oversees a network of stationary air monitors across the U.S. and its territories that regularly monitor hazardous air pollutants in ambient air [200]. These include 16 PAHs, which include the c-PAHs, are commonly referred to as the *EPA 16-PAHs* (listed in alphabetical order): ACE, ACY, ANT, BaA, BaP, BbF, BghiP, BkF, CHR, DahA, FLU, FLA, IcdP, NAP, PHE, and PYR [48]. The EPA 16-PAHs are part of a 1976 priority pollutant list established under the U.S. Clean Water Act, based on the criteria of 1) prevalence and persistence in the environment; 2) reference standards commercially available for chemical analysis; and 3) potential toxicity to humans and the environment [201].

1.2.6.1 Regulatory Measures to Assess and Control PAH Exposure

In the U.S., there are several policies in force to control PAH exposure. The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980, also known as "Superfund", created the ATSDR, which operates within the CDC [202]. The ATSDR is responsible for "investigating emerging environmental health threats in the U.S. and conducting research on the health impacts of hazardous waste sites" [203]. CERCLA also directed the US EPA to develop a National Priorities List (NPL) of hazardous waste sites in the U.S. eligible for clean-up action under the Superfund program, and to identify human health risks of contaminants at NPL waste sites [202]. The Superfund Amendments and Reauthorization Act (SARA) of 1986 strengthened CERCLA's enforcement provisions and increased focus on human health problems posed by exposure to chemicals at hazardous waste sites [204]. Of the 1,408 NPL sites in 2015, PAHs were found at over 600 sites [205]. In 1995, the ATSDR published the toxicological profile for 17 PAHs (the EPA 16-PAHs plus NAP), based primarily on animal data and a small number of epidemiologic studies [46].

Under the Clean Air Act Amendments (CAAA, 1990), the US EPA is directed to regulate PAHs as HAPs and regulate PAH emissions, primarily to reduce the incidence of cancer [206]. The US EPA was directed to develop and publish a list of PAH source categories by November 15, 1995 that accounted for 90% of aggregate PAH emissions in the U.S., as well as develop National Emission Standards for Hazardous Air Pollutants (NESHAP) for source categories (mainly industrial sources) to control PAH emissions by November 15, 2000 [206]. The EPA16-PAHs are listed on the U.S. national emissions factors to estimate polycyclic organic matter (POM) emissions under the 1990 Clean Air Act Amendments [48].

Under the Clean Water Act (1972), the US EPA developed water quality criteria for PAHs in 1980, set at 0.2 ng/L to reduce the potential of carcinogenic effects [70]. In 2000, the US EPA published maximum contaminant levels (MCLs) for 12 PAHs, ranging from 0.1ug/L-0.4ug/L of drinking water [207].

The US EPA established reference doses for BaP for neurobehavioral effects (oral exposure) and fetal survival (inhalation exposure), based on animal data [208]. A reference dose is "an estimate of the daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime …" [209], and used as a benchmark dose for risk assessment. The oral reference dose (RfD-oral) for BaP is 0.3 ug/kg of body weight/day [210]. The inhalation reference concentration (RfC-inhalation) is 2 ng/m^3[210]. The US EPA confidence level in both the RfD and the RfC is low to medium, due to the lack of epidemiological evidence and because a no observed adverse effect level (NOAEL) was not identified.

In a long-term health risk study, Liu, et al., (2017), summarized average daily concentrations of several PAHs in U.S. ambient air (1990-2014) and reported the mean BaP concentration at 0.35 and 0.32 ng/m^3 at urban and rural monitoring sites, respectively [115]. This indicates BAP concentrations in U.S. ambient air were five times below the US EPA RfD-inhalation for fetal survival, although this does not take in account BaP exposure from indoor air, dietary, or occupational sources of exposure. In addition, as stated earlier, people are usually exposed to PAH mixtures, and the US EPA does not have an RfD or an RfC for total PAH exposure.

1.3 Human Subjects and Institutional Review Board (IRB) Protocol.

This study did not work directly with study participants or study principal investigators, so an oversight determination of the IRB office at Oregon State University was not required, in accordance with 45 CFR 46.

1.4 Specific Aims

The goal of this research is to examine PAH exposure trends in the U.S., with specific consideration of PAH exposure trends in children, women of reproductive age, and racial/ethnic minorities; and to assess the weight of human evidence regarding prenatal and early-life PAH exposure on specific developmental endpoints in infants and children by

summarizing the available epidemiologic research. This goal was completed in three separate studies presented in the next three chapters. The first study evaluated the 14-year PAH exposure trends in the non-smoking U.S. population, using data from NHANES. The second study summarized the available epidemiologic evidence regarding prenatal PAH exposure and selected birth outcomes. The third study summarized the available epidemiologic evidence regarding prenatal and early-life PAH exposure and selected neurodevelopment outcomes in children. The specific aims and hypotheses of this research are outlined below.

Specific Aim 1a: Evaluate the fourteen-year temporal trend (2001-2014) of uPAH concentrations in the U.S. population using data collected by the National Health and Nutrition Examination Survey (NHANES), for survey years 2001-2002 through 2013-2014.
Hypothesis 1.1: Compared to uPAH concentrations in the 2001-2002 NHANES cycle, uPAH concentrations are expected to be lower in the U.S. general population over time after adjusting for urinary dilution and potential confounders (e.g., smoking status, diet, SES, and season of exam).

Specific Aim 1b: Estimate and compare if age, sex, and race/ethnicity modify the fourteen-year temporal trend of the geometric mean uPAH concentrations in the U.S. population using data collected by NHANES.
Hypothesis 1.2: Compared to adults 18 years old and older, children 6-17 years of age are expected to have lower uPAH concentrations over time, after adjusting for urinary dilution and potential confounders.
Hypothesis 1.3: Compared to men 18-49 years old, women of the same age range (i.e., reproductive age) are expected to have lower uPAH over time after adjusting for urinary dilution and potential confounders.
Hypothesis 1.4: Compared to non-Hispanic Blacks, Hispanics, and Asian/Other racial/ethnic (R/E) groups, non-Hispanic Whites are expected to have lower uPAH concentrations over time, after adjusting for urinary dilution and potential confounders.

Specific Aim 2: Conduct a systematic review and meta-analysis of eligible peer-reviewed scientific literature (i.e., primary studies) to evaluate the epidemiological weight-of-evidence

(i.e., the summary effect) regarding the association between prenatal measures of PAH exposure and birth outcomes in infants, (e.g., birth weight, preterm birth, head circumference, etc.). Measures of prenatal PAH exposure include air monitoring, emissions data, or questionnaire data collected during pregnancy; and biomarkers collected before, or shortly after the end of pregnancy (e.g., maternal blood or urine during pregnancy; fetal blood, urine; umbilical cord blood, etc.). The term *summary effect* is used in meta-analysis to describe the summation of the measures of association across primary studies.

Hypothesis 2.1: Higher prenatal PAH measures of exposure will be associated with adverse birth outcomes, after adjusting for potential confounders.

Specific Aim 3: Conduct a systematic review and meta-analysis of eligible peer-reviewed scientific literature to evaluate the epidemiological weight of evidence regarding prenatal and early-life PAH exposure and neurodevelopment outcomes in children (e.g., cognitive function, motor function, behavior problems, etc.). Measures of prenatal and early-life PAH exposure considered include air monitoring data, other modeled data, and biomarkers collected during or shortly after end of pregnancy, or during childhood and at least 6 months prior to the completion of the neurodevelopment assessment.

Hypothesis 3.1: Higher prenatal and/or early-life PAH measures of exposure will be associated with an adverse neurodevelopment outcomes in children, after adjusting for potential confounders.

This research produced three manuscripts, presented in the following chapters, with the goal of submitting all the manuscripts to scientific journals for publication. Thus far, the first manuscript was accepted for publication in the August 2021 issue of Chemosphere. Submission of the second and third manuscripts is pending completion of this dissertation.

1.5 Systematic Review and Meta-Analysis Methods – An Overview

As both specific aim 2 and 3 employ systematic review and meta-analysis methods to identify and summarize the weight of epidemiological evidence of prenatal/early-life PAH exposure and birth outcomes, and neurodevelopment outcomes respectively, this section is provided as an overview of these methods used to accomplish both specific aims, to reduce

redundancy for the reader, Appendix E provides the equations mentioned below and used in both Aim 2 and Aim 3 meta-analyses.

A familiar adage in science is that we are overfed information, but starved for insight. Scientists must contend with an overload of unfiltered information and lack of open access to information relevant to a particular research field [211]. Since the U.S. National Library of Medicine began indexing biomedical literature in 1865, the catalog has grown from 1,600 to over ten million [211]. In response to an immense amount of conflicting results in drug development research, the U.S. Food and Drug Administration created a regulatory framework in 1962 that required proof of efficacy before being considered for review by the agency [211]. This led to adoption of similar rules in other countries, as well as at other U.S. health-related agencies, establishing requirements for more reliable evidence being sought by policy-makers [211]. In 1972, Dr. Archie Cochrane published a seminal book with recommendations to obtain better evidence in biomedical research, which became the basis for the Cochrane Collaboration, and the Cochrane Database of Systematic Reviews, a globally-recognized digital repository of highly-structured critical summaries on randomized control trial (RCT) studies meeting *a priori* eligibility criteria [212]. Where appropriate and possible, some systematic reviews also attempted to calculate a statistical summary, or *summary effect*, from included studies, by calculating an odds ratio for each study, then pooling the results to get an overall effect estimate [212]. This approach of using statistical methods to summarize the results of independent studies became known as a meta-analysis.

A meta-analysis can provide more precise estimates of the health effects than those derived from individual studies included within a review [211–214]. They also facilitate investigations of the consistency of evidence across studies, and the exploration of differences across studies, known as between-study variance, or heterogeneity [211].

1.5.1 Meta-Analysis: Using a Random Effects versus a Fixed Effects Model

A fixed effects model is appropriate for a meta-analysis on studies on the same population, i.e., testing a group of the same students at different grade levels [215]. All tests share the same true effect size because they tested the same students. A random effects model is appropriate if a meta-analysis includes different populations that have enough in common to synthesize summary information, but there is no assumption of a common

underlying effect size. The assumption in random effects models is that the underlying true effects are normally distributed [215]. A random effects model assigns more balanced weights to studies so that large studies lose influence, while small studies with extreme values gain influence on the summary effect [215]. This is explained in more detail in the next section.

The purpose of a meta-analysis in environmental epidemiology is to summarize the effect of an environmental exposure on a health outcome reported in eligible primary studies. This rarely involves studies on the same population, so in most instances, the appropriate model to use in an environmental health meta-analysis is the random effects model.

1.5.2 Statistics in a Meta-Analysis Using a Random Effects Model

A meta-analysis synthesizes the weight of scientific evidence by estimating the true mean effect size and the distribution of true effects in the underlying population [216]. Simply put, this is done by sampling primary studies from the universe of relevant research, calculating the summary effect from the primary studies that met *a priori* eligibility criteria, and were included in the meta-analysis, and drawing conclusions regarding the pattern of effects [215]. To calculate the most precise summary effect, primary studies are weighted by the inverse of their variance. Larger studies tend to have better precision and smaller variance, so they are weighted higher than studies with larger variance [215].

The true mean effect size, μ, in the underlying population is estimated with two statistics: the summary effect, *M*, and tau-squared (T^2) [215]. Tau-squared estimates τ^2, the variance in true effects, (i.e., the true *between-study* variance) in the universe of populations from which a meta-analysis sampled [215]. In a primary study, the variance of observed effects (i.e., *within-study* variance, or random sampling error, s^2), is used to quantify the distribution of effects by calculating how much the effect of each observation varies about the mean. The mean of observed effects is assumed to be the same as the mean of the underlying population (i.e., true effects) 95% of the time when $\alpha = 0.05$. However, a meta-analysis distinguishes between the variance of observed effects (s^2) and the variance of true effects (T^2), and uses statistics unique to meta-analysis to quantify each variance, and to evaluate the relationship between the two [215]. It is common practice to use the Dersimonian and Laird (D-L) *method of moments* approach to calculate T^2, by subtracting the degrees of freedom (*df*, i.e., the

number of studies included in the meta-analysis, *k*, minus one), from *Q*, the observed weighted sum of squares (WSS) on a standardized scale [216,215].

Another common meta-analysis statistic is I-squared (I^2). I-squared is a descriptive statistic analogous to a signal-to-noise ratio that estimates the proportion of observed variation ($T^2 + s^2$) explained by the variance in the true effects, T^2. I-squared reflects how much of the between-study variation is estimated to be real, rather than from sampling error, but it does not indicate how much between-study variation exists, with the exception of when I^2 equals zero, in which case, T^2 also equals zero [215].

1.5.1.1 Summary Effects in Meta-Analysis

The summary effect is the estimate of the magnitude and direction of the mean of the relevant effects in primary studies, and is estimated as the weighted mean, divided by the sum of the weights. The hypothesis that the true mean effect size equals zero is tested by calculating a *z*-score, i.e., dividing the summary effect by the standard error, $\alpha = 0.05$. For $p < 0.05$, there is statistical evidence that true mean effect size does not equal zero. If there is a low level of precision in the estimate, i.e., a wide confidence interval, the summary distribution of effects may be more informative than the summary effect point estimate [215]. In the meta-analyses for Aims 2 and 3, the summary effect is calculated as an Odds Ratio (OR) for dichotomous outcomes, and as the standardized mean difference (Cohen's *d*) for continuous outcomes, with 95% confidence interval (95%CI) as the measure of precision for both outcomes.

1.5.1.1 Meta-Regression

Meta-regression is a statistical application that can help identify influential covariates, and explain the source of between-study variance in a meta-analysis. Meta-regression is similar to linear regression applied to a primary study, in that the goals are to 1) identify if a relationship exists between a predictor and outcome variable; 2) quantify the relationship if one exists; and 3) attempt to explain the variance between observed and predicted effects. Regression coefficients describe how the observed outcome changes with a unit increase in each covariate in the model, holding other covariates constant. However, in meta-regression, the observed effect is differentiated from the true effect in the underlying population [215].

There are four tests utilized to assess a meta-regression model [215]. The first tests the null hypothesis that the true value of the summary effect coefficient equals zero, ($\alpha = 0.05$). The second test addresses the question: *do any of the covariates in the model explain <u>any</u> of the variation in the summary effect?*, and tests the hypothesis that each covariate in the model does not change the coefficient of the summary effect, holding other covariates constant. The hypothesis is tested by either the confidence interval of the coefficient, or by a *z*-score (dividing the coefficient by the standard error) and its corresponding *p*-value ($\alpha = 0.05$). A confidence interval does not contain 0, or if $p < \alpha$, provides evidence the true summary effect coefficient value is greater than zero [215].

The third test is a goodness of fit test that addresses the question: *do the covariates in the model explain <u>all</u> of the variation in the summary effect?*, and tests the hypothesis that unexplained variance equals zero, i.e., the true mean effect of each primary study falls exactly on the regression line, and any variation is due to within-study error (a certain amount of variance due to sampling error in each primary study is expected). This hypothesis is tested with a *Q*-statistic, a *df* of $P - 1$ (where P is the number of covariates in the model, including the intercept), and a *p*-value ($\alpha = 0.05$). In this test, if $p < \alpha$, there is evidence that a change in at least one covariate is associated with a change in the summary effect [215]. Statistics from this test are also used to calculate T^2 and I^2.

The last test is a comparison of the model to the null model (the intercept-only model) to measure between-study heterogeneity, as well as R^2, which is a similar statistics to that reported in a linear regression analysis of a primary study. In meta-regression, R^2 is the proportion of T^2 explained by the covariate model when compared to the intercept-only model [215]. The R^2 statistic is the percentage of variation explained by the model, and how much residual (i.e., excess) variance remains. A *Q*-statistic and degrees of freedom, $k - P - 1$, are used to calculate T^2 in this test, and it is convention to set $\alpha = 0.10$. If $p < 0.10$, there is evidence that the covariates in the model do not explain all the observed between-study variance. Setting $\alpha=0.10$ increases the risk of a Type I error (false positive), but reduces the risk that a non-significant result will be interpreted as evidence of homogeneity [217]. Of more utility than simply testing for the presence of heterogeneity is determining the extent that between-study variance may affect the conclusions drawn from meta-analysis results [215,217].

The restricted maximum likelihood (REML) method is recommended as the heterogeneity variance estimator over the D-L method to calculate T^2 [218,219]. Simulated scenarios conducted by Langan et al., (2019) found the D-L method was negatively biased in scenarios with small study sizes, and with rare binary outcomes [219]. The REML method has relatively low bias and low mean squared error in studies with both small (n < 30) and large (n > 1,000) sample sizes [219].

1.5.1.2 Quantifying Heterogeneity

Heterogeneity is expected in a meta-analysis, especially for observational studies, as it brings together diverse studies in terms of study design, sample populations, exposure characterization, analytical methods, time period, and other important aspects [216]. Restricting a meta-analysis to only studies with low heterogeneity could result in the exclusion of relevant studies, defeating the purpose of a weight of evidence assessment. The presence of heterogeneity in an environmental health meta-analysis is informative; it identifies the distribution of effects in different sample populations and as such, is important to quantify, as it may influence what can be said about the generalizability of the meta-analysis results [213].

When $Q < df$, T^2 equals zero and all observed variation in the exposure-outcome analysis is assumed to be from random sampling error, s^2 [215]. When $Q > df$, there is excess variation, i.e., evidence of between-study variance, and this needs further evaluation through meta-regression to identify the source and magnitude of the variation. To quantify estimated heterogeneity, we used the prediction interval, which is ± two standard deviations (*Tau*) about the summary effect, *M*. The prediction interval reflects how the effects in primary studies are distributed about the summary effect, and addresses the question pertaining to heterogeneity in a meta-analysis, *how much do we expect the true mean effect size to vary in the underlying population*? [215].

Chapter 2 – FIRST MANUSCRIPT

Trends in Urinary Metabolites of Polycyclic Aromatic Hydrocarbons (PAHs) in the Non-Smoking U.S. Population, NHANES 2001-2014

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2.1 Abstract

Recent studies indicate airborne PAH levels have decreased in the U.S., but it is unclear if this has resulted in PAH exposure changes in the U.S. population.

Objective: Examine temporal trends in urinary metabolites of Naphthalene, Fluorene, Phenanthrene, and Pyrene in U.S. non-smokers, 6+ years old.

Methods: We used biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) program, 2001-2014, (N=11,053) using survey weighted linear regression. Models were adjusted for age, sex, race/ethnicity, creatinine, BMI, income, diet, and seasonality. Stratified models evaluated the effect of age, sex, and race/ethnicity on trends.

Results: Between 2001-2014, Naphthalene exposure increased 36% ($p<0.01$); Pyrene exposure increased 106% ($p <0.01$); Fluorene and Phenanthrene exposure decreased 55% ($p <0.01$), and 37% ($p<0.01$), respectively. Naphthalene was the most abundant urinary PAH, 20-fold higher than Fluorene and Phenanthrene, and over 50-fold higher than Pyrene compared to reference groups, effect modification was observed by age (Naphthalene, Pyrene), sex (Fluorene, Pyrene), and race/ethnicity (Naphthalene, Fluorene, Phenanthrene, Pyrene).

Significance: This study shows exposure to Naphthalene and Pyrene increased, while exposure to Fluorene and Phenanthrene decreased among the non-smoking U.S. general population between 2001-2014, suggesting environmental sources of PAHs have changed over the time period.

2.2 Introduction

Polycyclic aromatic hydrocarbons (PAHs) are organic compounds commonly found as complex mixtures in the environment[46]. PAHs form by incomplete combustion of organic materials. This can be from natural events such as wildfires, and from anthropogenic activities, such as burning wood and fossil fuels [46], industrial processes [48], smoking [46], food preparation methods such as smoking and grilling [46], and waste incineration [46]. PAH composition varies by source and environmental release conditions, such as temperature and oxygen level during combustion [46]. PAHs enter the body through inhalation, ingestion, dermal absorption, and placental transfer [46]. Once inside the body, PAHs are metabolized by the liver and excreted in urine and feces with an average half-life in the human body of <30-hours [130,220]. Most PAHs excreted in urine are the more soluble hydroxylated metabolites, although some unmetabolized PAHs are also detectable [130]. Due to the short PAH metabolite half-life and ability to be collected non-invasively, urinary samples are appropriate biomarkers of recent exposure and are often used for biomonitoring studies [221]. Biomonitoring studies in the U.S. show that nearly 100% of the general population have detectable levels of urinary PAH metabolites (uPAHs) [221]. The urinary metabolite of PYR, 1-hydroxypyrene, is often used as a surrogate urinary biomarker for all PAH exposure in human studies [222]. While more cost-effective and time-efficient, only measuring 1-hydroxypyrene does not capture exposure to more prevalent PAHs, such as NAP, which represents over 50% and 80% of the total airborne PAH concentration in indoor air [75] and outdoor air [115], respectively. Urinary biomarkers of exposure revealed NAP as the dominant uPAH in the U.S. population in 2001-2002 [223].

There are hundreds of different types of PAHs and several pose human health risks including increased risk of cancer [154], cardiovascular disease [157,224], respiratory illness [47], reproductive hormone disruption [163], and adverse developmental effects [193,225]. PAH toxicity and their widespread dispersion in the environment is a global health concern. In the U.S., public health surveillance actions and regulatory measures to monitor and control PAH exposure were initiated in the 1980s [48,126,226,227]. These efforts have documented that air pollution is a major source of PAH exposure and that regulatory actions have had an effect in reducing airborne PAH concentrations. An ambient air monitoring study in the Great Lakes region from 1996-2003 by Sun, et al. (2006) reported that FLU, PHEN, and PYR slightly

decreased [228] since the implementation of Clean Air Act Amendments (1990) that included the adoption of Tier 1 vehicle emission standards, cleaner fuels, higher fuel efficiency, and more stringent diesel engine emissions [229]. Another study by Liu et al. (2017) evaluated particle and gas-phase PAHs collected in ambient air by the U.S. Environmental Protection Agency (US EPA) from 1990-2014, and reported a general decreasing trend in PAH levels in ambient air except for NAP, which increased between 1990-2002 [84]. The authors showed traffic emissions were a major exposure source of NAP in ambient air [84], an observation that was also reported by Lu, et al. (2005), who found over half the NAP emissions in Southern California came from vehicle exhaust [230]. In another air monitoring study, Narváez, et al. (2008) used data from personal air monitors and stationary air monitoring sites in New York City to evaluate trends in traffic pollutant exposure in non-smoking pregnant women and found that overall, airborne PAHs declined from 1998-2006 [231]. The authors attributed the decrease in airborne PAH exposure to updates in the U.S. Clean Air Act (1970, as amended) requiring cleaner, lower emission diesel fuel, as well as local transit authority actions to increase the use of cleaner fuels in buses [231].

While these studies show evidence of decreasing PAH concentration in ambient air, it is unclear if these changes correspond to similar trends in the U.S. population. Therefore, we used National Health and Nutrition Examination Survey (NHANES) data to evaluate fourteen-years (2001-2014) of urinary NAP, FLU, PHEN and PYR metabolite concentrations among the non-smoking U.S. population. Our objective was to evaluate the trends in environmental PAH exposures at the population level by minimizing behavioral influences on these trends. Thus, we restricted our study to the non-smoking population because tobacco smoke contains high levels of PAHs. Additionally, we examined effect modification by age, sex, race/ethnicity, and reproductive age. Based on previous indoor and ambient air research [75,84,115,228,231,232], we hypothesized that uPAHs would decrease in the U.S. non-smoking population over this 14-year time period. We also hypothesized the trend in uPAH exposure would be lower in children compared to adults, lower in females compared to males overall and at reproductive age (18-49 years), and lower in Non-Hispanic Whites compared to other race/ethnicities.

2.3 Methods

2.3.1 Study Population

This analysis used seven NHANES cycles spanning 2001 to 2014. This publicly available data included 19,079 study participants aged 6+ years who were randomly selected to have their urine samples analyzed for uPAHs. NHANES is a complex, multi-stage survey design where the weighted sample is representative of the U.S. civilian non-institutionalized population [233]. NHANES data are collected by the National Center for Health Statistics (NCHS), which is part of the U.S. Centers for Disease Control and Prevention (CDC). All participants provided informed consent and the NCHS research ethics review board approved the study protocols.

Of the 19,079 participants eligible to provide urine samples, 782 were excluded because of missing uPAH data, 3 were excluded for missing urinary creatinine data, and 315 were excluded because they were diagnosed with weak or failing kidneys, or had undergone dialysis in the past year. Of the remaining 17,979 participants, 2,918 were excluded for missing: serum cotinine data (n=1,382); individual or family PIR data (n=1,267); and BMI data (n=505). There were 236 participants who had missing data for more than one of these covariates. Of the remaining 15,061 participants, 4,008 did not meet the inclusion criterion of being a non-smoker as determined by serum cotinine levels $\leq$1 ng/mL, leaving a final analytical sample size of 11,053 participants.

2.3.2 Exposure Assessment

Eight uPAH metabolites were included in this analysis and grouped by parent PAH[221] to create four uPAH measurements: NAP (1- and 2-hydroxyNAP, uNAP); FLU (2- and 3-hydroxyfluorene, uFLU); PHEN (1-, 2- and 3-hydroxyphenanthrene, uPHEN); and PYR (1-hydroxypyrene, uPYR). Sample collection and analysis are described in detail elsewhere [233]. Briefly, a spot urinary specimen was collected from participants at a Mobile Exam Center (MEC), stored at -20°C, then shipped to a CDC laboratory for analysis. The sample underwent enzymatic hydrolysis and solid-phase extraction, and analyzed using isotope dilution capillary gas chromatography combined with mass spectrometry [233]. The percentage of uPAH metabolite samples above the analytical limit of detection (LOD) was >96% with the exception of uPYR in NHANES cycle 2013-14, in which 71% of samples were above the LOD. Since the LOD for uPAH metabolites changed across NHANES cycles, we followed

the method applied by the CDC and assigned a value equivalent to the maximal LOD for each uPAH divided by the square root of two [226] for any uPAH below its respective LOD for uPAH metabolite data from NHANES cycles 2003-04 through 2013-14. We did not apply a maximal LOD imputation to uPAH metabolite data for the 2001-02 NHANES cycle as information regarding observations at/above or below the LOD was not publicly available. The LOD of each PAH metabolite, published in the Laboratory Procedure Manual for each NHANES cycle [234], is provided in Table A.1.

Urinary creatinine was measured by clinical analyzer [233]. The specified instrumentation for measuring creatinine changed within the sampling frame, but the LOD remained constant at 1 mg/mL, except for the 2013-2014 cycle when the LOD was lowered to 0.10 mg/dL [233]. We assigned the maximal LOD of 1 mg/ml for creatinine divided by the square root of two for samples below the LOD. Urinary creatinine was used as a separate, independent variable in regression analysis to adjust for urinary dilution [235].

2.3.3 Covariates

We conducted a literature review to identify potential confounders and covariates that were associated with uPAH exposure. These include smoking, age, sex, race/ethnicity, diet, BMI, household income, time of year NHANES exam occurred (i.e., seasonality), work characteristics, and housing characteristics. To examine changes in environmental PAH exposure over time that are independent of changes in behavioral exposures, our sample population inclusion criteria selected non-smokers, as determined by serum cotinine levels $\leq$ 1 ng/mL. Serum cotinine is a biomarker of tobacco smoke exposure and has a longer half-life (15–20 hours), compared to nicotine (0.5–3 hours) [236]. Detection and quantification methods for serum cotinine are described elsewhere [233]. The LOD for serum cotinine was 0.5 ng/mL across NHANES cycles of interest [233]. Observations below the LOD had been imputed by the CDC as the LOD divided by the square root of two. We adjusted for income and dietary sources of PAHs, and included covariates that can affect metabolism (age, sex, race/ethnicity, and BMI). We also used urinary creatinine concentration to adjust for urinary dilution, and adjusted for the time of year when participants took part in the NHANES medical exam.

Age in years was recoded as a categorical variable following guidance from NCHS for age group cutoffs [237]. We created five age categories: 6-17 years, 18-29 years, 30-49 years, 50-64 years, and 65+ years. To investigate the trend difference between children and adults, age was also recoded as a dichotomous variable, with children age 6-17 years, and adults age 18+ years. Sex was a binary variable (male and female). Race/ethnicity groups were recoded as Non-Hispanic White, Mexican American, Non-Hispanic Black, and Other Hispanic/Other/ Asian/Multi-Racial.

The amount of PAHs in foods can be affected by cooking or food processing methods [238]. The NHANES 24-hour dietary recall data, and individual food code and description files, were used to create a dietary PAH variable in which foods expected to be high in PAHs and consumed by each participant were identified, using a list of keywords such as "grilled", "smoked" or "cured" (Table A.1). Participants were categorized as either having consumed, or not consumed food expected to be high in PAHs.

Body mass index (BMI) was included as a covariate because PAH exposure is associated with childhood obesity [160,239]. BMI was categorized for children and teens using CDC established percentile ranges based on growth charts for age and sex [240]. Adult BMI was calculated as the ratio of weight in kilograms by height in meters squared, and using the cut-off values specified by the CDC [241]. For this study, child BMI for age percentiles were categorized as less than 85th percentile for "normal weight" (which included underweight due to small sample sizes), 85th-94th percentile for "overweight" and 95th or higher percentile for "obese." Adults were categorized using the BMI cut-off values of less than 25 for "normal weight", 25 to less than 30 for "overweight"; and $\geq$ 30 for "obese".

Household income was characterized using the poverty-to-income ratio (PIR). PIR is calculated by dividing annual household income by the poverty threshold for family size in the state of residence within a given year, based on federal guidelines [233]. For this study, PIR was recoded to a dichotomous variable, PIR < 2.00; PIR $\geq$ 2.00.

Seasonal fluctuations of airborne PAH compounds were expected because PAHs are more prevalent in ambient air during months when home heating is needed [84,242]. The NHANES data includes a variable designating a six-month window when a participant took part in the medical exam. This information was used to create a seasonality variable: November 1st through April 30th, and May 1st through October 31st.

2.3.4 Statistical Analysis

Survey design factors including sample weights, pseudo strata, and pseudo sampling units, were applied according to NHANES analytical guidelines [237]. Natural log-transformation was applied to the right-skewed uPAH and creatinine data. Survey weighted multiple linear regression models were constructed with each natural log-transformed uPAH as the outcome and NHANES cycle as the predictor.

Each model was adjusted for urinary creatinine, age, sex, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality. Sensitivity analyses included adjustments for work and housing characteristics, respectively. Models were used to yield estimated survey weighted and adjusted geometric mean (aGM) and 95%CI of uPAH metabolites grouped by parent compound for each NHANES cycle from 2001-2002 to 2013-2014, overall, and at the 25^{th}, 50^{th}, 75^{th} and 95^{th} percentile. Effect modification between NHANES cycle and: 1) age, 2) sex, 3) reproductive age (age 18-49 years), and 4) race/ethnicity was examined by including two-way interaction terms. Residual diagnostics were examined to assess the assumptions of multiple linear regression models. Data analysis was conducted in Stata, version 15.1 (StataCorp LLC, College Station, TX).

2.4 Results

The sample population's selected socio-demographic characteristics in each NHANES cycle, as well the characteristics of participants excluded from the final sample, are described in Tables 2.1 and A.3, respectively. The overall temporal trends in uPAH biomarkers adjusted for covariates are presented in Table 2.2. On average during 2001-2014, NAP was the most abundant uPAH with a weighted aGM (95%CI) of 5.65 ug/L (5.55, 5.74). This was 20 times higher than FLU (0.29 ug/L; 0.29, 0.30), and PHEN (0.29 ug/L; 0.28, 0.29), and 57 times higher than PYR (0.10 ug/L; 0.09, 0.10). The trends in uPAH biomarkers at the 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles are also in Table 2.2 and illustrated in Figure 2.1. The change in PYR concentrations between 2001-02 and 2013-14 are within the maximal LOD of 0.07 ug/L at the 25^{th} and 50^{th} percentile, indicating that there is no meaningful change in PYR exposure over this time period amongst the participants whose exposure is below the median.

From 2001-02 to 2013-14, NAP and PYR concentrations increased in the U.S. general non-smoking population, while FLU and PHEN concentrations decreased over the same time period. The average trend in NAP between 2001-02 and 2013-14, expressed as the absolute difference divided by the average, changed from an aGM of 4.19 ug/L (95%CI: 4.05, 4.33) to 6.04 ug/L (5.78, 6.30; $p < 0.01$), a 36% increase. PYR increased 106%, from an aGM of 0.04 ug/L (95% CI: 0.04, 0.05) to 0.13 ug/L (95% CI: 0.12, 0.13; $p < 0.01$). FLU decreased 55%, from an aGM of 0.37ug/L (95% CI: 0.36, 0.38) to 0.21 ug/L (95% CI: 0.20, 0.22; $p < 0.01$). PHEN decreased 37%, from aGM of 0.32ug/L (95% CI: 0.31, 0.34) to 0.22 ug/L (95% CI: 0.21, 0.23; $p < 0.01$). NAP and PYR had the largest percent change from the previous cycle in 2003-04, which were increases of 23% and 100%, respectively. The trends for FLU and PHEN fluctuated between 2001-02 and 2011-12, but were lower after 2011-12and had the largest percent change from the previous cycle in 2013-14, with decreases of 22% and 15%, respectively.

When respective uPAHs were grouped by percentiles, the greatest increase over time was observed amongst the highest exposures. Specifically, from 2001-01 to 2013-14, urinary biomarkers of NAP exposure increased by 18%, 28%, 42%, and 58% amongst the 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles, respectively. Whereas the trend for FLU was a 42%, 57%, 61%, and 62% decrease from 2001-02 to 2013-14, among the 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles, respectively. For PHEN, the trend was a 37%, 47%, 46% and 45% decrease from 2001-02 to 2013-14, among the 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles, respectively. For PYR, the trend was a 21%, 33%, 45% and 66% increase from 2001-02 to 2013-14, among the 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles, respectively. The stratified analyses are presented in Figures A.1-A.3, and in Table A.4.

2.4.1 Effect Modification by Race/Ethnicity

Overall, effect modification was observed between race/ethnicity and NAP and PYR, where Mexican American and Non-Hispanic Black participants had higher concentrations and a greater increase over time, compared to the reference group, Non-Hispanic Whites (NHW; p for trend: < 0.01; Figure A.3). The trend in NAP exposure was also higher in the Other/Multi-Racial group compared to NHW, except in 2003-04 ($p < 0.01$). Effect modification was also observed for FLU, where Non-Hispanic Black participants had a

higher concentration compared to NHW ($p < 0.01$) or any other race/ethnic group. Mexican American participants had higher FLU exposure compared to NHW, except in 2005-06 ($p = 0.01$). Effect modification was observed for PHEN, but only in Non-Hispanic Black participants ($p < 0.01$), who had higher exposure and greater increase over time compared to NHW.

When grouped by 25th, 50th, 75th and 95th percentiles, effect modification was observed between race/ethnicity and NAP, where Mexican Americans, Non-Hispanic Black, and Other/Multi-Racial participants had higher exposure and a greater increase over time, compared to NHW in all exposure percentiles ($p < 0.01$; Table A.5). The 25th, 50th, and 75th percentile of NAP in Mexican American and Non-Hispanic Black participants was comparable to the 50th, 75th, and 95th percentile in NHW, respectively. This indicates that Mexican Americans and Non-Hispanic Blacks had far higher NAP exposure, compared to NHW, over this time period (Figure 2.2). Effect modification was observed by race/ethnicity in FLU and PHEN at the 25th, 50th, 75th and 95th percentiles in Mexican American, Non-Hispanic Black, and Other/Multi-Racial participants, when compared to NHW ($p < 0.01$), except for the 25th percentile in Other/Multi-Racial participants ($p = 0.68$ and $p = 0.60$) for FLU and PHEN, respectively. Effect modification was also observed by race/ethnicity in PYR at 25th, 50th, 75th and 95th percentiles in Mexican American, Non-Hispanic Black, and Other/Multi-Racial participants, compared to NHW at all percentiles ($p < 0.01$). However, the change in PYR concentrations at the 25th and 50th percentiles were very small and within the analytical measurement error for this compound.

2.4.2 Effect Modification by Age

Overall, effect modification was observed between age and NAP where adults, age 18+ years, had higher concentrations and a greater increase over time from 2003-04 through 2005-06, compared to children ages 6-17 years. However, this trend disappeared after 2007-08, and children experienced the greatest increase in NAP exposure over time, compared to adults (p for trend: <0.01; Table A.4). Effect modification was observed for PYR, where children had higher concentrations and experienced a greater increase in PYR exposure over time, compared to adults (p for trend: <0.01), although the absolute trend difference was small and within the analytical measurement error for this compound. No effect modification by age was observed for FLU or PHEN.

When grouped by the 25th, 50th, 75th and 95th percentiles, effect modification was observed between age and NAP, where adults generally had higher exposure, compared to children ($p < 0.01$; Figure 2.3). However, at the 95th percentile, the trend in NAP change and children had the greatest increase in exposure. Although the absolute difference in PYR was small, from 2001-02 through 2013-14, the 95th percentile exposure trend tripled in both children and adults; from 0.11 ug/L, [95%CI: 0.10, 0.12] to 0.33 ug/L, [0.31, 0.36; $p < 0.01$], and from 0.08 ug/L, [0.07, 0.09] to 0.25 ug/L, [0.23, 0.27; $p < 0.01$], in children and adults, respectively.

2.4.3 Effect Modification by Sex

Overall, effect modification was observed between sex and FLU where males, age 6+ years, had higher concentrations compared to females ($p < 0.01$, Table A.4). Males also had higher concentrations of PYR, compared to females (p for trend: <0.01), although the absolute difference in the overall trend was small and within the analytical measurement error of uPYR. Overall, no effect modification by sex was observed for NAP or PHEN.

When grouped by 25th, 50th, 75th and 95th percentiles, effect modification was observed in FLU and PHEN exposure, where males had higher exposure, compared to females (p for trend: < 0.01; Figure 2.4). Effect modification was also observed by sex and NAP, where males had higher exposure in the 25th, 50th and 75th percentiles (p for trend: < 0.01), and in the 95th percentile until 2007-08, but this trend reversed, and females had higher NAP exposure between 2009-10 to 2013-14 (p for trend: < 0.01). Also, in 2011-12, the 95th percentile of NAP exposure was significantly higher in females (12.9 ug/L [12.1, 13.8]), compared to males (11.3 ug/L, [10.7, 12.0; $p < 0.05$]). For PYR, effect modification was observed in the 75th percentile, where males had higher exposure, and greater increase in exposure over time, compared to females (p for trend < 0.01). In the 95th percentile, males had higher PYR exposure until 2005-06, then females had higher PYR exposure, and greater increase in exposure through 2013-14, compared to males (p for trend < 0.01).

Overall, effect modification was observed between the sexes at reproductive age (age 18-49 years) and NAP, FLU, PHEN, and PYR ($p < 0.01$, respectively; Table A.4). Compared to men, women had lower NAP exposure from 2001-02 to 2003-04, and in 2007-08, but had higher exposure in 2005-06, after 2009-10 (p for trend: < 0.01). Women of

reproductive age had lower FLU, PHEN and PYR exposure trends, compared to men in the same age range, across NHANES cycles (*p* for trend: 0.01).

When grouped by the 25th, 50th, 75th and 95th percentiles, effect modification between the sexes at reproductive age and NAP, FLU, PHEN, and PYR was observed in all percentiles ($p < 0.01$; Figure 2.5). Compared to men age 18-49 years, women in the same age range generally had lower NAP exposure in the 50th and the 75th percentiles, except in 2005-06 and 2013-14 (*p* for trend: < 0.01). Women had higher NAP exposure in the 25th and 95th percentiles in 2005-06 and after 2007-08 (*p* for trend: < 0.01). Women of reproductive age also had a lower FLU exposure trend, compared to men, except in 2009-10 and 2013-14 in the 75th and 95th percentiles (p for trend: < 0.01). For PHEN, women of reproductive age had a higher exposure trend in the 75th percentile in 2009-10 and 2013-14 (p for trend: 0.01), and in the 95th percentile after 2007-08 (*p* for trend < 0.01). For PYR, women of reproductive age generally had lower exposure in the 25th and 50th percentiles (*p* for trend: < 0.01), but higher exposure in the 75th percentile in 2009-10 and 2013-14 (*p* for trend: < 0.01), and in the 95th percentile after 2005-06 (*p* for trend: < 0.01). These results suggest a trend of increasing PAH exposure at the higher exposure levels for non-smoking U.S. women of reproductive age.

Sensitivity analyses were performed among the subset of participants who had work-related and housing characteristics data, provided in Tables A.6 and A.7. The overall results from the sensitivity analyses were consistent with the main analyses.

2.5 Discussion

The widespread dispersion of PAHs in the environment and their toxic effects have made these compounds the focus for public health surveillance and regulatory action. Our trend analysis of the U.S. non-smoking population found that overall, when grouped by percentiles, and across age, sex and race/ethnicity groups, NAP and PYR exposure increased between 2001-2014, while FLU and PHEN exposure decreased. We also found significant differences in PAH exposure based on race/ethnicity. Our study showed that Non-Hispanic Black participants had higher NAP, FLU, PHEN and PYR exposure, and Mexican American participants had higher NAP, FLU, and PYR exposure, as well as greater increases in exposure over time, compared to Non-Hispanic Whites. Our results also showed a changing

trend in NAP exposure where children experienced a greater increase in exposure in more recent years, compared to adults.

Although we hypothesized that females would have lower PAH exposure, our findings revealed that the trend in NAP was highest in females 6+ years of age at the 95th percentile after 2005-06, compared to males. In addition, women 18-49 years generally had higher exposure to NAP and PYR at the 75th and 95th percentile, compared to men. This last finding is of particular interest because research shows PAHs can affect fertility [243] and can cross the placenta and can have adverse health effects in infants and children [244].

Our results are consistent with findings from previous studies examining PAH exposure in the U.S. Hendryx and Luo (2017) used NHANES data from 2003-2012 to evaluate the trend in uPAHs in U.S. children 6-19 years of age [245]. They found that the 2-naphthol, 2-hydroxy-phenanthrene, and 1-hydroxypyrene increased over the time period, while 1-naphthol and 3-hydroxyphenanthrene decreased [245]. We also saw increases in NAP and PYR in our study, but our analysis combined 1-, 2- and 3-hydroxyphenanthrene into a single biomarker since these urinary metabolites are derived from the same parent compound, uPHEN, which we observed a decrease from 2001-2014. We also observed that Mexican Americans and Non-Hispanic Blacks, and Other/Multi-Racial participants had higher overall NAP and PYR exposure, compared to Non-Hispanic Whites. Mexican Americans and Non-Hispanic Blacks also had higher FLU exposure, and Non-Hispanic Blacks had higher PHEN exposure, compared to Non-Hispanic Whites. Given the health effects of PAH exposures, it is important that future studies explore why non-smokers in these race/ethnicity groups have higher uPAHs.

In relation to previous studies that evaluated PAH exposure in the U.S. with urinary biomarkers, our findings show that NAP and PYR exposure is increasing, although the absolute differences are small. Hill, et al., (1995), utilized NHANES III (1988-1994, non-random sample data) data to examine pesticide residues in urine of adults 20-59 years of age, and reported creatinine-corrected 1-naphthol, and 2-naphthol mean concentrations of 15, and 5.4 ug/g, respectively [246]. However, the authors did not state if their analyses were adjusted for tobacco smoke exposure. Buckley, et al. (1997), reported that 18 non-smoking adults living near Brownsville, TX during the spring and summer of 1993, had a 1-naphthol, 2-naphthol, and 1-hydroxypyrene creatinine-corrected median concentration of 2.8, 2.6 ug/L

(both spring and summer), and 0.01 ug/L(spring) and 0.05 ug/L (summer), respectively. Compared to our study, these values equate to the uNAP concentration (aGM) we observed prior to 2005-06, and the uPYR concentration we observed prior to 2007-08. In the 1999-2000 NHANES cycle, the CDC reported creatinine-corrected geometric mean (95%CI) of uNAP was 1.96 ug/g (1.50, 2.45), uFLU: 0.57 ug/g (0.42, 0.77), uPHEN: (0.35 ug/g (0.29, 0.41), and uPYR: 0.07 ug/g (0.06, 0.09) [247]. The analyses were not adjusted for tobacco smoke exposure, and the age range for the 1999-2000 NHANES measure of uNAP was 6-59 years. Data for the PAH metabolites of interest for our study were not publicly available for the 1999-2000 NHANES cycle. These studies and reports suggest that human exposure to NAP may have decreased from the time of the Hill and Buckley studies, but has increased since 1999-2000. PYR exposure has also increased since Buckley, although the absolute difference is 0.04 ug/L, which is within the range of the maximal analytical measurement error of 0.07 ug/L FLU and PHEN exposure has decreased since 1999-2000 and the difference is above the analytical measurement error, but again, the absolute difference is small.

Our findings are similar to the trends observed in previously mentioned studies that evaluated PAH in ambient air in the U.S., suggesting that ambient air is an important source of PAH exposure for non-smokers [84,228,231]. By examining the difference in PAH ambient concentrations during the week compared to the weekend from 1990-2014, Liu, et al. found that a major contributor to temporal changes in NAP and PYR in urban ambient air was diesel engine exhaust [84]. This finding may be influenced by the different phase-in schedules to reduce vehicle emissions under the U.S. Clean Air Act Amendments of 1990. Light-duty engines that tend to use gasoline were in scope of the emission standard beginning in 1994, whereas the phase-in schedule for larger engines that tend to use diesel began in 2004 and will continue based on engine size through 2025 . In addition to PAHs, vehicle emissions, especially from diesel fuel, can produce $PM_{2.5}$, which suspends in ambient air [249]. More stringent U.S. federal $PM_{2.5}$ air quality standards since 1997 have helped reduce ambient $PM_{2.5}$ concentrations by 43% from 2000 to 2019 [250], and subsequently may have contributed to an overall decrease in PAHs in ambient air. The recent U.S. regulatory action to reduce mercury emissions from coal-fired power plants (i.e., the Mercury Air Toxics Standards or MATS, 2012) may also contribute to the observed PAHs decreases in ambient air.

Indoor environments are also likely to be an important source of PAH exposure for non-smokers. Naumova, et al. (2002) and Johnson, et al. (2010) found that PAHs were actually higher in indoor air in non-smoking homes than in outdoor air [106,251]. Shin, et al., (2013) modeled indoor and outdoor PAH emissions with uPAH biomarker data from the 2001-02 NHANES survey and found the estimated dose of NAP, FLU, PHEN, and PYR inferred from urinary biomarkers closely matched the *z*-scores of modeled indoor air inhalation [232]. PAHs in indoor can come from many sources. For instance, NAP is used to make polyvinyl chloride and high levels have been detected in vinyl- and foam-based home products [252]. Kang, et al., (2012) found that some vinyl home furnishings had higher NAP content than mothballs [252]. In addition, use of natural gas appliances and heating are major sources of PAHs in non-smoking homes [253].

House dust can be another source of PAH exposure in the indoor environment. Whitehead, et al., analyzed PAHs in the dust collected from California homes and found the median concentration of PHEN and PYR in 290 homes, 2001-2007, was 120 ng/g and 160 ng/g, respectively [254]. In a follow-up study in 2010, the authors found that median concentration of PHEN in 204 homes had decreased to 100 ng/g, but PYR concentration had increased to 190 ng/g [254]. A similar trend was seen in a New York birth cohort study that measured PAHs in indoor air, and uPAHs in children 3 years of age from 2001-2009 (n=409), and found the GM concentration of 1-napthol decreased by 44%, but 2-naphthol and PYR increased 162% and 46%, respectively [115 Supplementary Material]. Our findings are consistent with the results of these indoor air PAH trend studies.

Regulatory actions at the federal level tend to be more focused on reducing environmental toxics in ambient air, while building codes are meant to address indoor environmental factors, although these codes are not uniformly applied across the U.S. However, modern humans in the U.S. spend over 90% of their time indoors [255], and monitoring the indoor air environment is a public health challenge. Unlike ambient air, the indoor air environment is susceptible to several factors including ventilation, age of home, lifestyle choices (smoking, burning candles or incense, etc.), indoor combustion sources (e.g., stoves, furnaces, fireplaces, etc.), outgassing of structural building materials, and use of personal products. PAH exposure from indoor air is especially concerning for women and children, who tend to spend more time indoors compared to men [255].

The strength of this study lies in the high quality of NHANES procedures and laboratory analyses, the large sample size that supports a well powered analysis, the application of survey design variables that make the results generalizable to the U.S. non-smoking population, and the 14-year time period to evaluate PAH exposure trends. The limitations to this cross-sectional study design are that biomarkers cannot identify the source of exposure because they integrate personal exposures from all sources. The short half-life of PAHs mean that a spot urine sample only reflects recent exposures. Our analysis was limited to the PAH metabolite data made publicly available for analysis by the NCHS. In addition, data on work and housing characteristic data was not available for all NHANES cycles of interest, which limited our ability to control for these variables in our trend analysis.

2.6 Conclusion

This study illustrates that efforts to reduce PAH exposure have not had uniform effects among non-smoking U.S. residents, 2001-2014. Specifically, our findings that NAP and PYR exposure increased over the study period indicate control measures in the U.S. have fallen short, especially in reducing these exposures in children, females, people of reproductive age, and racial/ethnic minorities. Further research is needed to fully understand the sources of PAHs to allow for more effective ways of controlling exposure.

2.7 Acknowledgements

This research was partially funded by the National Institute of Environmental Health Sciences (P42 ES016465), the 2020-2021 American Association of University Women American Fellowship, and the 2019-2020 Warren & Frederica Schad Scholarship Fund. The authors would like to thank the College of Public Health and Human Sciences at Oregon State University (OSU), and acknowledge Dr. David Bernell in OSU College of Liberal Arts for his insights into environmental policies in the United States.

Table 2.1. Characteristics of the final sample population of 11,053[(a)] participants, 6+ years of age, by NHANES cycle. Values presented are unweighted sample size, n, and weighted percent (%).

	Total n (%)	**2001-02 n (%)**	**2003-04 n (%)**	**2005-06 n (%)**	**2007-08 n (%)**	**2009-10 n (%)**	**2011-12 n (%)**	**2013-14 n (%)**
Overall	11,053 (100)	1,704 (13.8)	1,584 (13.1)	1,563 (13.7)	1,563 (14.4)	1,651 (15.5)	1,365 (13.9)	1,623 (15.6)
Sex								
Males	5,110 (45.5)	765 (44.8)	714 (44.5)	715 (45.5)	728 (45.5)	795 (45.9)	645 (45.6)	748 (46.2)
Females	5,943 (54.5)	939 (55.2)	870 (55.5)	848 (54.5)	835 (54.5)	856 (54.1)	720 (54.4)	875 (53.8)
Age								
6-17 years	3,721 (20.1)	639 (20.7)	608 (22.1)	617 (21.9)	447 (18.6)	501 (19.8)	418 (29.6)	491 (18.7)
18-29 years	1,617 (15.3)	264 (15.7)	245 (14.9)	258 (14.4)	184 (15.1)	240 (15.4)	210 (17.0)	216 (14.5)
30-49 years	2,281 (29.7)	349 (34.8)	283 (31.8)	287 (28.8)	344 (30.4)	358 (28.8)	288 (27.0)	372 (27.1)
50-64 years	1,626 (19.8)	211 (16.5)	161 (15.3)	186 (20.7)	284 (20.5)	264 (20.0)	247 (22.4)	273 (22.3)
65+ years	1,808 (15.1)	241 (12.3)	287 (16.0)	215 (14.2)	304 (15.4)	288 (16.0)	202 (14.1)	271 (17.4)
Race/Ethnicity [(b)]								
Mexican American	2,666 (10.4)	478 (9.0)	470 (10.4)	455 (10.7)	375 (11.0)	381 (10.2)	191 (9.5)	316 (12.0)
Non-Hispanic White	4,339 (67.5)	763 (72.3)	627 (68.9)	604 (68.6)	621 (67.8)	712 (67.5)	433 (64.7)	579 (63.5)
Non-Hispanic Black	2,309 (10.2)	347 (9.1)	369 (10.8)	388 (11.7)	314 (10.3)	267 (9.6)	335 (10.8)	289 (9.5)
Other/Multi-Racial	1,739 (11.9)	116 (9.6)	118 (9.9)	116 (9.0)	253 (11.0)	291 (12.8)	406 (14.9)	439 (15.1)
Poverty-to-Income Ratio (PIR) [(c)]								
PIR < 2.00	5,167 (31.6)	712 (28.6)	767 (30.9)	698 (28.7)	747 (32.6)	825 (32.6)	681 (35.6)	737 (32.0)
PIR $\geq$ 2.00	5,886 (68.4)	992 (71.4)	817 (69.1)	865 (71.3)	816 (67.4)	826 (67.4)	684 (64.4)	886 (68.0)
Body Mass Index [(d)]								
Normal weight (includes underweight)	4,539 (39.1)	753 (41.1)	697 (40.5)	654 (38.3)	560 (37.3)	605 (36.1)	629 (45.4)	641 (36.3)
Overweight	3,210 (30.2)	527 (31.0)	464 (30.2)	445 (29.1)	492 (31.5)	500 (32.0)	324 (26.2)	458 (30.8)
Obese	3,304 (30.7)	424 (27.9)	423 (29.3)	464 (32.6)	511 (31.3)	546 (32.0)	412 (28.4)	524 (32.9)
Consumed foods likely to be high PAHs[(e)]								
No	2,903 (25.1)	398 (22.7)	367 (23.8)	349 (20.4)	391 (23.6)	433 (26.5)	430 (29.4)	535 (28.5)
Yes	8,150 (74.9)	1,306 (77.3)	1,217 (76.2)	1,214 (79.6)	1,172 (76.4)	1,218 (73.5)	935 (70.6)	1,088 (71.5)
Seasonality								
Nov 1 – Apr. 30	5,513 (42.5)	824 (35.9)	834 (44.2)	760 (42.2)	770 (40.7)	808 (40.8)	682 (47.1)	835 (46.1)
May 1 – Oct. 31	5,540 (57.5)	880 (64.1)	750 (55.8)	803 (57.8)	793 (59.3)	843 (59.2)	683 (52.9)	788 (53.9)

Table 2.1. Continued.

(a) Excluding participants with missing urinary PAH metabolite data (*n*=782), missing urinary creatinine data (*n*=3), diagnosed with weak or failing kidneys (*n*=315), missing serum cotinine data (*n*=1,382), family PIR data (*n*=1,267), BMI data (*n*=505) and serum cotinine level > 1 ng/mL (*n*=4,008). There were 236 participants who had missing data in more than one covariate category.

(b) Race/ethnicity category: Race/ethnicity categories of "Other Hispanic", "Non-Hispanic Asian" and "Other including multi-Racial" were combined into one category "Other/Multi-Racial" due to low sample sizes.

(c) Poverty-to-income ratio (PIR) is specific to a poverty index for each state and year. PIR is calculated by dividing family (or individual if household size = 1) income by the poverty guidelines specific to the survey year. A PIR of 2.00 reflects an annual family income that is two times the poverty level for the specific state of residence and survey year. Values at or above 5.00 were coded as $\geq$ 5.00 because of protection of privacy concerns [197].

(d) BMI for children (age 6-17 years) is based on the percentile of a child's weight and height, by sex and age, relative to growth charts published by the CDC [256]. BMI for adults (age 18+ years) is weight (kg) multiplied by height (m^2).

(e) Participants completed a 24-hour dietary recall interview as part of the NHANES exam. Using the food code and description in the NHANES 24-hour dietary recall questionnaire, foods were assigned a number if the description of the food contained key words associated with PAHs. Examples include: "broiled", "charcoaled", "roasted", "BBQ", "grilled", "smoked", etc.

Table 2.2. Estimated weighted and adjusted[a] geometric mean (aGM) and 95%CI of uPAH biomarkers (in ug/L),[b] overall and by percentile, at each NHANES cycle. See Figure 2.1 for graphical representation.

	n	All NHANES Cycles	2001-02	2003-04	2005-06	2007-08	2009-10	2011-12	2013-14	*p for trend* [c]
uNAP										
aGM overall	11,028	5.65 (5.55, 5.74)	4.19 (4.05, 4.33)	5.17 (4.94, 5.40)	5.89 (5.61, 6.17)	6.31 (6.07, 6.54)	5.93 (5.68, 6.17)	5.87 (5.59, 6.14)	6.04 (5.78, 6.30)	< 0.01
25th Pctl.	2,342	2.03 (1.99, 2.07)	2.43 (2.29, 2.57)	2.99 (2.73, 3.27)	3.52 (3.17, 3.91)	3.56 (3.28, 3.86)	3.29 (3.00, 3.61)	3.08 (2.81, 3.38)	3.08 (2.76, 3.42)	< 0.01
50th Pctl.	2,610	4.15 (4.11, 4.20)	3.96 (3.81, 4.11)	4.86 (4.58, 5.16)	5.42 (5.20, 5.66)	5.84 (5.60, 6.09)	5.45 (5.17, 5.74)	5.35 (4.99, 5.75)	5.28 (4.95, 5.63)	< 0.01
75th Pctl.	2,730	6.31 (6.26, 6.36)	5.51 (5.32, 5.71)	6.86 (6.60, 7.14)	7.59 (7.32, 7.88)	8.32 (7.94, 8.72)	7.93 (7.49, 8.40)	7.85 (7.50, 8.22)	8.12 (7.77, 8.49)	< 0.01
95th Pctl.	2,537	9.13 (9.04, 9.22)	8.23 (7.75, 8.74)	10.07 (9.62, 10.55)	11.77 (11.16, 12.41)	12.66 (11.87, 13.50)	12.30 (11.78, 12.83)	12.19 (11.61, 12.79)	13.24 (12.39, 14.16)	< 0.01
uFLU										
aGM overall	10,989	0.29 (0.29, 0.30)	0.37 (0.36, 0.38)	0.30 (0.29, 0.32)	0.33 (0.31, 0.34)	0.32 (0.30, 0.33)	0.27 (0.26, 0.28)	0.27 (0.26, 0.28)	0.21 (0.20, 0.22)	< 0.01
25th Pctl.	2,527	0.11 (0.10, 0.11)	0.21 (0.020, 0.22)	0.17 (0.15, 0.19)	0.20 (0.18, 0.22)	0.18 (0.17, 0.20)	0.15 (0.14, 0.16)	0.14 (0.13, 0.15)	0.11 (0.10, 0.12)	< 0.01
50th Pctl.	2,675	0.22 (0.22, 0.22)	0.35 (0.34, 0.37)	0.29 (0.27, 0.31)	0.30 (0.29, 0.32)	0.30 (0.28, 0.32)	0.25 (0.24, 0.26)	0.24 (0.23, 0.25)	0.19 (0.17, 0.20)	< 0.01
75th Pctl.	2,757	0.33 (0.33, .0.33)	0.49 (0.47, 0.52)	0.41 (0.39, 0.43)	0.43 (0.41, 0.44)	0.42 (0.40, 0.45)	0.37 (0.36, 0.39)	0.37 (0.35, 0.40)	0.29 (0.28, 0.30)	< 0.01
95th Pctl.	2,286	0.47 (0.47, 0.48)	0.73 (0.69, 0.77)	0.60 (0.56, 0.64)	0.65 (0.63, 0.68)	0.64 (0.61, 0.68)	0.58 (0.55, 0.62)	0.57 (0.54, 0.59)	0.47 (0.44, 0.51)	< 0.01
uPHEN										
aGM overall	11,012	0.29 (0.28, 0.29)	0.32 (0.31, 0.34)	0.31 (0.30, 0.33)	0.32 (0.30, 0.33)	0.30 (0.29, 0.32)	0.28 (0.27, 0.29)	0.26 (0.25, 0.27)	0.22 (0.21, 0.23)	< 0.01
25th Pctl.	2,658	0.11 (0.11, 0.11)	0.19 (0.18, 0.19)	0.18 (0.16, 0.20)	0.19 (0.18, 0.21)	0.17 (0.16, 0.19)	0.16 (0.15, 0.17)	0.14 (0.13, 0.15)	0.11 (0.10, 0.12)	< 0.01
50th Pctl.	2,936	0.21 (0.21, 0.22)	0.31 (0.29, 0.33)	0.30 (0.28, 0.33)	0.30 (0.28, 0.32)	0.28 (0.26, 0.31)	0.26 (0.25, 0.27)	0.24 (0.23, 0.25)	0.19 (0.18, 0.20)	< 0.01
75th Pctl.	2,791	0.32 (0.32, 0.33)	0.43 (0.40, 0.45)	0.42 (0.40, 0.44)	0.41 (0.39, 0.43)	0.40 (0.38, 0.42)	0.38 (0.37, 0.39	0.36 (0.34, 0.38)	0.29 (0.28, 0.31)	< 0.01
95th Pctl.	2,024	0.45 (0.45, 0.46)	0.61 (0.58, 0.65)	0.59 (0.57, 0.61)	0.60 (0.57, 0.63)	0.61 (0.59, 0.64)	0.57 (0.53, 0.62)	0.53 (0.49, 0.57)	0.44 (0.41, 0.48)	< 0.01

Table 2.2 Continued.

	n	All NHANES Cycles	2001-02	2003-04	2005-06	2007-08	2009-10	2011-12	2013-14	*p for trend* [(c)]
uPYR										
aGM overall	10,955	0.10 (0.09, 0.10)	0.04 (0.04, 0.05)	0.08 (0.07, 0.08)	0.09 (0.08, 0.09)	0.11 (0.11, 0.12)	0.12 (0.11, 0.12)	0.11 (0.10, 0.11)	0.13 (0.12, 0.13)	< 0.01
25th Pctl[(d)]	2,353	0.04 (0.04, 0.04)	0.03 (0.02, 0.03)	0.04 (0.04, 0.05)	0.05 (0.05, 0.06)	0.06 (0.06, 0.07)	0.07 (0.06, 0.070)	0.06 (0.06, 0.06)	0.07 (0.06, 0.07	< 0.01
50th Pctl.[(d)]	2,342	0.07 (0.07, 0.07)	0.04 (0.04, 0.04)	0.07 (0.07, 0.08)	0.08 (0.08, 0.08)	0.10 (0.10, 0.11)	0.10 (0.10, 0.11)	0.10 (0.09, 0.10)	0.11 (0.11, 0.12)	< 0.01
75th Pctl.[(d)]	2,839	0.10 (0.10, 0.11)	0.06 (0.06, .06)	0.10 (0.10, 0.11)	0.11 (0.11, 0.12)	0.15 (0.14, 0.16)	0.15 (0.15, 0.16)	0.14 (0.14, 0.15)	0.17 (0.16, 0.18)	< 0.01
95th Pctl.	2,579	0.16 (0.15, 0.16)	0.09 (0.09, 0.10)	0.16 (0.15, 0.16)	0.17 (0.7 0.18)	0.22 (0.21, 0.23)	0.25 (0.23, 0.27)	0.23 (0.21, 0.24)	0.29 (0.28, 0.31)	< 0.01

[(a)] Linear regression for the log-transformed uPAH biomarker, after LOD correction, adjusted for natural log-transformed urinary creatinine, age, sex, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality.

[(b)] uNAP; sum of urinary Naphthalene metabolites (1- & 2-naphthol). uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene). uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene). UPYR: urinary Pyrene metabolites.

[(c)] *p*-value of weighted and adjusted geometric mean of trend across NHANES cycles was assessed by the adjusted Wald test, $\alpha = 0.05$.

[(d)] The delta in trend values between 2001-02 and 2013-14 are within the maximal analytical error for urinary Pyrene metabolite (0.07 ug/L). See Table A.2 for more information on uPAH metabolite limit of detection values.

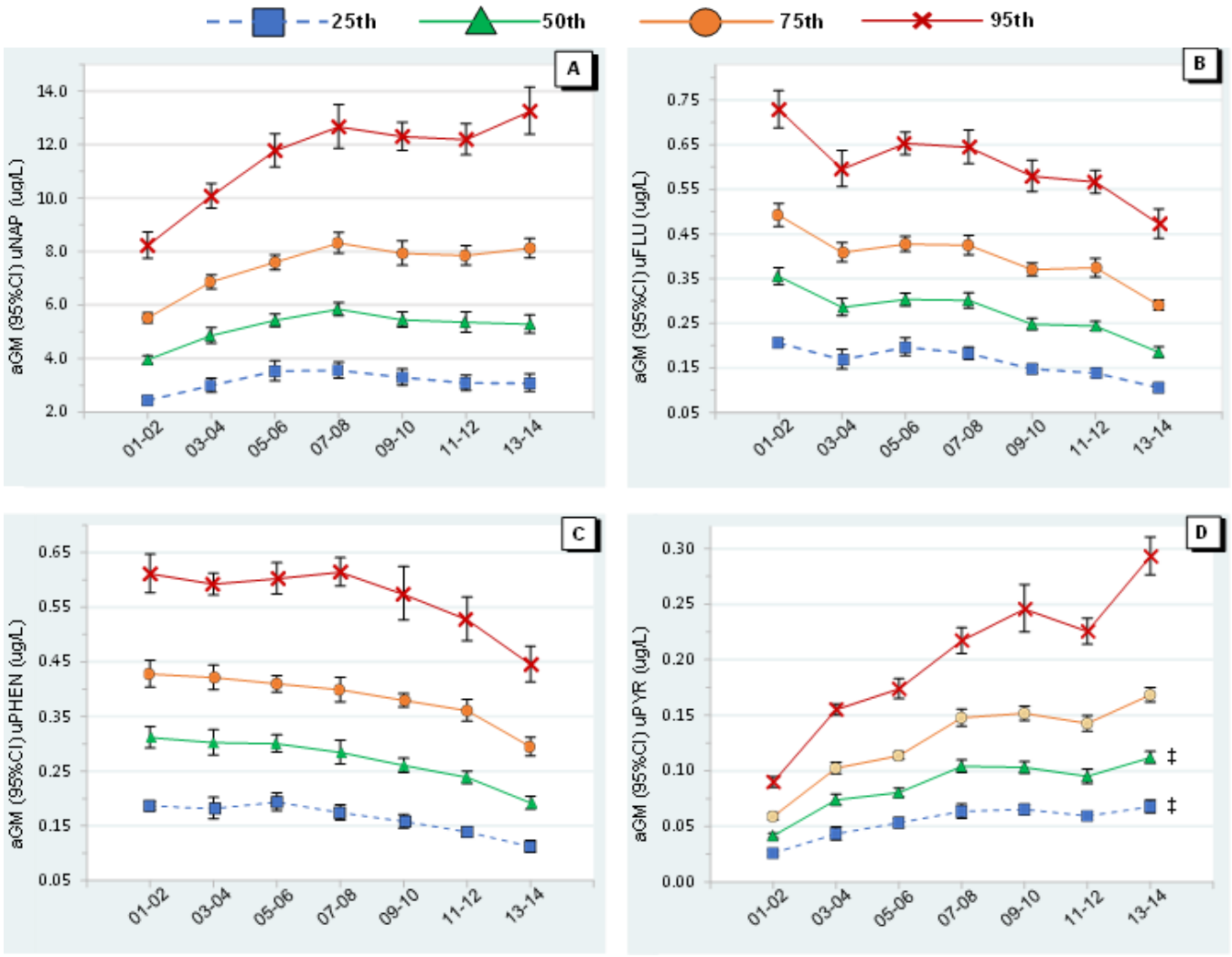
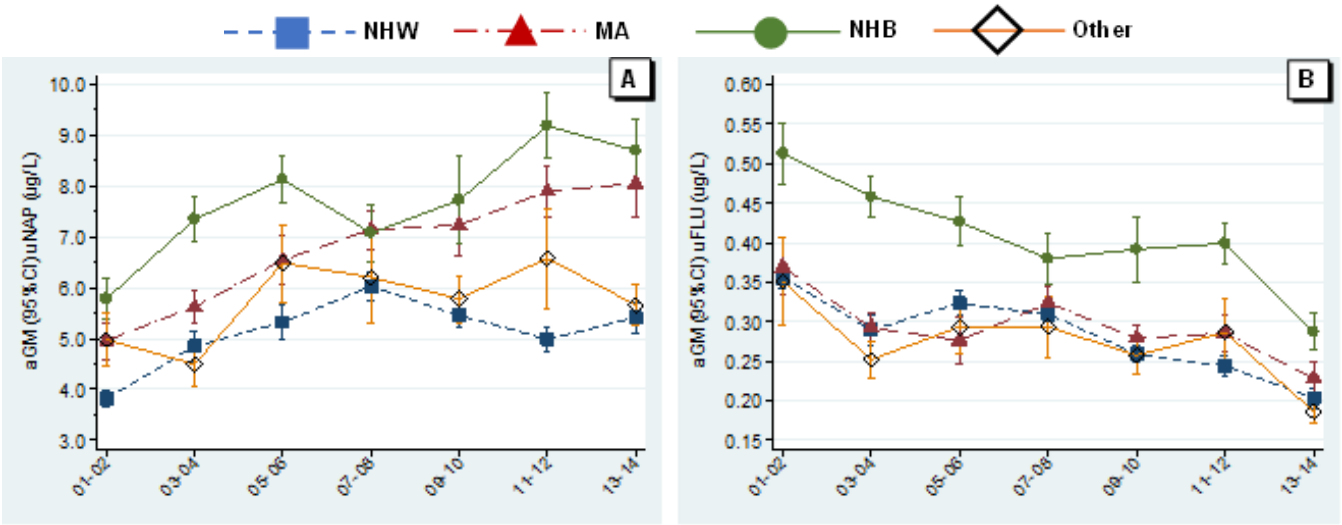
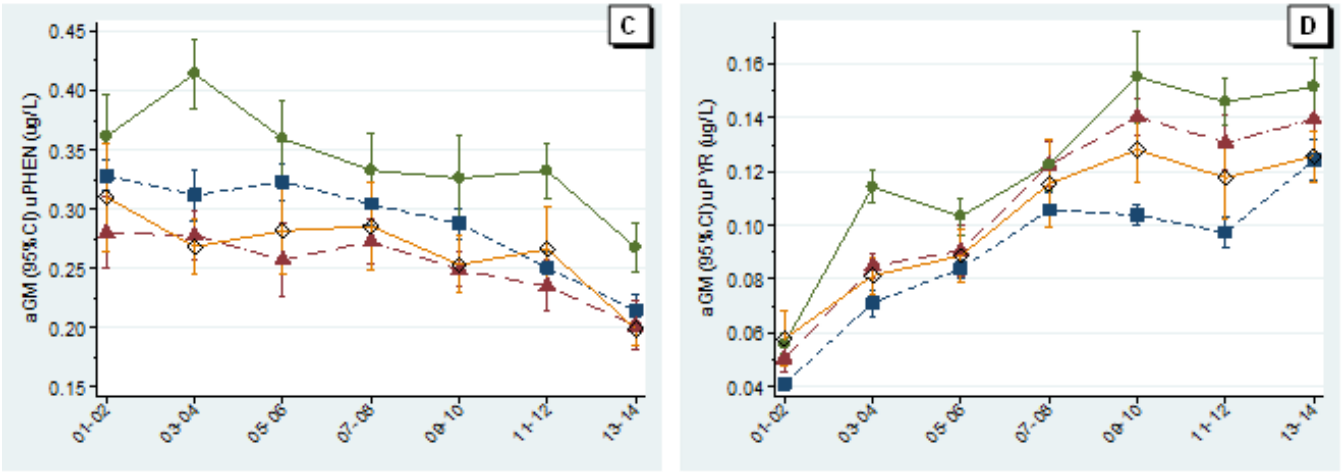


Figure 2.1. Trends in uPAHs (ug/L) in the U.S. non-smoking population, age 6+ years, by 25th, 50th 75th and 95th percentile, 2001-2014. Weighted aGM and 95%CI for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, age, sex, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol); (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene); (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene); (D) uPYR: urinary Pyrene metabolites. See Table A.4 to view these results in tabular form.

(‡) The delta in trend values between 2001-02 and 2013-14 for the 25th and 50th percentiles are within the maximal analytical error for urinary Pyrene metabolite (0.07 ug/L).



Comparing MA[(b)] to NHW:	$p < 0.01$	Comparing MA to NHW:	$p = 0.01$
Comparing NHB to NHW:	$p < 0.01$	Comparing NHB to NHW:	$p < 0.01$
Comparing Other/Multi-Racial to NHW:	$p < 0.01$	Comparing Other/Multi-Racial to NHW:	$p = 0.10$



Comparing MA to NHW:	$p = 0.17$	Comparing MA to NHW:	$p < 0.01$
Comparing NHB to NHW:	$p < 0.01$	Comparing NHB to NHW:	$p < 0.01$
Comparing Other/Multi-Racial to NHW:	$p = 0.22$	Comparing Other/Multi-Racial to NHW :	$p = 0.11$

Figure 2.2. Trends in uPAH metabolites by race/ethnicity in U.S. non-smokers, age 6+ years, 2001-2014. Weighted aGM and 95%CI) for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, age, sex, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##race/ethnicity. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol). (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene). (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene). (D) uPYR: urinary Pyrene metabolite. MA: Mexican American; NHW: Non-Hispanic White; NHB: Non-Hispanic Black; Other/Multi: Other/Multi-Racial. See Table A.5 for more information.

(‡) The change in urinary pyrene concentrations between 2001-02 and 2013-14 for Non-Hispanic White and Other/Multi-Racial groups are within the maximal analytical error.

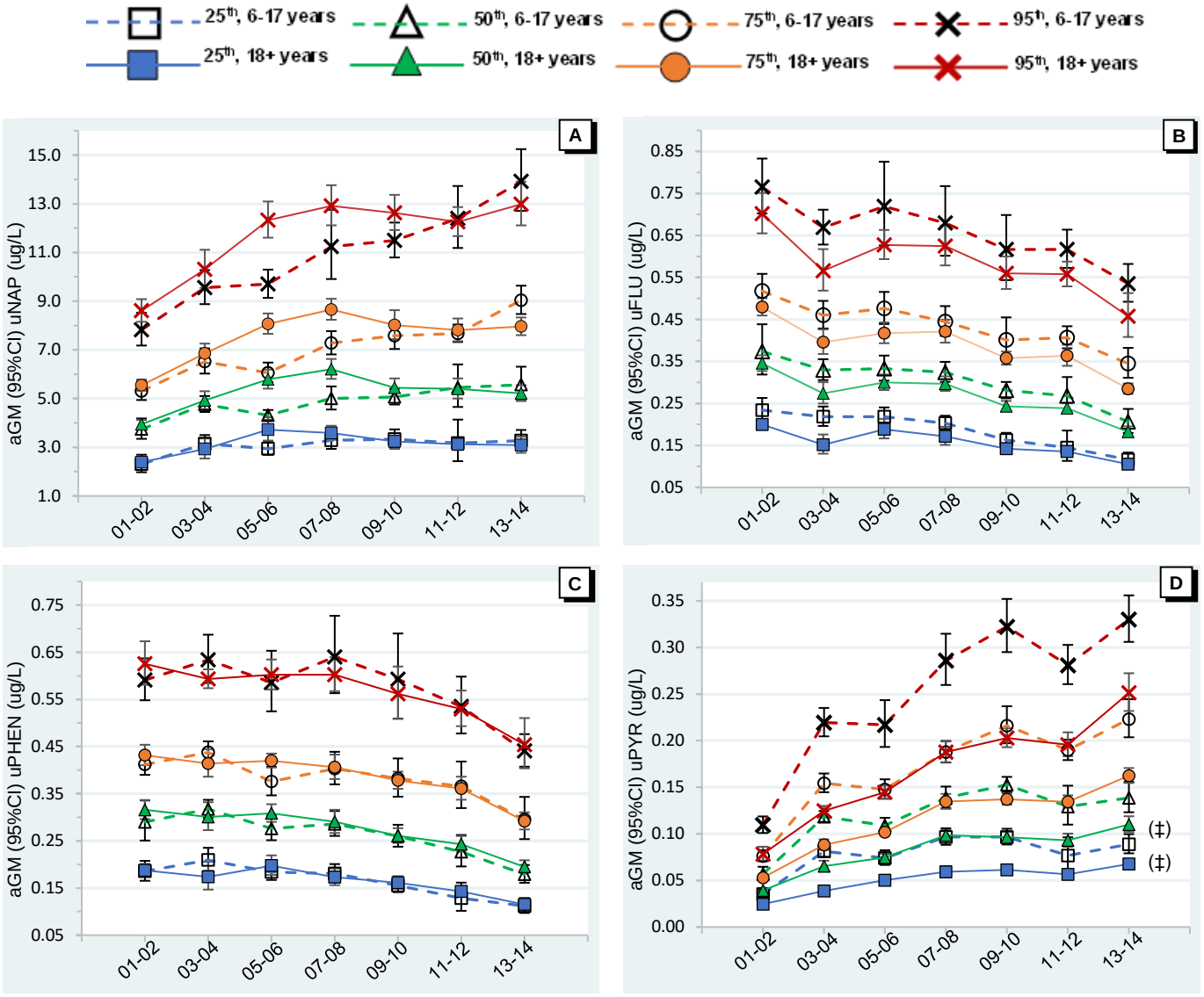


Figure 2.3. Trends in uPAH metabolites for children 6-17 years and adults 18+ years, in U.S. non-smokers, 2001-2014. Weighted aGM and 95%CI for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, sex, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##age. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol), n = 11,028. (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene), n = 10,989. (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene), n = 11,012. (D) uPYR: urinary Pyrene metabolites, n = 10,955. See Table A.4 for more information.

(‡) The delta in trend values between 2001-02 and 2013-14 for the 25th and 50th percentiles are within the maximal analytical error for urinary Pyrene metabolite (0.07 ug/L).

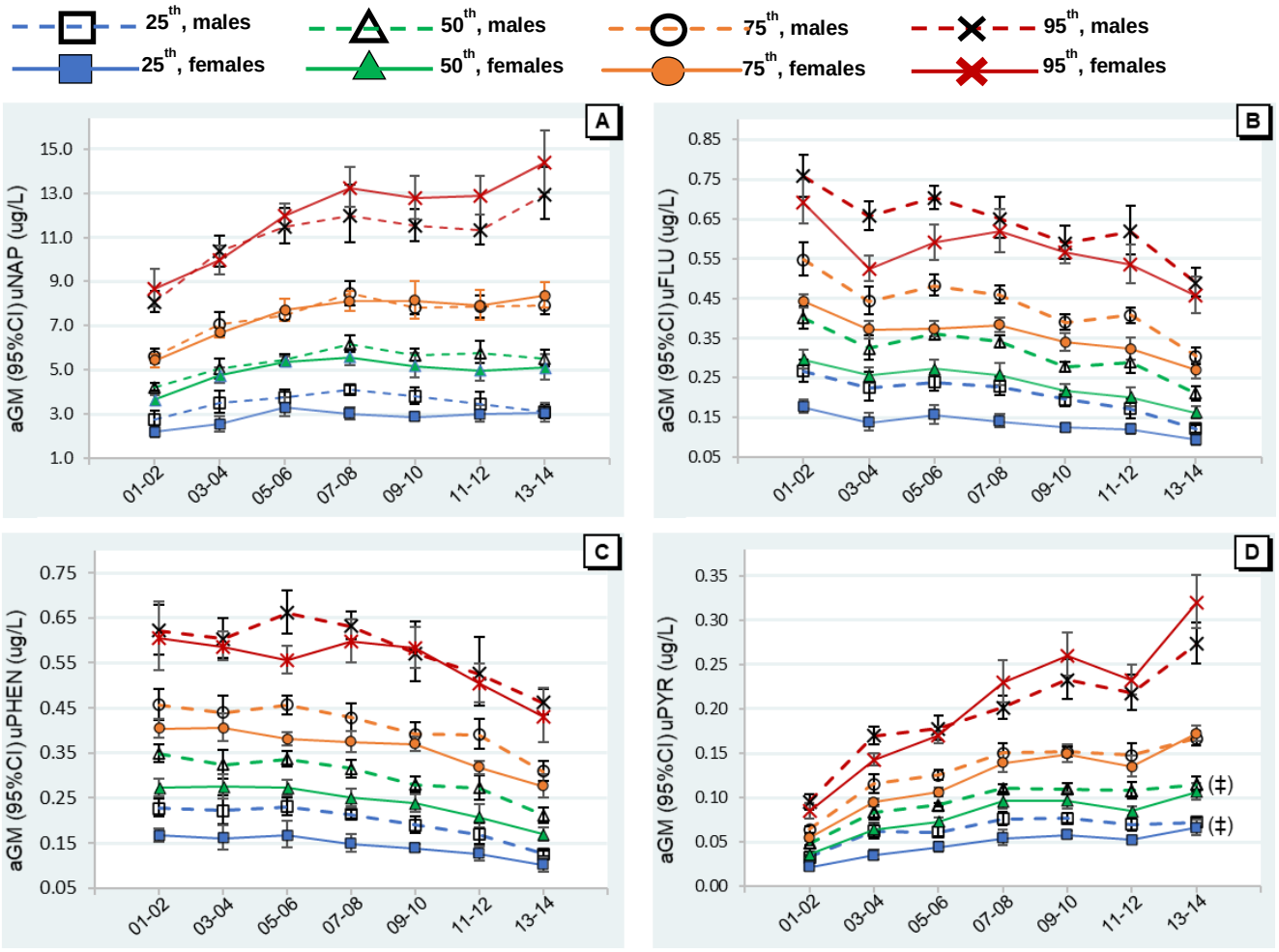


Figure 2.4. Trends in uPAH metabolites for males and females, age 6+ years, in U.S. non-smokers, 2001-2014. Weighted aGM and 95%CI for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, age, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##sex. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol), n = 11,028. (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene), n = 10,989. (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene), n = 11,012. (D) uPYR: urinary Pyrene metabolites, n = 10,955. See Table A.4 for more information.

(‡) The delta in trend values between 2001-02 and 2013-14 for the 25th and 50th percentiles are within the maximal analytical error for urinary Pyrene metabolite (0.07 ug/L).

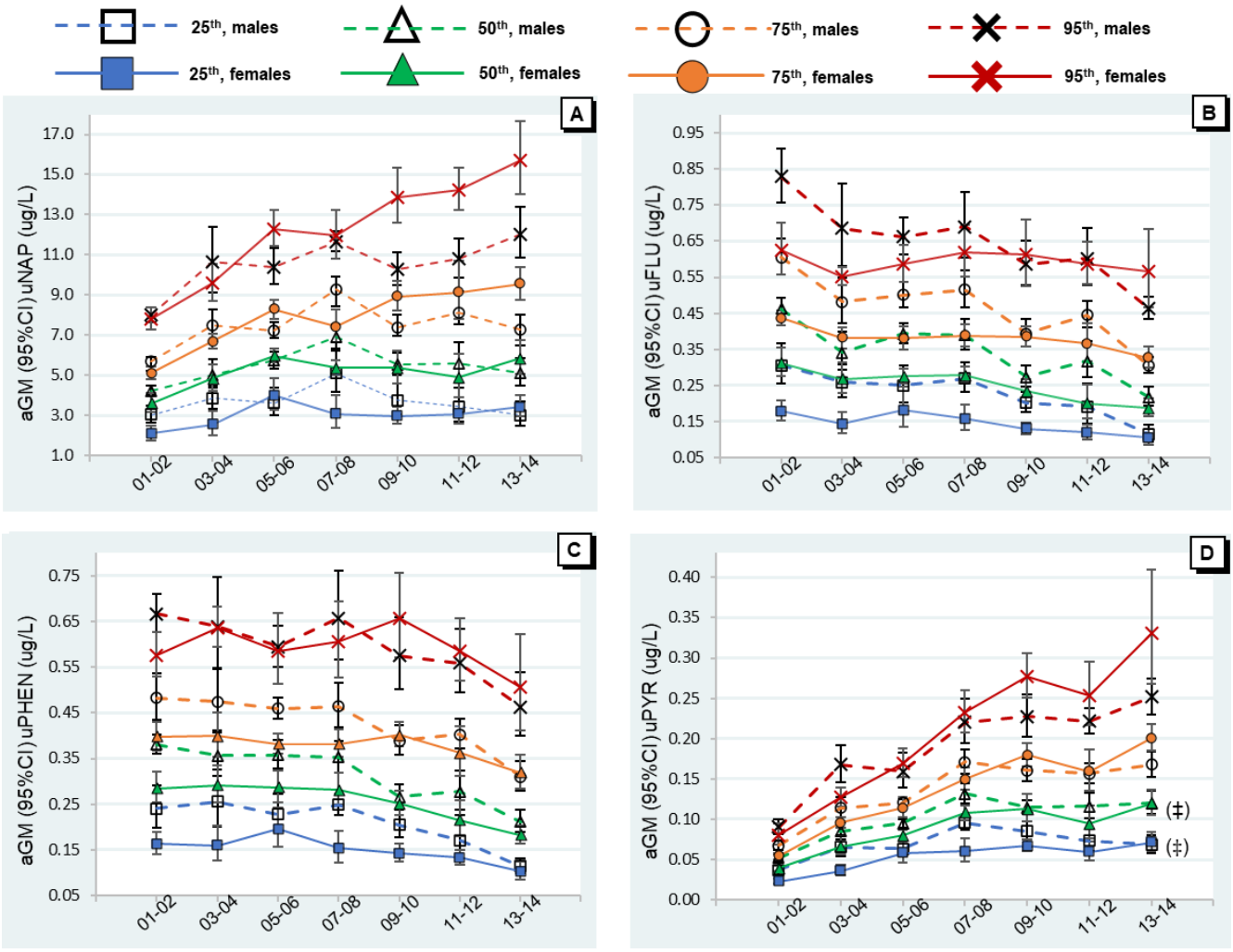


Figure 2.5. Trends in uPAH metabolites for males and females at reproductive age (18-49 years), in U.S. non-smokers, 2001-2014. Estimated weighted aGM[(b)] and 95%CI by NHANES cycle. Weighted aGM and 95%CI for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, age, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##sex, age restricted to 18-49 years. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol), n = 11,028. (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene), n = 10,989. (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene), n = 11,012. (D) uPYR: urinary Pyrene metabolites, n = 10,955. See Table A.4 for more information.

(‡) The delta in trend values between 2001-02 and 2013-14 for the 25th and 50th percentiles are within the maximal analytical error for urinary Pyrene metabolite (0.07 ug/L).

Chapter 3 – Second Manuscript

Prenatal Exposure to Polycyclic Aromatic Hydrocarbons (PAHs) and Adverse Birth Outcomes: A Systematic Review and Meta-Analysis

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3.1 Abstract

Background: Recent research indicates prenatal exposure to Polycyclic Aromatic Hydrocarbons (PAHs) may be associated with adverse birth outcomes. Several primary studies have evaluated the association of various measures of prenatal PAH exposure on birth weight, preterm birth, head circumference, and other birth outcomes, but there are conflicting research results. A weight of evidence approach is needed.

Objective: Examine, quantify, and summarize the weight of evidence of prenatal PAH exposure on birth outcomes in infants.

Methods: We conducted a systematic review to identify eligible studies of peer-reviewed data available for inclusion in a meta-analysis. An *a priori* search strategy included search terms in PubMed, Wed of Science, and Google Scholar. Eligibility criteria included English language primary studies that modeled or measured PAH exposure during pregnancy or at the end of pregnancy. Birth outcomes excluded fetal death and neural tube defects. No limits were put on study time period or geographic location. Study screening and full-text review followed PRISMA protocol and was performed by two reviewers working independently using Covidence software. Studies included in the meta-analysis were evaluated using Comprehensive Meta-Analysis software, v3. Risk of bias was evaluated using the Navigation Guide protocol. Of 2,244 studies identified in the initial search, 40 were eligible for inclusion in the meta-analysis. Birth outcomes were grouped into either dichotomous (summary effect measure: odds ratio) or continuous outcomes (summary effect measure: standardized mean difference, i.e., Cohen's *d*). The most common continuous birth outcomes examined were birth weight (60% in 40 studies) birth length (47.5%), head circumference (40%), gestational age (15%), and ponderal index (10%). The most common dichotomous birth outcomes were preterm birth (17.5%), and combined fetal growth restriction measures: low birth weight/fetal growth < 85% of normal (17.5% combined), and intrauterine growth restriction/small for gestational age (17.5% combined). We report the summary effect size of each birth outcome, 95%CI, and evaluate the source and magnitude of between-study variance.

Results: In meta-analysis, we found a statistically significant ($\alpha = 0.05$) positive association in dichotomous outcomes between prenatal PAH and the combined low birth weight/fetal growth

restriction < 85% of normal (OR: 1.07; 95%CI: 1.03, 1.11; p <0.001; n_{pooled} = 545,587; I^2 = 76.9%), and in the combined small for gestational age/intrauterine growth restriction (OR: 1.19; 95%CI: 1.03, 1.37; p =0.016; n_{pooled} = 226,096; I^2 = 88.2%). We found a marginally statistically significant positive association between prenatal PAH exposure and preterm birth (OR: 1.09; 95%CI: 0.99, 1.20; p = 0.074; n_{pooled} = 92,310; I^2 = 77.9%). In continuous outcomes, we found a statistically significant negative association between prenatal PAH exposure and birth weight (Cohen's d: -0.160, 95%CI: -0.29, -0.03; p = 0.017; n_{pooled} = 41,493; I^2 = 96.6%), and in head circumference (Cohen's d: -0.091, 95%CI: -0.17, -0.02; p = 0.019; n_{pooled} = 5,772; I^2 = 71.0%). We found a marginally statistically significant negative association between prenatal PAH exposure and birth length (Cohen's d: -0.161; 95%CI: -0.34, 0.02; p = 0.080; n_{pooled} = 39,857; I^2 = 97.7%). We did not find a statistically significant association between prenatal PAH exposure and gestational age or ponderal index.

Conclusion: Based on the Navigation Guide protocol, there is limited human evidence to determine that prenatal PAH exposure reduces birth weight and head circumference; and increases low birth weight/ fetal growth < 85% normal, preterm birth, and small for gestational age/intrauterine growth restriction. The human evidence linking prenatal PAH exposure to other birth outcomes was inconclusive. Between-study variance (heterogeneity) was moderate to considerable in all birth outcome assessments, with I^2 ranging from 63.7 to 97.7%, and this led to downgrading the evidence from sufficient to limited. However, heterogeneity is expected in observational research, and limited human evidence of adverse effects associated with prenatal exposure to a common environmental pollutant is cause for concern.

3.2 Introduction

Polycyclic aromatic hydrocarbons (PAHs) are complex mixtures, commonly found in the environment, that form complex mixtures via incomplete combustion of organic materials[46]. His study focused on parent PAHs and their metabolites in the human body. Humans are exposed to PAHs via inhalation, ingestion, dermal absorption, and placental transfer [46,140]. PAHs are primarily metabolized by the liver and excreted in urine and feces. Urinary biomarkers of PAH metabolites are a common exposure surrogate in biomonitoring studies because it is a non-invasive and repeatable method to assess PAH exposure [257]. National surveillance of PAH exposure in the U.S., Germany, and Canada revealed nearly 100% of participants had detectable levels of PAHs in urine samples [258–260]. Most PAHs excreted in urine are in the more soluble hydroxylated form, although some unmetabolized PAHs are also detectable [130]. The half-life of PAH metabolites in urine is relatively short (< 30-hours) and can only indicate recent exposure [130,220].

PAH exposure is linked to human disease. The association between PAH exposure and cancer has been known for almost a century [154,261]. In addition to cancer, PAH exposure is linked to cardiovascular disease [157,224], respiratory illness [47,53] and endocrine disruption [163]. There is also a growing body of evidence that prenatal PAH exposure is associated with adverse birth outcomes such as low birth weight (< 2,500 g) [174,262,263], below normal birth length [264–266] and head circumference [189,267] (both in cm, defined by WHO as < one standard deviation, SD, of national average) [268] , preterm birth (< 37 weeks gestation) [96,269,270], and fetal growth restriction measures such as small for gestational age (SGA, defined by WHO as < two SD below of national average) [268,271], although there are conflicting results in the published research [68,272–274].

Fetal development is a complicated cascade of chemical processes; the timing of each developmental process may be a critical window of susceptibility to environmental assaults that can have adverse effects over the human life-course [275]. For example, in their meta-analysis on the relationship between low birth weight and IQ, Gu, et al. (2017), found that children and adults born with low birth weight had an approximately 10-point IQ decrease, compared to those with normal birth weight [276]. In their review on preterm birth as a risk factor for chronic disease in adulthood, Luu, et al., reported a significant association between

preterm birth and hypertension (including gestational hypertension in pregnant women who had been born preterm), metabolic syndrome, respiratory problems, and low bone mineral density in adulthood [277]. Risnes, et al., (2009) reported a link between smaller than average head circumference at birth and a higher mortality risk from heart disease, compared to those born with average head circumference [278].

Adverse birth outcomes come at a societal cost as well. In their review on the economic benefit of reducing air pollution, Shea, et al., (2020) estimated the per-case cost (in 2015 U.S. dollars) for low birth weight or preterm birth was approximately $16,000 and $70,000, respectively [279]. In terms of the medical and financial costs to the individual, the family, and society, it is therefore important to understand the weight of scientific evidence with regards to prenatal PAH exposures and birth outcomes.

The purpose of this systematic review and meta-analysis is to identify eligible studies that quantified the association between prenatal PAH exposure and birth outcomes, and to summarize and rate the quality and strength of the human evidence. This systematic review and meta-analysis were registered on April 16, 2018, in PROSPERO (CRD42018088403).

3.3 Methods

3.3.1 Study Population

The study population included pregnant mothers and their infants who took part in studies published in peer-reviewed literature prior to May 31, 2021. There were no restrictions on time-period before May 31, 2021, or geographic location of primary studies.

3.3.2 Systematic Review Protocol

The systematic review protocol followed the Navigation Guide methodology [280]. This methodology provides a framework to conduct a systematic review in a scientifically rigorous and transparent manner; to rate the quality and strength of the evidence from primary studies; and provide a grade of overall strength of association. The Navigation Guide also provides a framework to assess the risk of bias (RoB) in primary studies. Table B.7 lists criteria to assess the quality of primary studies that were adapted from the Navigation Guide for this review. In reporting results, we also followed the steps recommended by the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [281]. PRISMA is an evidence-based approach that establishes

search strategy protocols and reporting items in a flow diagram, and a checklist to ensure transparency in reporting of results[282].

3.3.2.1 Study Search Strategy

The *a priori* protocol started with development of a search strategy, eligibility criteria, and inclusion and exclusion criteria for the selection of primary studies. Search engines used were PubMed®, Web of Science®, and Google Scholar®. Search terms are listed in Table B.3. The term "PAH" refers to any single parent PAH species or a combination, or total PAHs reported in primary studies. Study eligibility criteria is summarized in Table B.4. Measures of exposure included PAHs detected during pregnancy from biomarkers, personal air sampling, or modeled exposure, or in biomarkers collected shortly after delivery. Information reported on analytical methods and quality assurance procedures were considered in assessing study quality and risk of bias.

Inclusion and exclusion criteria are listed in Table B.5. Inclusion criteria required that primary studies be available in English and published by a peer-reviewed source. This included peer-reviewed journal articles, text resources, e-books, and print books. Gray literature sources included conference proceedings, government documents, and technical reports. Authors of relevant conference proceedings were contacted to inquire about unpublished studies. Reviews, dissertations, and theses were included in the screening step for citation reviews. Additional records were identified through hand searching and screening of the reference list of included papers which had not been captured through the electronic searches.

3.3.2.2 Study Screening Strategy

Two reviewers working independently screened study titles and abstracts, and completed a full-text review relative to the inclusion criteria, using Covidence® software (Veritas Health Innovation, Melbourne, Australia, www.covidence.org). Potentially eligible studies cited in reviewed studies were added to the title and abstract screening. Each study was rated as "include", "exclude with justification" or "inconclusive". Cohen's kappa coefficient to measure inter-rater reliability of title and abstract screening was 0.57 (moderate agreement), and 0.31 in full-text review (fair agreement) [283]. Conflicts were discussed between the two reviewers until consensus was reached.

3.3.2.3 Data Extraction

Specific data from eligible studies was extracted using Covidence®, following guidance from the PRISMA checklist and the Navigation Guide. Briefly, extracted data included the study name and date, study design, location, study time period, sample size, measure of exposure, PAH species, PAH concentration or adduct level and units, analytical method, birth outcome(s), comparator group (if reported), covariates, measure of association, and measure of precision. A risk of bias rating, based on Navigation Guide criteria, was created in Covidence® and this rating was also extracted. Table B.6 describes the data extraction fields.

3.3.3 Exposure Estimation

Studies were limited to those in which prenatal PAH concentration was measured by personal air sampling, or modeled from stationary air monitoring data, emissions data, dietary exposure questionnaires, or occupational exposure questionnaires during pregnancy, or measured in a human biomarker (e.g., cord blood, maternal blood, maternal urine, or placental tissue), during pregnancy or at the end of pregnancy, to establish temporality between the exposure and the birth outcome.

Some studies reported subgroups of analysis by evaluating multiple PAH species, more than one exposure matrix, or more than one birth outcome. Each exposure-outcome analysis reported in a primary study was assessed individually [216]. For example, Perera, et al., (2003) measured prenatal PAH exposure via personal air sampling and reported the association of c-PAH-8 exposure with birth weight, birth length, and head circumference [88]. In our meta-analysis, each reported c-PAH-8/ birth outcome result was assessed as a separate sub-study. For transparency, we report both the number of studies (k), and the number of sub-studies (k_{sub}) per exposure-outcome analysis.

3.3.4 Outcome Measures

Reported birth outcomes in the primary studies included birth weight (BW, measured in grams), birth length (BL, cm), head circumference (HC, cm), preterm birth (PTB, < 37 weeks gestation) [284], ponderal index (PI), cephalization index, low birth weight (LBW), gestational age (GA, in weeks), small for gestational age (SGA, < 10^{th} percentile for gestational age), fetal growth < 85% of normal weight and size for gestational age

(FG<85%), or intra-uterine growth restriction (IUGR). Ponderal index is a measure of weight relative to height; in infants, ponderal index is equal to 100 * weight in g/height in cm^3 (g/cm^3). Cephalization index is the ratio of head circumference to body weight, with units of cm/g. Low birth weight is defined as < 2,500 g [285]. IUGR is when fetal weight is below the 10^{th} percentile, and abdominal circumference is below the 25^{th} percentile for gestational age [286].

Generally, measures of BL, BW, GA, abdominal circumference, and HC were recorded by the hospital or health care facility where the infant was born, or by the health care provider that attended a home birth. Most GA measures were calculated from the date of the mother's last menstrual cycle. While not specifically reported in all primary studies, assessment of PTB, PI, cephalization index, LBW, FG < 85%, SGA, and IUGR were likely determined by the primary study authors, based on birth outcome data available in medical records, and in measures based on percentiles (i.e., IUGR, FG<85%, SGA), in comparison with national or international infant growth standards, based on sex of the infant.

While the recommended number of studies for each exposure-outcome analysis (k_{sub}) is ten [215], some birth outcome categories had a small number of exposure-outcome sub-studies: FG< 85% (k_{sub} = 2), IUGR (k_{sub} = 2), cephalization index (k_{sub} = 8) and SGA (k_{sub} = 9). We evaluated if it was biologically feasible and statistically reasonable to combine birth outcomes, to present a fuller assessment of relevant evidence. We assessed the impact on the precision of the summary effect of LBW (k_{sub} = 14) if it were combined with FG< 85%, SGA, IUGR, respectively. We also assessed the impact on LBW's weighted sum of squared deviations (Q). We used a 10% change criteria, similar to what is commonly applied when evaluating covariates in regression analysis. The LBW+FG<85% combination did not change the precision of the LBW estimate, and increased LBW's Q value by 9.1%, an acceptable increase and allowed the inclusion of two eligible sub-studies (n = 554) in the meta-analysis. The combination of LBW+IUGR, LBW+FG<85%+IUGR, and LBW+SGA, increased LBW's Q value by 13.1%, 22.2%, and 164.8%, respectively.

We performed the same assessment of combining SGA with IUGR. There was no impact on the precision of the summary effect of SGA, and Q increased by 3.75%, again, an acceptable increase, that allowed the inclusion 11 sub-studies (n = 226,543) in the meta-analysis. We assessed combining cephalization index with head circumference, ponderal

index, LBW, or SGA, but this caused a large increase in the precision of the summary effect. Thus, cephalization index measures (n = 1,910) are not included in this analysis.

3.3.5 Covariates

Figure 3.1 shows the percentage of covariates reported in primary studies. Reported covariates included maternal characteristics (e.g., age, race/ethnicity, BMI, marital status, measure of socio-economic status, education, occupation), maternal exposures during pregnancy (e.g., tobacco smoke, alcohol consumption, diet), maternal history of pregnancy complications (Hx-PC), information on maternal residence during pregnancy (location, home heating type, drinking water supply), and seasonality of gestation/birth. Diet is an important covariate as it is considered one of the main sources of PAH exposure in non-smokers [47]. We created dummy variables (i.e., did the primary study adjust for the specific covariate: Y/N) for covariates that can confound the measure of association between prenatal PAH exposure and birth outcomes: tobacco smoke exposure, maternal age, education, diet, BMI, socioeconomic status (SES), parity, and Hx-PC. Additional covariates created for the meta-analysis included the exposure matrix (blood, urine, air model, etc.), when an exposure measure was collected relative to the pregnancy (approximates exposure period), and the time range of study (by decade: 1990-1999, 2000-2009, 2010-2019, not reported, or "other" because the time range took place in more than one decade). Studies that measured PAH exposure in either the first or second trimester were combined due to the low number of studies in these two exposure periods.

3.3.6 Statistical Analysis

Data from eligible studies were aggregated and analyzed using Comprehensive Meta-Analysis software (CMA, v. 3.3.070, November 20, 2014) to generate a summary effect and the 95%CI for each exposure-outcome analysis, and a *z*-score with corresponding *p*-value, statistics measuring the between-study dispersion under a random-effects model. Separate analysis was performed on continuous (BL, BW, GA, HC, and PI) and dichotomous (LBW+FG<85%, PTB, and SGA+IUGR) outcomes. The summary effect measure for continuous outcomes is the standardized mean difference (Cohen's d). The summary effect measure for dichotomous outcomes is the odds ratio (OR). A 95%CI is the measure of precision for both outcome measures. Measures of association reported on the raw scale in

primary studies were transformed to natural log scale using methods recommended by Higgins, et al., 2008[287]. Correlation coefficients, when non-zero, can be skewed [288], so they were transformed to Fisher's *z*' scale to approximate a normal distribution. A prediction interval was calculated using the Prediction Interval software from CMA.

Results reported are based on the summary effect of at least ten sub-studies in each exposure-outcome analysis to increase the precision of the estimates [289]. When possible, we used measures of association from adjusted analysis to provide a more conservative estimate of the true mean effect size, as recommended by the Cochrane Handbook [213]. When the exposure comparator was reported in quantiles, we used the result reported for the upper v. lower quantile. We excluded some observations from sub-analysis, i.e., we did not include results reported in non-smokers when the overall sample population of smokers and non-smokers was available. We also did not include interaction results (e.g., effect modification of birth outcome from PAH exposure interacted with tobacco smoke exposure).

Meta-regression was performed, but due to the low number of studies in some birth outcomes, only univariate meta-regression was performed on each birth outcome and each covariate, and bivariate meta-regression was performed on each birth outcome with each covariate. Reported meta-regression results are the summary effect and 95%CI from bivariate analysis, and a *z*-score with corresponding *p*-value to test the null hypothesis that there is no association between a respective covariate and birth outcome (i.e., the meta-regression summary effect could be zero). If an effect exists, we report the magnitude and direction of effect. We report R^2, the amount of variance explained by the model, and measures of between-study variance (T^2, T and I^2), at $\alpha = 0.10$.

3.3.6.1 Statistical Power

Statistical power is calculated after completion of the meta-analysis, as the number of included studies is not known *a priori*. Table B.8 is the power calculations results for this meta-analysis, using Equation 8a in Appendix E [215]. All exposure-outcome analyses were adequately powered (> 0.80), except for the gestational age analysis (power = 0.018). Although the pooled sample size was 1,1189, the small effect size (absolute value of 1 – the summary effect), and moderate number of sub-studies (k_{sub} = 18) weakened the statistical power for this birth outcome.

3.3.6.2 Data Visualization

We generated forest plots summarizing included primary sub-studies for each exposure-outcome analysis, along with the summary effect, and 95%CI. Funnel plot for both continuous and dichotomous outcomes, were also generated to visualize the risk of publication bias. We also provide a figure of the geographical location of included studies as a visual queue of the evidence of prenatal PAH exposure and birth outcomes, and to highlight a recommendation for future research.

3.3.7 Assumptions

The basic assumption for our meta-analysis is that maternal PAH exposure can lead to an internal dose that can cross the placenta and enter the bloodstream of the fetus, where it interferes with normal fetal growth processes. Our analysis assumed the effect size and variation reported in primary studies was estimated accurately and that log-transformed values followed an approximately normal distribution. We also assumed that Tau, the estimated standard deviation of true effects, is a reasonably precise estimate of the true effect dispersion, with a distribution that is approximately normal. We use Tau to calculate the prediction interval to evaluate how much effect size varies across studies included in the meta-analysis. In doing so, we assume the prediction interval is also reasonably precise, with a distribution that is approximately normal.

3.4 Results

3.4.1 Characteristics of Included Studies

Of the 2,244 studies retrieved in the initial search, 412 were duplicate studies. Screening titles and abstracts culled 1,006 studies that did not meet eligibility criteria. Of the remaining 826 studies, two additional studies were added from citation reviews in the screening step, and 674 studies were judged to be ineligible and were excluded. First phase data extraction excluded 107 of the 152 remaining studies, leaving 45 to complete data extraction. Five additional studies were removed when it was determined the sample population was the same as that reported in another study [291–294], or when requests for additional information from corresponding authors received no response. Thus, there were 40 studies and 255 sub-studies included in the meta-analysis. Fifteen studies were of

longitudinal study design, nine were case-controls, and 16 were cross-sectional. Twenty-six studies reported continuous, and 15 studies reported dichotomous, birth outcomes, respectively, with one study BW, BL and HC as continuous, and SGA and FG<85% as dichotomous outcomes [271]. Figure 3.1 is the PRISMA diagram of record selection, and a list of included studies, along with some important study characteristics, are listed in Tables B.1 and B.2.

In our meta-analysis, Maxwell, et al. (1994) was the first study (conducted from 1989 to 1990) to measure prenatal PAH exposure and a birth outcome (birth weight), in a sample population of 651 women/infant dyads in Nigeria [295]. Agarwal et al. (2020), was the latest study (conducted from 2017 to 2018). Thus, the research included in our meta-analysis spans a 29-year timeframe. The pooled sample size (n_{pooled}) across all included studies was 848,623. The median sample size per sub-study was 200, the mean sample size was 16,012, and the sample size range was from 14 to 283,303. Of the included studies, two gestational age observations (NAP, total PAHs) from Yang, et al. (2018) were not included in the meta-analysis because the measure of association reported was zero [266].

3.4.2 Overall Analysis

The results by birth outcome are provided in Table 3.1. We found a statistically significant positive association in dichotomous outcomes between prenatal PAH and the combined LBW+FG<85% (OR: 1.07; 95%CI: 1.03,1.11; p <0.001; n_{pooled} = 545,587; I^2 = 76.9%), and in the combined SGA+IUGR (OR: 1.19; 95%CI: 1.03,1.37; p =0.016; n_{pooled} = 226,096; I^2 = 88.2%). We found a marginally statistically significant positive association between prenatal PAH exposure and preterm birth (OR: 1.09; 95%CI: 0.99,1.20; p = 0.074; n_{pooled} = 92,310; I^2 = 77.9%). In continuous outcomes, we found a statistically significant negative association between prenatal PAH exposure and birth weight (Cohen's d: -0.160, 95%CI: -0.29, -0.03; p = 0.017 n_{pooled} = 41,493; I^2 = 96.6%), and in head circumference (Cohen's d: -0.091, 95%CI: -0.17, -0.02; p = 0.019 n_{pooled} = 5,772; I^2 = 71.0%). We found a marginally statistically significant negative association between prenatal PAH exposure and birth length (Cohen's d: -0.161, 95%CI: -0.34, 0.02; p = 0.080 n_{pooled} = 39,857; I^2 = 97.7%). We did not find a statistically significant association between prenatal PAH exposure and gestational age (Cohen's d: 0.061,

95%CI: -0.11, 0.23; p = 0.483 n_{pooled} = 1,189; I^2 = 80.5%), or ponderal index (Cohen's d: -0.002, 95%CI: -0.11, 0.10; p = 0.965 n_{pooled} = 2,304; I^2 = 63.7%).

Figure 3.2 is a summary forest plot of continuous, and dichotomous birth outcomes, respectively. Meta-regression results follow the results by birth outcomes.

3.4.2.1 Continuous Birth Outcomes

Some studies assessed prenatal PAH exposure in multiple exposure matrices, so details about exposure matrices in this section may not equal the total number of studies by birth outcome. All studies reporting continuous outcomes either excluded smokers from the sample population, or adjusted for tobacco smoke exposure in regression analysis, with the exception of the 1989-1990 study in Nigeria and birth weight [295].

3.4.2.1.1 Birth Length

Nineteen studies (k_{sub} = 39; n_{pooled} = 39,857) measured exposure to 11 PAHs (including total PAHs) and assessed the effect on birth length in sample populations from 1992 to 2017 [174,189,225,244,264–267,273,274,296–304]. The summary effect, M, was marginally statistically significant (Cohen's d: -0.161; 95%CI: -0.34, 0.02; p = 0.080). From the prediction interval (i.e., $M \pm 2T$), we expect the distribution of standardized mean difference to be within the range of -1.40 to 1.08 in 95% for all comparable populations, and I^2 = 97.7%.

Six studies assessed the effects of prenatal PAH exposure on birth length using cord blood [189,225,274,296,300,304], and one study used placental tissue at end of pregnancy (EOP)[174]. Of these, four studies measured PAH-DNA adducts [189,225,300,304], and three measured PAH concentration. Eight studies measured PAHs in maternal urine; two studies measured PAHs in samples collected in the second trimester [265,301]; one in the third trimester [303]; and five at EOP [174,266,267,273,298]. Two studies modeled dietary [264,299], and one study model occupational [302] maternal PAH exposure during nine months of pregnancy. Two studies measure PAH using personal air sampling (PAS) in the second[238] and third trimester [291].

Five studies were conducted in China [267,273,274,298,304], four in the U.S.[225,244,297,300], three in Poland [189,265,301], and one study each in Japan [303], Netherlands [302], Norway [264], Saudi Arabia [174], South Korea [299], and Spain [296].

3.4.2.1.2 Birth Weight

Twenty-three studies (*k*$_{sub}$ = 84; n$_{pooled}$ = 41,493) measured exposure to 17 PAHs (including total PAHs) and assessed the effect on birth weight in sample populations from 1989 to 2018 [174,189,225,244,263–267,273,274,295–307]. The summary effect was statistically significant (Cohen's *d*: -0.160; 95%CI: -0.29, -0.03; *p* = 0.017). The prediction interval was from -1.32 to 1.00, and I^2 = 96.56%.

Nine studies assessed the effects of prenatal PAH exposure on birth weight using cord blood [189,225,263,274,295,296,300,304,306]; one study used maternal blood [306]; and three studies used placental tissue at end of pregnancy (EOP) [174,305,307]. Of these, six studies measured PAH-DNA adducts [189,225,263,300,304,307], and three measured PAH concentration. The studies that used maternal urine, occupational and dietary PAH exposure models, and PAS to assess prenatal PAHs and birth length, used the same exposure matrices to assess the effects on birth weight. In addition to the same countries where studies assessed prenatal PAH exposure and birth length, one country conducted a study in India [305], one in Nigeria [295], and one each in Czech Republic, Denmark, England, and Greece by the same authors [263].

3.4.2.1.3 Gestational Age

Six studies (*k*$_{sub}$ = 18; n$_{pooled}$ = 1,189) measured exposure to 11 PAHs (including total PAHs) and assessed the effect on head circumference in sample populations from 1998 to 2017 [266,267,271,274,303,308]. The summary effect was not statistically significant (Cohen's *d*: 0.061; 95%CI: -0.11, 0.23; *p* = 0.483). The prediction interval was from 0.00 to 0.72, and I^2 = 80.54%.

One study measured PAH concentration in cord blood to assess the effects on gestational age [274]; and one study used placental tissue [308]. Three studies used maternal urine; one study collected samples in the third trimester [303]; the other two at EOP [266,267]. One study evaluated PAHs from PAS in the third trimester [271]. Three studies were conducted in China [266,267,274]; two in the U.S. [271,308]; and one in Japan [303].

3.4.2.1.4 Head Circumference

Sixteen studies (*k*$_{sub}$ = 37; n$_{pooled}$ = 5772) measured exposure to seven PAHs (including total PAHs) and assessed the effect on head circumference in sample populations

from 1992 to 2017 [174,189,225,244,265,267,273,296–304]. The summary effect was statistically significant (Cohen's *d*: -0.091; 95%CI: -0.17, -0.02; $p = 0.019$). The prediction interval was from -0.46 to 0.28, and $I^2 = 71.04\%$.

Five studies assessed the effects of prenatal PAH exposure on head circumference using cord blood [189,225,296,300,304]; and one study used placental tissue at end of pregnancy (EOP) [174]. Of these, four studies measured PAH-DNA adducts [189,225,300,304], and the other measured PAH concentration. Seven studies measured PAHs in maternal urine; two studies measured PAHs in samples collected in the second trimester [265,301]; one in the third trimester [303]; and four at EOP [174,267,273,298]. One study modeled dietary [299], and one study model occupational [302] maternal PAH exposure during nine months of pregnancy. Two studies measure PAH using personal air sampling (PAS) in the second[238] and third trimester [291].

Four studies were conducted in China [267,273,298,304], four in the U.S.[225,244,297,300], four in Poland [189,265,297,301], and one study each in Japan [303], Netherlands [302], Saudi Arabia [174], South Korea [299], and Spain [296].

3.4.2.1.5 Ponderal Index

Four studies ($k_{sub} = 10$; $n_{pooled} = 2{,}404$) measured exposure to six PAHs (including total PAHs) and assessed the effect on ponderal index in sample populations from 2005 to 2011 [174,265,273,301]. The summary effect was not statistically significant (Cohen's *d*: -0.002; 95%CI: -0.11, 0.10; $p = 0.965$). The prediction interval was from -0.24 to 0.24, and $I^2 = 63.65\%$.

One study measure PAH concentration in placental tissue [174]; and three studies measured maternal urine; two in the second trimester [265,301], and one at EOP [273]. Two studies were conducted in Poland, and one each in China and Saudi Arabia.

3.4.2.2 Dichotomous Outcomes

3.4.2.2.1 Pre-term Birth

Seven studies ($k_{sub} = 30$; $n_{pooled} = 92{,}310$) measured exposure to 17 PAHs (including total PAHs) and assessed the effect on PTB in sample populations from 1990 to 2017 [96,262,269–271,309,310]. The overall mean effect size showed a marginally statistically significant increase in PTB (OR: 1.09; 95%CI: 0.99,1.20; $p = 0.074$). The prediction interval was 0.75 to 1.43, and $I^2 = 77.92\%$.

Of the seven studies, two measured prenatal PAH exposure in either placental tissue [262] or personal air sampling [271] and excluded smokers from the sample population. Two studies that modeled prenatal PAH exposure for nine months of pregnancy using either emissions data [309] or occupational data [310] adjusted for tobacco smoke exposure in final models. Three studies that modeled exposure using air monitoring data [96,270] or emissions data [269] did not include tobacco smoke exposure as a covariate. Five studies were conducted in the U.S. [96,269–271,309]; and one study each was conducted in India [262], and Sweden [310].

3.4.2.2.2 Low Birth Weight + Fetal Growth Restriction < 85%

Seven studies (k_{sub} = 16; n_{pooled} = 545,587) measured exposure to six PAHs (including total PAHs) and assessed the effect on the combined birth outcome of LBW + FG< 85% in sample populations from 1990 to 2012 [102,269,271,309–312]. There was a statistically significant increase in LBW + FG<85% (OR: 1.07; 95%CI: 1.03,1.11; $p < 0.001$). The prediction interval was 0.99 to 1.16, and I^2 = 76.86%.

One study measured prenatal PAH exposure using cord blood and in maternal blood[312], collected at EOP and measured PAH concentration. Two studies used ambient air data [102,311], one study used emission data [309], and one used occupational data [310] to model prenatal PAH exposure over nine months of pregnancy. One study used PAS data collected in the third trimester [271]. Four studies were conducted in the U.S. [102,271,309,311]; and one study each was conducted in India [262], and Sweden [310]. The emissions study conducted in the U.S. did not adjust for tobacco smoke exposure in final models [309].

3.4.2.2.3 Small for Gestational Age + Intrauterine Growth Restriction

Seven studies (k_{sub} = 11; n_{pooled} = 226,096) measured exposure to three PAHs (including total PAHs) and assessed the effect on SGA in sample populations from 1994 to 2016. The overall effect was a statistically significant increase in SGA+IUGR (OR: 1.19; 95%CI: 1.03,1.37; p =0.016). The prediction interval was 0.84 to 1.54, and I^2 = 88.15%. All studies either excluded smokers from their sample population, or adjusted for tobacco smoke exposure in their regression analysis. Two studies, one in the Czech Republic [164], and one in Texas [272] modeled prenatal PAH exposure from air monitoring data. One study conducted in Spain [296] measured prenatal PAH concentration in cord blood. Another study in New York

[271] evaluated prenatal PAH exposure in the third trimester with personal air sampling. One study each modeled exposure with emissions data in New Jersey [309], occupation data from Sweden [310], and from dietary questionnaires in the U.S. [313].

3.4.2.3 Meta-Regression Results

In bivariate analysis, we examined the differences between studies that utilized biomarkers, compared to studies that modeled prenatal PAH exposure. Table 3.2. presents these results by continuous and dichotomous birth outcomes, respectively, with the difference between groups assessed by *z*-test, $\alpha = 0.05$. There were no statistically significant differences between exposure matrix groups.

Table 3.3 contains the univariate analysis results by outcome type (continuous/ dichotomous), and lists the covariates included in final models of primary studies. Table 3.3 also provides the results from bivariate meta-regression analysis between covariates and individual birth outcomes that were statistically significant and explained at least part of the variance in the summary effect (i.e., $R^2 > 0$). In univariate meta-regression analysis of the dichotomous outcomes' dataset, the following covariates met the aforementioned criteria: exposure matrix ($R^2 = 0.28$), primary study model adjustment for Hx-PC (adj. Hx-PC, $R^2 = 0.27$), country ($R^2 = 0.24$), adjustment for maternal diet during pregnancy (adj. diet, $R^2 = 0.08$) , and adjustment for maternal exposure to tobacco smoke during pregnancy (adj. smoke, ($R^2 = 0.01$). In the continuous birth outcomes' dataset, these covariates were country ($R^2 = 0.47$), exposure matrix ($R^2 = 0.25$), PAH congener ($R^2 = 0.12$), adj. Hx-PC ($R^2 = 0.11$), adjustment for highest level of maternal education (adj. educ., $R^2 = 0.10$), adjustment for maternal pre-pregnancy BMI (adj. BMI, $R^2 = 0.09$), adjustment for parity (adj. parity, $R^2 = 0.07$), and adjustment for either maternal or household SES (adj. SES, $R^2 = 0.06$).

In bivariate meta-regression analysis, out of the eight birth outcomes, the following covariates were statistically significant, with $R^2 > 0$: study design, and model adjustment for maternal pre-pregnancy BMI in primary study (seven birth outcomes, respectively); exposure matrix, and country where study took place (six, respectively); exposure period, time range, and model adjustment of maternal diet during pregnancy (five, respectively); adjustment for maternal education, and adjustment for parity (four, respectively); adjustment for SES, and adjustment for maternal history of pregnancy complications (three, respectively); adjustment

of maternal age at delivery (two); and PAH congener, and PAH measure, i.e., PAH-adducts or PAH concentration (one, respectively).

The country, exposure matrix and adj. Hx-PC covariates explained 83%, and 79% of the variation in overall continuous, and dichotomous birth outcomes, respectively. In our meta-analysis, there were 25 studies (k_{sub} = 118) that did not, and 15 studies (k_{sub} = 112) that did report adjusting for Hx-PC. Pregnancy complications, such as high blood pressure [314], gestational diabetes [315], or persistent nausea [316] can contribute to high-risk pregnancies and affect birth outcomes. Analysis on the potential sources of variance in the country and exposure matrix covariates is provided in the next section.

3.4.2.3.1 Assessment of Heterogeneity

Country

The variation based on the country where a study took place was somewhat expected, as the sample populations from different countries can vary considerably. In some countries, the sample population was likely to be somewhat homogenous in terms of race/ethnicity, diet, BMI, socio-economic factors, and exposure risk, while sample populations in other countries were likely to be more diverse. For example, the study in Saudi Arabia [174] reported results from 1,543 non-smoking pregnant women with no history of occupational exposure, and measured BaP and total PAHs in placental tissue, and PYR and urinary cotinine in maternal urine collected after delivery. The study's sample population resided approximately 250 miles west of the Ghawar oil field and refineries, the largest in the world. In addition, even though participants stated they were non-smokers, the authors detected a wide range of creatinine-adjusted cotinine levels, from 0.539 to 202,079.13 ug/g, which likely contributed to this study's variance. The seven studies with sample populations from China evaluated different PAH exposure sources in ten cities. Three of the seven studies evaluated sample populations living near unregulated e-waste processing areas from 2008-2009 [274], from 2011-2012 [298], and from 2016-2017 [267]. One study evaluated two birth cohorts, one cohort was born while a local coal-fired power plant was active; the other cohort was born after the power plant was deactivated [304]. One study [273] evaluated a sample population living in an area with coal-powered industry and major roads. Two studies evaluated sample populations living in major metropolitan areas [266,306]. The different

socioeconomic conditions in these sample populations likely contributed to the variation in PAH exposure profiles. Two of three studies in India were part of an ongoing cross-sectional study with non-overlapping enrollment periods [262,305]. The sample populations in these two studies were drawn from Agra District, in Northern India, an industrial area where high levels of PAHs have been detected in the environment [262]. The third study conducted in India was in the Eastern region of Assam, the predominant tea cultivation area in India, but also an area where oil and natural gas are extracted [299]. All three studies measured PAH concentration in placental tissue.

Exposure Matrix

Studies that measured prenatal PAH exposure in placenta tissue (R^2 = 0.06), cord blood (R^2 = 0.01), or modeled exposure using occupational data (R^2 = 0.04) were the only covariates to account for variation in continuous birth outcomes. In dichotomous outcomes, studies that modeled prenatal PAH exposure in air (R^2 = 0.32), or from occupational exposure data (R^2 = 0.17) accounted for >90% of the between-study variation. Of the six studies that modeled air monitoring data across nine months of pregnancy, five were conducted in the U.S., and one in the Czech Republic. Of the five U.S. studies, two studies were conducted in Los Angeles County, California: one assessed BAP, BghiP, and total PAHs on low birth weight, Jan. 2000-Dec. 2004 [102]; the other examined BaP, BghiP, NAP, and total PAHs on preterm birth, Jun. 2004-Mar. 2006 [270]. Another study conducted in Fresno, California assessed the association of total PAHs on preterm birth, 2001-2006 [96]. Two studies were conducted in Texas. Of these, one used air monitoring data and emissions data for the entire state to assess the effect of BaP and BghiP exposure on low birth weight, from 1996 to 2008 [311]. The other study focused on air monitoring data in El Paso County to assess BaP, NAP, and total PAH exposure on small for gestational age, 2005-2007 [272]. The Czech Republic study examined the association of total PAHs on intrauterine growth restriction in Teplice and Prachatice, 1994-1998 [164]. Covariates that did not explain any between-study variation in bivariate analysis in dichotomous outcomes included PAH congener, adj. SES, adj. smoke, or adj. educ., or PAH measure (adducts/concentration).

3.4.3 Bias Assessment

3.4.3.1 Sensitivity Analysis

We tested for the effect of influential sub-studies by utilizing the "one-study removed" feature in the CMA software. This feature recalculates the mean effect size after removing each sub-study, so that influential sub-studies are more easily identified. Sensitivity analysis was conducted by analyzing the mean effect size with an influential sub-study included and removed from subgroup analysis and meta-regression models, and were excluded if removing the sub-study changed the mean effect size by 10%. No sub-studies met the exclusion criteria. We also performed meta-regression to identify influential covariates. Each covariate was analyzed in univariate and bivariate analysis with birth outcomes to reduce the risk of collinearity. Finally, we assessed publication bias using the Duvall and Tweedie's Trim and Fill method, which is described below.

3.4.3.2 Publication Bias

Publication bias results when studies relevant to the research question are not published or not made available. Some studies are more likely to be unavailable than others. Large studies (based on sample size, n>100), or long-term studies are likely to be published, regardless the result because of the expense involved in conducting the study [215]. Short-term medium-sized studies ($n \geq 30$, <100) and small studies (n<30) with large effect sizes are also likely be published [215]. However, small studies with small effect sizes or null results are the most likely to be unavailable for meta-analysis [215]. Figures B.2 and B.3 are the publication bias funnel plots for dichotomous and continuous outcomes, respectively. In our meta-analysis, our literature search resulted in only five out of 40 studies with samples sizes less than 100, so we expected publication bias to be low. We used Duval and Tweedie's Trim and Fill method to impute estimates of missing studies under a random effects model. For dichotomous outcomes, this resulted in a slightly smaller predicted mean effect size (OR: 1.053; 95%CI: 1.042, 1.064), compared to our overall estimate (OR: 1.055; 95%CI: 1.044, 1.065), but did not change the significance of our findings, and confirmed that publication bias in our study is most likely low. For continuous outcomes, the imputed estimate was smaller, (Cohen's *d*: -0.343; 95%CI: -0.353, -0.333), compared to our observation

(Cohen's *d*: -0.050; 95%CI: -0.062, -0.038), meaning the likelihood unpublished studies would change the direction of our findings is very low.

3.4.3.3 Risk of Bias Assessment

We employed the Risk of Bias (RoB) assessment method outlined in the Navigation Guide, developed by the Program on Reproductive Health and the Environment at University of California at San Francisco [280]. We modified the RoB evaluation criteria published in Lam, et al., 2016 [317] to rate each exposure-outcome analysis in nine domains: 1) study design; 2) source population; 3) exposure assessment; 4) outcome assessment; 5) confounding and analysis; 6) incomplete outcome data; 7) selective outcome reporting; 8) funding and conflicts of interest; and 9) other sources of bias. Each domain had four RoB categories. These categories are, from lowest to highest: 1) low risk of bias; 2) probably low risk of bias; 3) probably high risk of bias; and 4) high risk of bias. The RoB criteria we used in this meta-analysis is provided in Appendix D.

In a departure from the Navigation Guide protocol, we assigned one point for low RoB; two points for probably low RoB; three points for probably high RoB; and four points for high RoB, for each domain. The lowest theoretical RoB score was nine, and the highest theoretical RoB score was 36. The purpose of this was two-fold: 1) to distinguish studies with lower overall RoB from those with higher RoB; and 2) to assess the strength, precision, and thoroughness of the search strategy, eligibility criteria, and inclusion/exclusion criteria we employed in the systematic review. The results of the RoB analysis from our meta-analysis are presented as a heat map in Table 3.4. The average RoB score for studies included in the meta-analysis was 14.7, with a standard deviation of 2.28. The median was 14.5, and the range was 10-20. Thus, the included studies were determined to have low to probably low RoB overall. There were only two instances of high RoB in a domain and both were in the category of confounding and analysis, as neither study provided enough information on adjustment for confounding [295,308]. The study design category had the highest overall RoB score (100), representing the range of study designs included in the meta-analysis. The category with the next highest score was confounding and analysis (83), followed by exposure assessment (78).

3.4.4 Quality and Strength of Evidence.

We used the Navigation Guide criteria to rate the quality and strength of evidence across all included studies, and to determine an overall rating. This information is provided in Table 3.5. The quality of evidence rating scale of low, moderate, or high quality is based on assessment for several factors, including downgrade criteria (risk of bias, indirectness, inconsistency, imprecision, publication bias), and upgrade criteria (magnitude of effect, dose response, all possible confounding would confirm a null result). The quality rating of human evidence begins at 'moderate'. We downgraded the evidence included in our meta-analysis for indirectness (-1), as 17 out of 40 studies reported modeled prenatal exposure. We also downgraded the evidence for inconsistency (-1), due to the high level of heterogeneity in the overall analysis, although most sources of heterogeneity were identified through meta-regression. We upgraded the evidence for dose response (+1). Eleven studies reporting results in tertiles, or quartiles all showed a statistically significant dose response. We also upgraded the evidence for all possible confounding confirming a null result (+1). We evaluated the impact on the summary size on whether studies adjusted for tobacco smoke exposure, maternal age, BMI, diet, education, SES, parity, or Hx-PC and found those studies that did not adjust for these covariates had lower, non-significant summary effects, compared studies that included adjustment for these covariates. Thus, the quality rating of human evidence stayed at *moderate*.

We evaluated the strength of human evidence based on 1) the quality of evidence; 2) directness of effect; 3) the confidence in the effect; and 4) other compelling attributes that may influence certainty. The summary of human evidence is sufficient to determine that prenatal PAH exposure is associated with adverse effects on birth weight, head circumference, LBW+FG<85%, and SGA+IUGR; and marginally significant for birth length and PTB. However, confidence in the estimate is constrained by the heterogeneity (inconsistency) of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion. Based on these factors, we determined there is *limited evidence of toxicity*.

3.5 Discussion

The widespread dispersion of PAHs in the environment and their toxic effects have made these compounds a public health concern, and the focus of regulatory action. The primary public health objective of this meta-analysis was to evaluate the weight of epidemiological evidence of prenatal PAH exposure on birth outcomes in infants. We found a body of evidence with considerable between-study variation for each exposure-outcome analyzed. The inconsistency across included studies caused a downgrading of the human evidence in our analysis from sufficient to limited human evidence. We did not find a statistically significant link between prenatal PAH exposure and gestational age or ponderal index.

While the link between PAH exposure and cancer in humans has been known for almost a century [261], evidence that adverse birth outcomes was linked to smoking while pregnant [318], or living in highly polluted areas [319–321] prompting research on the chemicals in air pollution, such as PAHs. This led to the discovery of PAHs detected in human placental[322] and fetal tissue [140]. Since then, there has been increasing attention regarding the effect of prenatal PAH exposure on birth outcomes [189,323,324]. We initially found 2,244 peer-reviewed studies in English, but only 45 studies met eligibility criteria, and 40 met inclusion criteria. Of these, exposure-birth outcome analysis took place between 1989 and 2018, and the earliest study was not investigating PAHs, per se, but rather measuring a naphthalene metabolite (2-naphthol) from using mothballs [295]. The earliest to study designed specifically to investigate the effect of prenatal PAH exposure on birth outcomes was a birth cohort initiated in Poland, January 1992 [189]. Another birth cohort was initiated in the Czech Republic initiated in April 1994 [164]. The exposed groups in these early studies resided in highly polluted areas from coal-burning for industry and home-heating. The control groups were participants who resided in more rural areas, although the control group in Poland had twice as many coal stoves in use for home-heating, compared to the exposed group. The Czech Republic modeled air pollution exposure and found that prenatal PAH exposure led to a significant increase in IUGR overall, with the highest effect link to exposure in the first gestational month [164]. The Polish study measured PAH-DNA adducts in cord blood and found prenatal PAH exposure significantly decreased head circumference, even with the potential confounding of coal stove use in the control group [189]. A recent study investigated

the effect of lower prenatal PAH exposure levels. The 2019 study assessed the effect of prenatal exposure to persistent organic pollutants and size for gestational age and was conducted in the low industrialized Canary Islands, off the west coast of Africa [296]. The authors found that higher levels of PAHs measured in cord blood was associated with increased occurrence of small for gestational age in boys, but not girls [296].

The timeframe of our meta-analysis spanned almost three decades, allowing for the analysis of prenatal PAH exposure over time, which in this meta-analysis, was not statistically significant. A recent PAH exposure trend analysis on non-smokers in the U.S. found that while fluorene and phenanthrene exposure decreased from 2001-2014, naphthalene and pyrene exposure increased, and this may at least partially due to time spent indoors, and the move to gas appliances and home heating in the U.S. [325].

The mechanism of how prenatal PAH exposure affects fetal development is currently not well understood, especially in humans. It is likely that more than one mode of action exerts influence. Our meta-analysis presents evidence that prenatal PAH exposure is associated with adverse effects in several measures of fetal development, supporting a multiple mode of action hypothesis. However, an in-depth mechanistic review is beyond the scope of our study. We briefly highlight three possible modes of action that relate to the birth outcomes in infants included in our meta-analysis. One such mechanism involves increased cellular oxidative stress from PAH binding to the AhR, which can induce P450 enzymes, important for xenobiotic metabolism [326]. P450 enzyme activation generates reactive metabolites, such as quinones, that eventually deplete endogenous antioxidants needed to neutralize reactive oxygen species (ROS) [327]. Fetal development occurs in a low oxygen environment, but early gestation is a period of rapid cell division, differentiation, and translocation, producing ROS [328,329]. Normally, there is a balance between oxidant and anti-oxidant production to prevent ROS toxicity [329]. However, prenatal PAH exposure may tip the process out of balance. In experimental studies, continued ROS buildup was observed in fetal tissue, after maternal exposure to BaP was ceased, suggesting a lag between maternal prenatal PAH exposure and fetal exposure [330]. The possible oxidant-antioxidant imbalance may increase energy demand to overcome inadequately functioning fetal cellular machinery, or to make up for a cellular deficit during development, leading to fetal hypoxia or malnutrition. A related mode of action may be on placental restriction of oxygen available to

the fetus. The placenta expresses a high level of AhR (cite), especially in endothelial cells of blood vessels and umbilical cord veins [331]. Prenatal PAH exposure may act to reduce placental perfusion. Another mechanism under investigation is endocrine disruption [185]. The placenta produces several hormones important for fetal development, including estrogen, human chorionic gonadotropin and insulin growth factors [332]. In experimental studies, the hydroxylated metabolites of BaP and CHR exhibited estrogenic activity [333], which may impede the cascade of time-sensitive cell signaling needed for normal fetal development. A final mechanism may be direct changes to fetal DNA [334]. PAH-DNA adducts change the physical structure of DNA, and therefore, can change the transcription of DNA [335]. PAH-DNA adducts could also lead to reduced detoxifying ability in the placenta [336].

3.5.1 Strengths

One of the strengths of our study is that systematic reviews are considered by many to be more rigorous, transparent and useful in summarizing the scientific weight-of-evidence than a narrative review [280,337]. In addition, a meta-analysis is considered of more value because it provides both magnitude and direction of the mean effect that can be more informative for a broader audience, such as clinicians, policymakers. Another key advantage of meta-analysis is the ability to assess the range of effects overall, and in different subgroups. The value of our meta-analysis is the estimation of the mean effect of prenatal PAH exposure on birth outcomes in infants, given the conflicting results in primary studies.

We incorporated several tools accepted by the scientific community to improve the rigor and transparency, to identify and reduce bias, and to improve the reporting quality of the findings. Analysis of risk of bias indicated that our primary study search strategy, eligibility criteria, and inclusion/exclusion criteria led to the selection of well-designed studies with low to probably low risk of bias overall. The results aligned with our expectation that highest risk of bias was found in the study design domain. The next highest RoB domains: confounding and analysis, and exposure assessment, speaks to the challenge with which primary study authors must contend. Space constraints in peer-reviewed journals mean authors must choose parsimonious methods to convey their research results. However, this also means that data essential for conducting a meaningful meta-analysis may be missing, forcing the meta-analyst to seek information from primary study authors, spending

time deriving appropriate values from available data, or omitting relevant studies when needed information remains unavailable.

We limited eligible studies to only those that reported a surrogate of PAH exposure during pregnancy or shortly after delivery, to establish temporality of exposure prior to the outcome. Two reviewers working independently in the screening and full-text review of articles had fair to moderate agreement, and consensus was reached through review and discussion. Analytical methods reported in primary studies were assessed for appropriateness, given the exposure measure. We set a threshold of ten sub-studies to increase precision of mean effect estimates, and used the more conservative covariate-adjusted results, when available. We found enough studies that statistical power was adequate for birth length, birth weight, head circumference, and preterm birth.

Validity of a meta-analysis is dependent on access to relevant literature to reduce the potential for publication bias. In our meta-analysis, most studies were of moderate or large sample size, reducing the likelihood of publication bias. The results of the Duvall and Tweedie Trim and Fill assessment confirmed there is low likelihood that unpublished study results would change the mean effect size or significance of our meta-analysis.

3.5.2 Limitations

Measures of exposure, outcome and modeled covariates varied across primary studies. The precision and validity of a meta-analysis relies on the integrity of the science and reporting methods utilized in primary studies. Fundamental errors in a low-quality study could affect the overall quality of the meta-analysis. Utilizing the Navigation Guide and the PRISMA checklist were attempts to address this limitation by rating the quality of studies and being transparent in reporting the results. However, the possibility of unmeasured confounding or undetected bias exists.

Measurements of PAH concentration in most biomarkers of exposure had a relatively short half-life and could only indicate recent exposure. Urine samples are a convenient method to measure maternal exposure, but placental tissue and cord blood are more direct measures of fetal exposure, although the half-life of PAH metabolites in human blood, including cord blood, is not well characterized. Many biomonitoring and modeled studies assume relatively constant maternal PAH exposures throughout pregnancy, which may or

may not be the case. For example, Kumar, et al. (2020) found an uneven distribution of PAHs in maternal blood, cord blood and placental tissue, with PAHs detected in maternal blood, but not in the other biomarkers [312]. The mechanisms of action previously discussed are likely to play a part, but this needs future research.

The statistical analysis for gestational age, and the combined birth outcomes on fetal growth, were under-powered due to the low number of available studies, and there were not enough studies to evaluate the weight of evidence of prenatal PAH exposure and cephalization index. There was also moderate to high between-study variation. We used meta-regression to identify sources of heterogeneity and quantify the impact on the mean effect size. The null hypothesis in the test for heterogeneity is that all studies share a common effect size, so heterogeneity across all studies equals zero. However, this is rarely the case [217]. The intent of a systematic review and meta-analysis in environmental epidemiology is to bring together studies that evaluated the exposure-outcome association from diverse populations and conditions. To stay true to that intent, the focus should be on the effect heterogeneity may have on the conclusions drawn, rather than on the presence of heterogeneity [217]. What is critical is to include enough studies that meet eligibility criteria so that the extent of the between-study variation can be quantified reliably with meta-regression[215].

3.5.3 Gaps in the Literature & Recommendations

In our analysis, we did not find any eligible studies measuring the effects of prenatal PAH on ponderal index after 2011, or on low birth weight after 2012. We also did not find any studies meeting our eligibility criteria that assessed gestational age by measuring prenatal PAH exposure specifically in the first or second trimester, or modeled over a nine-month pregnancy. We did not find any studies assessing preterm birth by measuring PAH exposure in the first/second trimester, although six studies modeled exposure over a nine-month pregnancy period. Only one study evaluated preterm birth by collecting personal air sampling data in the third trimester [271]. A similar gap in research was found in assessing fetal growth restriction in the first or second trimester; and for modeling the impact of prenatal PAH exposure on ponderal index across a 9-month pregnancy.

Although sample populations from 16 countries and 13 U.S. states were included in our meta-analysis, we recognize there are research gaps in in terms of geography. We highlight this by showing the number of studies by country on world map in Figure B.4. For example, only one 1994 study conducted in Africa; one 2013 study conducted in the Middle East, and no studies conducted in Russia, Canada, Central or South America met our eligibility criteria. Finally, we recommend primary studies report overall results and quantiles (i.e., tertiles or quartiles) so that dose-response can be summarized in a meta-analysis.

3.6 Conclusions

There is limited evidence of toxicity regarding prenatal PAH exposure and several birth outcomes. While there is sufficient human evidence, there is also high between-study variance, which downgrades the evidence from sufficient to limited. We found a statistically significant association between prenatal PAH exposure is associated and decreased birth weight and head circumference, and marginally significant association with decreases in birth length. Additionally, we found a statistically significant association between prenatal PAH exposure an increased combined outcome of low birth weight/fetal growth < 85% of normal, an increased combined outcome of small for gestational age/intrauterine growth restriction, and a marginally significant association with preterm birth. Confidence in these estimates is constrained by inconsistency of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion.

3.7 Acknowledgements.

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Table 3.1. Summary of overall meta-analysis statistics for birth outcomes.

Outcome [a]	*k*	k_{sub}	n_{pooled}	# PAHs [b]	Est. Summary Effect Size, 95% CI: Summary Effect	95%CI Lower	95%CI Upper	*p* [c]
Continuous Outcomes – Summary Effect Measure: Cohen's *d*								
Birth Length	19	49	39,857	11	-0.161	-0.34	0.02	0.080
Birth Weight	23	84	41,493	17	-0.160	-0.29	-0.03	**0.017**
Gestational Age	6	18	1,189	11	0.061	-0.11	0.23	0.483
Head Circumference	16	37	5,772	7	-0.091	-0.70	-0.02	**0.019**
Ponderal Index	4	10	2,304	6	-0.002	-0.11	0.10	0.965
Dichotomous Outcomes – Summary Effect Measure: Odds Ratio								
LBW [d]	6	14	545,033	6	1.153	1.08	1.23	<0.001
FG< 85%	1	2	554	1	1.277	0.49	3.36	0.620
LBW+FG< 85%	7	16	545,587	6	1.071	1.03	1.11	**<0.001**
Preterm Birth	7	30	92,310	17	1.092	0.99	1.2	0.074
SGA	6	9	221,242	3	1.146	0.991	1.324	0.065
IUGR	1	2	4,854	1	1.758	1.058	2.920	0.029
SGA + IUGR	7	11	226,096	3	1.189	1.03	1.37	**0.016**

Outcome	Test of Heterogeneity: *Q*	*df*	*p* [e]	I^2 (%)	Est. True Effects Variance: T^2	SE	*T*	Prediction Interval [f]: 95% Lower	95% Upper
Continuous Outcomes									
Birth Length	2,087.89	48	<0.001	97.70	0.385	0.248	0.620	-1.40	1.08
Birth Weight	2,415.04	83	<0.001	96.56	0.335	0.199	0.578	-1.32	1.00
Gestational Age	87.37	17	<0.001	80.54	0.109	0.048	0.329	0.00	0.72
Head Circumference	124.37	36	<0.001	71.04	0.034	0.015	0.184	-0.46	0.28
Ponderal Index	24.76	9	<0.001	63.65	0.014	0.013	0.199	-0.24	0.24
Dichotomous Outcomes									
LBW	181.76	13	<0.001	92.30	0.007	0.005	0.086	0.98	1.33
FG< 85%	5.196	1	0.023	80.75	0.395	0.691	0.628	0.02	2.53
LBW+FG< 85%	64.81	15	<0.001	76.86	0.002	0.002	0.047	0.98	1.16
Preterm Birth	131.36	29	<0.001	77.92	0.029	0.019	0.171	0.75	1.43
SGA	78.27	8	<0.001	89.78	0.029	0.027	0.170	0.78	1.46
IUGR	1.335	1	0.248	25.09	0.036	0.202	0.189	1.38	2.14
SGA + IUGR	84.38	10	<0.001	88.15	0.030	0.028	0.174	0.84	1.54

[a] LBW: low birth weight. FG<85%: fetal growth <85% of normal. SGA: small for gestational age. IUGR: intrauterine growth restriction.

[b] Includes total PAHs.

[c] Significance of hypothesis test that the true summary effect is equal to zero. α=0.05. Bold values: $p < \alpha$.

Table 3.1 – Continued.

[d] Statistics for LBW, FG< 85%, SGA, and IUGR are shown individually (shaded rows, statistics shown except for prediction interval), and grouped as LBW+FG< 85%, and SGA+IUGR. The grouping allowed the inclusion of studies reporting FG<85% (k_{sub}=2) and IUGR (k_{sub} = 2) in the meta-analysis.

[e] Test of heterogeneity. Two-tailed test of the null hypothesis that the true mean effect does not vary across studies, $\alpha = 0.10$.

[f] The prediction interval is an estimate of the dispersion of true effects, which cannot be measured. This interval indicates the range in which we would expect the true effect size to fall in all 95% of all comparable populations.

Table 3.2. Stratified analysis by birth outcome, comparing studies that utilized biomarkers, compared to studies that modeled exposure, to examine prenatal PAH exposure effects on birth outcomes.

	Biomarker Only Studies[a]						Modeled Only Studies[b]						
Continuous Outcomes	*k*	k_{sub}	n_{pooled}	Cohen's *d*	95%CI	p^c	*k*	k_{sub}	n_{pooled}	Cohen's *d*	95%CI	p^c	p^d
Birth Length	14	41	4,335	-0.118	-0.224, -0.011	**0.030**	5	8	35,415	-0.243	-0.675, 0.189	0.270	0.811
Birth Weight	18	76	5,906	-0.171	-0.269, -0.073	**0.001**	5	8	35,418	-0.014	-0.419, 0.392	0.948	0.757
Gestational Age	5	16	653	0.118	-0.047, 0.282	0.162	1	2	536	-0.368	-1.082, 0.345	0.311	0.468
Head Circumference	12	30	4,212	-0.105	-0.193, -0.016	**0.021**	4	7	1,637	-0.022	-0.146, 0.102	0.726	0.801
Ponderal Index	4	10	2,304	-0.002	-0.108, 0.103	0.965	--	--	--	--	--	--	--
Dichotomous Outcomes	*k*	k_{sub}	n_{pooled}	OR	95%CI	*p*	*k*	k_{sub}	n_{pooled}	OR	95%CI	*p*	*p*
LBW + FG<85%	1	6	175	1.206	0.697, 2.085	0.503	6	10	513	1.072	1.030, 1.115	**0.001**	0.827
Preterm Birth	1	17	84	1.218	0.992, 1.496	0.060	6	13	214,989	1.062	0.951, 1.185	0.284	0.720
SGA + IUGR	--	--	--	--	--	--	7	11	226,096	1.189	1.032, 1.369	**0.016**	--

[a] Biomarker only studies measured prenatal PAH exposure in maternal blood, cord blood, maternal urine, or placental tissue.

[b] Modeled only studies measured prenatal PAH exposure based on data from stationary air monitors, personal air sampling, emissions reporting, dietary questionnaires, and occupational exposure assessments.

[c] Significance at each birth outcome, $\alpha = 0.05$. Bold values: $p < \alpha$.

[d] Significance of difference between groups tested with a *z*-test, $\alpha = 0.05$.

Table 3.3 Meta-regression statistics of statistically significant exposure-birth outcome analyses, overall, and by covariate. Univariate results listed in order of R^2, highest to lowest. Bivariate results are first listed by covariate with highest number of statistically significant birth outcome associations, and then by R^2.

			Meta-Regression Results						
Outcome Type	Covariate [a]	Outcome [b]	Q^c	df^d	p^e	I^{2f}	T^{2g}	R^{2h}	Note [i]
Univariate Analysis									
Dichotomous	Exp. Matrix	--	14.65	7	0.041	71.84	0.03	0.28	
Dichotomous	Adj. Hx-PC	--	5.38	1	0.020	81.15	0.03	0.27	
Dichotomous	Country	--	10.94	4	0.027	82.74	0.03	0.24	
Dichotomous	Adj. Maternal Diet	--	2.86	1	0.091	83.19	0.04	0.08	MS
Dichotomous	Adj. Smoke Exposure	--	3.96	1	0.046	83.10	0.04	0.01	MS
Continuous	Country	--	71.64	14	0.000	73.34	0.09	0.47	
Continuous	Exp. Matrix	--	33.00	6	0.000	81.73	0.13	0.25	
Continuous	PAH Congener	--	24.49	16	0.079	81.42	0.15	0.12	MS
Continuous	Adj. Hx-PC	--	10.36	1	0.001	82.76	0.18	0.11	
Continuous	Adj. Maternal Educ.	--	7.40	1	0.007	82.90	0.18	0.10	
Continuous	Adj. Maternal BMI	--	7.13	1	0.008	82.87	0.18	0.09	
Continuous	Adj. Parity	--	7.43	1	0.006	83.73	0.19	0.07	
Continuous	Adj. SES	--	4.59	1	0.032	83.09	0.19	0.06	
Bivariate Analysis									
Dichotomous	Study Design	LBW+FG<85%	21.68	14	0.086	35.41	0.00	0.72	MS
Dichotomous	Study Design	PTB	118.75	28	0.000	76.42	0.04	0.37	
Dichotomous	Study Design	SGA+IUGR	25.54	9	0.002	64.76	0.06	0.29	
Continuous	Study Design	GA	72.33	15	0.000	79.26	0.11	0.11	
Continuous	Study Design	BW	951.66	81	0.000	91.49	0.20	0.06	
Continuous	Study Design	HC	110.72	35	0.000	68.39	0.03	0.04	
Continuous	Study Design	BL	551.25	47	0.000	91.47	0.19	0.01	
Dichotomous	Adj. Maternal BMI	LBW+FG<85%	45.94	14	0.000	69.53	0.01	0.54	
Dichotomous	Adj. Maternal BMI	SGA+IUGR	73.38	9	0.000	87.74	0.04	0.49	
Dichotomous	Adj. Maternal BMI	PTB	87.32	28	0.000	67.94	0.06	0.17	
Continuous	Adj. Maternal BMI	GA	76.84	16	0.000	79.18	0.11	0.14	
Continuous	Adj. Maternal BMI	BW	2,275.68	82	0.000	96.40	0.21	0.03	
Continuous	Adj. Maternal BMI	HC	122.55	35	0.000	71.44	0.03	0.03	
Continuous	Adj. Maternal BMI	BL	1754.07	47	0.000	97.32	0.19	0.01	
Dichotomous	Exposure Matrix	SGA+IUGR	16.83	0	<0.001	64.35	0.00	0.72	
Continuous	Exposure Matrix	GA	45.28	14	<0.001	69.08	0.06	0.53	
Continuous	Exposure Matrix	PI	13.71	8	0.090	41.67	0.01	0.32	MS
Continuous	Exposure Matrix	BW	712.16	77	<0.001	89.19	0.17	0.21	
Continuous	Exposure Matrix	BL	365.77	43	<0.001	88.24	0.18	0.08	
Continuous	Exposure Matrix	HC	115.09	31	<0.001	73.06	0.03	0.05	
Dichotomous	Country	LBW+FG<85%	44.39	13	0.000	70.71	0.01	0.57	
Continuous	Country	BW	455.83	69	0.000	84.86	0.12	0.46	
Continuous	Country	HC	64.17	29	0.000	54.81	0.02	0.46	
Dichotomous	Country	SGA+IUGR	70.18	7	0.000	90.03	0.05	0.37	
Continuous	Country	GA	66.05	15	0.000	77.29	0.09	0.26	
Continuous	Country	BL	213.53	40	0.000	81.27	0.17	0.09	

Table 3.3 – Continued.

Outcome Type	Covariate [a]	Outcome [b]	Q^c	df^d	p^e	I^{2f}	T^{2g}	R^{2h}	Note [i]
Continuous	Adj. Maternal Diet	HC	55.51	35	0.015	36.95	0.01	0.73	
Dichotomous	Adj. Maternal Diet	SGA+IUGR	74.63	9	0.000	87.94	0.05	0.45	
Continuous	Adj. Maternal Diet	BL	2,017.87	47	0.000	97.67	0.17	0.13	
Continuous	Adj. Maternal Diet	BW	2,273.50	82	0.000	96.39	0.21	0.04	
Continuous	Adj. Maternal Diet	GA	81.13	16	0.000	80.28	0.12	0.03	
Continuous	Exposure Period	GA	82.71	16	0.000	78.00	0.10	0.17	
Continuous	Exposure Period	HC	104.58	33	0.000	68.45	0.03	0.09	
Continuous	Exposure Period	BL	405.47	45	0.000	88.90	0.18	0.04	
Dichotomous	Exposure Period	PTB	129.38	27	0.000	79.13	0.07	0.03	
Continuous	Exposure Period	BW	850.51	80	0.000	90.59	0.21	0.01	
Dichotomous	Time Range	LBW+FG<85%	33.53	12	0.001	64.21	0.00	0.72	
Dichotomous	Time Range	SGA+IUGR	16.94	7	0.018	58.68	0.00	0.72	
Continuous	Time Range	GA	38.96	15	0.001	61.50	0.04	0.67	
Continuous	Time Range	HC	88.30	32	0.000	63.76	0.02	0.24	
Continuous	Time Range	BW	1,169.98	79	0.000	93.25	0.21	0.04	
Dichotomous	Adj. Parity	SGA+IUGR	30.59	9	0.000	70.58	0.00	0.72	
Continuous	Adj. Parity	HC	80.27	35	0.000	56.40	0.02	0.47	
Dichotomous	Adj. Parity	LBW+FG<85%	59.21	14	0.000	76.36	0.01	0.16	
Continuous	Adj. Parity	BW	1,301.61	82	0.000	93.70	0.19	0.13	
Continuous	Adj. Maternal Educ.	GA	82.43	16	0.000	80.59	0.12	0.04	
Continuous	Adj. Maternal Educ.	HC	123.54	35	0.000	71.67	0.03	0.03	
Continuous	Adj. Maternal Educ.	BL	1,719.49	47	0.000	97.27	0.19	0.02	
Continuous	Adj. Maternal Educ.	BW	2,238.08	82	0.000	96.34	0.21	0.01	
Dichotomous	Adj. Maternal Age	LBW+FG<85%	33.25	14	0.003	57.90	0.00	0.72	
Continuous	Adj. Maternal Age	BW	2,415.04	82	0.000	96.60	0.21	0.03	
Dichotomous	Adj. Hx-PC	PTB	70.30	28	0.000	60.17	0.04	0.43	
Continuous	Adj. Hx-PC	BL	673.12	47	0.000	93.02	0.17	0.13	
Continuous	Adj. Hx-PC	BW	1,852.12	82	0.000	95.57	0.21	0.04	
Continuous	Adj. SES	GA	42.72	16	0.000	62.55	0.04	0.64	
Continuous	Adj. SES	BW	1,603.81	82	0.000	94.89	0.19	0.11	
Continuous	Adj. SES	HC	107.16	35	0.000	67.34	0.03	0.09	
Continuous	PAH Congener	BW	1,038.98	67	0.000	93.55	0.20	0.09	
Continuous	PAH Measure	BW	2,224.37	82	0.000	96.31	0.21	0.01	

[a] Covariates. Exp. Matrix: Exposure Matrix (exposure biomarkers: cord blood, maternal blood, maternal urine, or placental tissue; exposure models: data from stationary air monitoring, personal air monitoring, emissions reports, dietary questionnaires, or occupational exposure) . Exposure Period: estimation of prenatal PAH exposure, based on when exposure biomarker was collected and half-life, or the length of estimated exposure in modeled data (first/second trimester; third trimester, entire pregnancy, or end of pregnancy). Country: country where primary study was conducted. Study Design: cohort, case-control, cross-sectional. PAH Congener: individual parent PAH, (i.e., NAP, FLU, BaP, etc., including total PAHs). PAH Measure: PAH-DNA adducts or PAH concentration. Time Range: decade when study took place (1990-1999; 2000-2009; 2010-2019; not reported; or Other-spans multiple decades).

Table 3.3 – Continued.

Adj. covariates are binary covariates (Y/N) if primary study adjusted for the covariate in final models. Adj. Hx-PC: history of pregnancy complications. Adj. Maternal Diet: maternal diet during pregnancy. Adj. Smoke Exposure: maternal exposure to tobacco smoke during pregnancy. Adj. Maternal Educ.: highest level of maternal education at time of enrollment. Adj. Maternal Age: maternal age at delivery. Adj. Maternal BMI: maternal pre-pregnancy BMI. Adj. Parity: maternal parity. Adj. SES: maternal or household socioeconomic status.

[b] Outcomes. BL: birth length. BW; birth weight. GA: gestational age. HC: head circumference. LBW+FG<85%: combined low birth weight with fetal growth <85% of normal. PTB: preterm birth. SGA+IUGR: combined small for gestational age with intrauterine growth restriction.

[c] Q. Weighted sum of primary study squared deviations from the summary effect on a standardized scale.

[d] *df*. Degrees of freedom, the number of studies included in the meta-regression, (k) minus one.

[e] *p*. Two-tailed test of the null hypothesis that the summary effect = 0, $\alpha = 0.05$.

[f] I^2. Ratio of the total amount of variation in the meta-regression explained by variance in true effects, T^2.

[g] T^2. Variance of true effects, using the restricted maximum likelihood (REML) method to estimate variance.

[h] R^2. Ratio comparing the covariate model with the intercept-only model, and estimate of the amount of variation in the model explained by the covariate.

[i] Note. Results of hypothesis test were marginally significant, $\alpha > 0.050$, <0.099.

Table 3.4. Risk of Bias Heat Map of Included Birth Outcome Studies.

Study ID	Study Design	Selection Bias	Exp. Assess.	Outcome Assess.	Conf ounding	Incomplete Outcome Data	Selective Outcome Reporting	COI	Other	RoB Score
Agarwal 2018	3	1	2	2	2	1	2	1	1	15
Agarwal 2020	3	1	1	1	2	1	1	1	2	13
Al-Saleh 2013	3	2	1	1	2	1	3	3	2	18
Cabrera-Rodriguez 2019	3	1	3	2	3	3	3	1	1	20
Chen 2014	3	1	1	1	2	1	1	1	2	13
Choi 2006	1	1	1	2	1	1	1	2	1	11
Choi 2008	1	1	1	2	2	2	1	1	1	12
Dejmek 2000	2	3	3	2	1	1	1	2	1	16
Duarte-Salles 2012	3	1	1	1	2	1	1	1	1	12
Duarte-Salles 2013	3	1	2	1	2	1	1	1	1	13
Ghosh 2012	2	1	2	1	3	1	1	1	1	13
Gong 2018	2	1	3	1	3	2	1	1	1	15
Guo 2012	3	2	1	2	2	3	2	1	1	17
Huang 2020	3	2	3	1	2	3	1	1	1	17
Huo 2019	3	2	2	1	2	1	1	1	1	14
Kumar 2020	3	2	2	2	1	1	1	1	1	14
Lamichhane 2016	3	1	3	1	3	1	1	1	1	15
Langlois 2014	3	1	2	2	1	1	1	1	1	13
Maxwell 1994	3	1	3	1	4	2	1	2	1	18
Maypole-Keenan 2016	2	1	3	2	3	1	1	2	1	16
Nie 2018	3	1	2	1	1	2	1	1	1	13
Norlen 2019	3	2	2	1	3	2	1	1	1	16
Padula 2014	2	1	2	2	2	2	1	2	1	15
Pedersen 2013	2	1	1	1	2	2	1	1	1	12
Perera 1998	2	1	1	1	1	1	1	1	1	10
Perera 2003	2	1	2	1	1	1	2	2	1	13
Perera 2004	2	1	2	1	1	1	1	2	1	12
Perera 2005	2	1	2	2	1	2	2	1	1	14
Polanska 2010	3	1	2	1	2	2	1	2	1	15
Polanska 2014	3	1	2	1	1	3	1	1	1	14
Porter 2014	3	1	3	2	3	3	1	1	1	18
Snijder 2012	3	1	2	1	2	1	1	1	1	13
Sram 2006	1	3	1	2	3	3	1	2	1	17
Suter 2019	2	1	1	2	4	1	1	1	1	14
Suzuki 2010	2	2	2	2	2	3	1	2	1	17
Tang 2014	2	1	1	2	2	2	2	1	1	14
Vassilev 2001a	3	1	3	2	2	3	1	2	1	18
Vassilev 2001b	3	1	3	2	2	3	1	2	1	18
Wilhelm 2011	2	1	3	2	3	2	1	1	1	16
Yang 2018	3	1	1	2	2	2	2	1	1	15

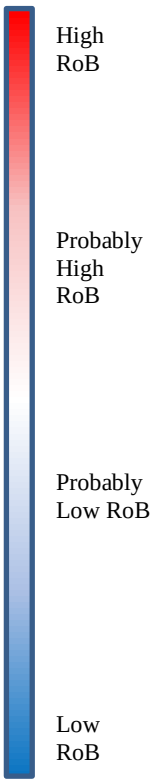


Table 3.5. Quality and Strength of Evidence, and Overall Rating, all included studies [338].

Quality of Evidence	Human evidence begins at "Moderate Quality".	
Downgrade criteria	**Assessment**	**Downgrade**
Risk of Bias	Evidence of probably low risk of bias exists across studies, RoB score range: 10-20. This provides evidence that a priori eligibility criteria and inclusion/exclusion criteria helped to focus on well-conducted relevant research on prenatal PAH exposure and the effect on birth outcomes.	0
Indirectness	• Only human studies included. • Only studies that measured prenatal PAH exposure included. • Direct measure of outcome using biomarkers (23/40 included studies). • Modeled exposure assessments (17/40 included studies) are an indirect measure of fetal exposure. • Some biomarkers collected at EOP, and can only indicate recent exposure.	-1
Inconsistency	• Heterogeneity was high across birth outcomes, but this was expected. • Country, exposure matrix, adjustment for history of pregnancy complications analyzed explained 83% of variance in continuous outcomes, and 79% of the variance in dichotomous outcomes. • Time range, adjustment for maternal diet and smoke exposure during pregnancy explained the rest of the variance in dichotomous outcomes. PAH congener, adjustment for maternal pre-pregnancy BMI, maternal education, parity, and SES, explained an additional 13% of the variance in continuous outcomes. • Only 4% of overall variance unexplained.	-1
Imprecision	• The confidence intervals around mean effect of each birth outcome are reasonably precise, based on sample size. • The precision of the mean effect estimates for GA, and ponderal index are larger, relative to the precision of the mean effect estimate for BL, BW, HC, LBW+FG<85%, PTB, and SGA+IUGR, but both GA and ponderal index had adequate number of exposure-outcome analyses, *ksub* = 15, and 10 respectively; and adequate pooled sample sizes, 1,081 and 2,435, respectively.	0
Publication Bias	• Low probability of publication bias, based on assessment using Duval and Tweedie's Trim and Fill method. • Adequate number of studies with small, moderate, and large sample sizes, with null, and small to moderate effects. • Inclusion criteria of eligible studies available in English may excluded available non-English studies.	0

Table 3.5 – Continued.

Upgrade criteria	Assessment	Upgrade
Large magnitude of effect	• Summary effect size was statistically significant for BW, HC, LBW+FG<85%, and SGA+IUGR, and marginally significant for BL, and PTB. However, the magnitude of effect was not especially large in any birth outcome, i.e., no dichotomous birth outcome summary effect, OR, > 2.00, and no continuous birth outcome effect, Cohen's d, >0.80.	0
Dose response	• Of the 11 studies reporting results in tertiles or quartiles, all showed a statistically significant dose response. • Highest effect seen in highest exposure category. • Most reported exposure was for total PAHs, followed by NAP, PHE, and BaP.	+1
All possible confounding would confirm a null result	• Evaluated impact on results if studies adjusted for smoke exposure, maternal age, BMI, diet, education, SES, parity, Hx-PC. • Other covariates were maternal age, BMI, education, SES, and parity. Adjusting for HX-PC was marginally significant • The statistical significance of other adjusted covariates did not change whether studies adjusted for the covariates or not. • Possibility remains of unmeasured confounding.	+1

Final Decision on Overall Quality of Human Evidence

- The quality of evidence was downgraded for:
  - High heterogeneity, although most between-study variation was explained in further analysis (-1).
- The quality of evidence was upgraded for:
  - Evidence of dose response (+1).
  - Evidence that all possible confounding would confirm a null result (+1).

Overall, the meta-analysis is rated as **Moderate to High Quality**.

Strength of Evidence - Considerations	
• Quality of evidence	Moderate
• Directness of effect	Human studies, prenatal exposure
• Confidence in effect	Moderate confidence in effect
• Other compelling attributes of the data that may influence certainty	Exposure period Adjustment for important covariates Unmeasured confounding
Overall Rating	**Limited human evidence of toxicity.**
Reasoning:	The summary of human evidence is sufficient regarding the exposure-birth outcome relationship observed. Evidence is sufficient to determine the effects of the prenatal PAH exposure on birthweight, head circumference, LBW+FG<85%, SGA+IUGR, and marginal for birth length and preterm birth. However, confidence in the estimate is constrained by inconsistency of findings across individual studies, which downgrades the overall rating from sufficient to limited. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion.

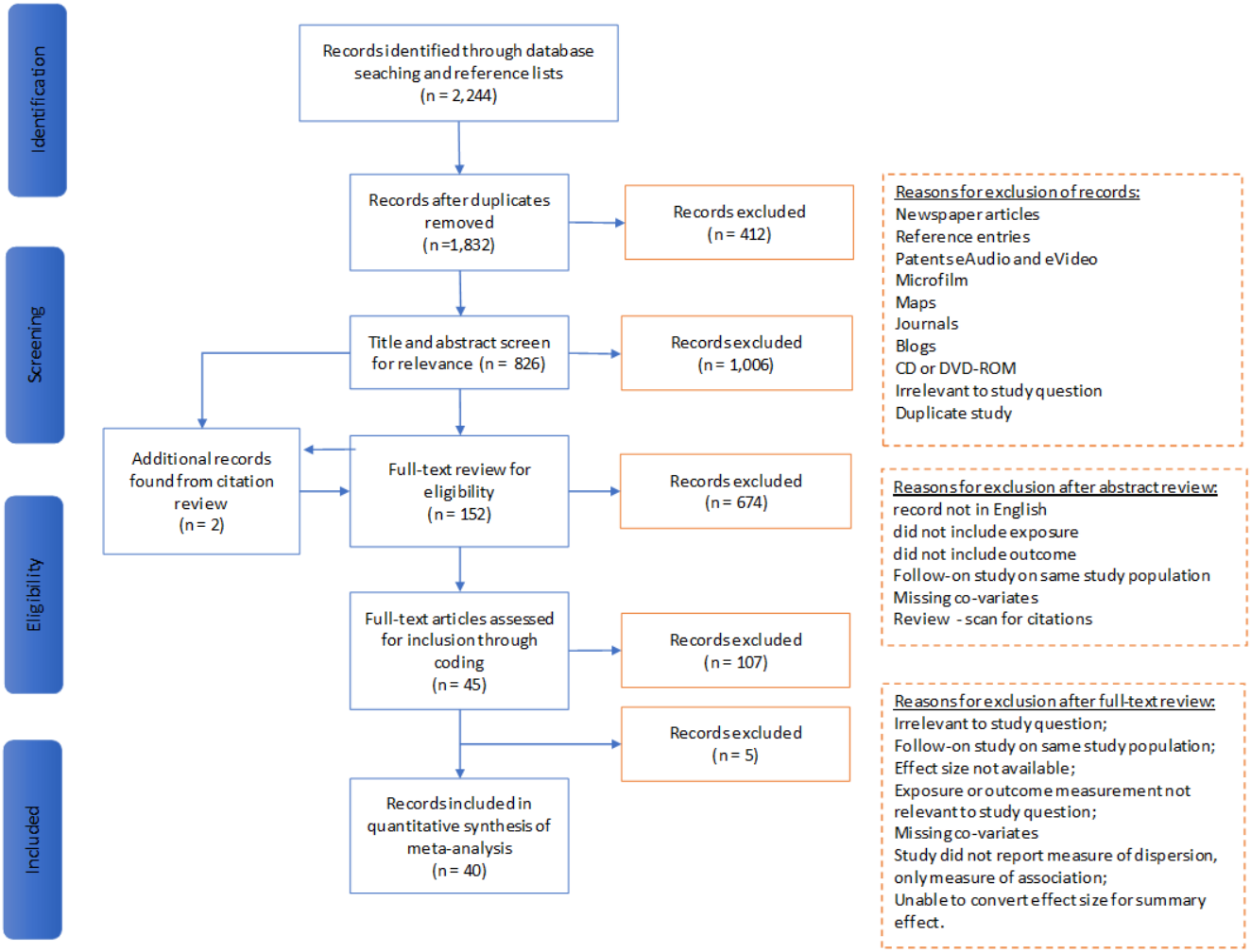
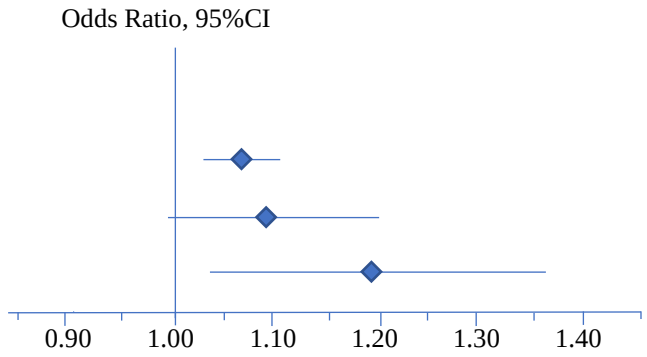


Figure 3.1. PRISMA diagram of study selection – birth outcomes

Dichotomous Outcomes

Birth Outcome[a]	OR	95% Lower	95% Upper	*p*[b]
LBW+FG<85%	1.071	1.030	1.113	**<0.001**
Preterm Birth	1.092	0.991	1.203	0.074
SGA+IUGR	1.189	1.032	1.369	**0.016**



Continuous Outcomes

Birth Outcome[a]	Cohen's *d*	95% Lower	95% Upper	*p*[b]
Birth Length	-0.161	-0.340	0.019	0.080
Birth Weight	-0.160	-0.292	-0.028	**0.017**
GA	0.061	-0.110	0.232	0.483
HC	-0.091	-0.166	-0.015	**0.019**
PI	-0.002	-0.108	0.103	0.965

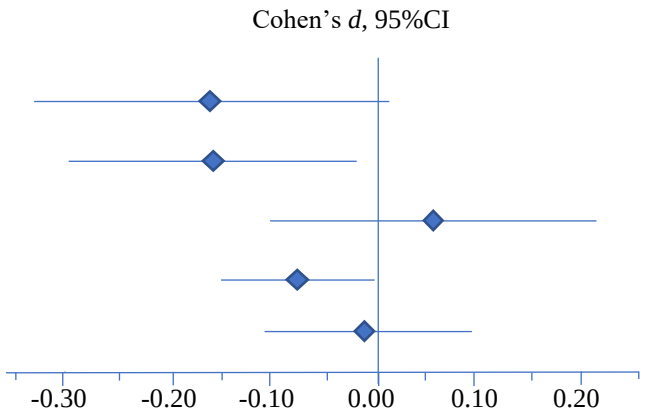


Figure 3.2. Forest plot summaries, by outcome type and birth outcome.

[a] Birth Outcome. LBW+FG<85%: combined outcomes of low birth weight and fetal growth <85% of normal. SGA+IUGR: combined outcomes of small for gestational age and intrauterine growth restriction. GA: gestational age. HC: head circumference. PI: ponderal index.

[b] Two-tailed significance at each birth outcome, $\alpha = 0.05$. Bold values: $p < \alpha$.

Chapter 4 – Third Manuscript

Prenatal and Early-Life Exposure to Polycyclic Aromatic Hydrocarbons (PAHs) and Adverse Neurodevelopment Outcomes: A Systematic Review and Meta-Analysis

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4.1 Abstract

Background: Recent research indicates prenatal exposure to Polycyclic Aromatic Hydrocarbons (PAHs) may be associated with adverse neurodevelopment outcomes. Several primary studies have evaluated the association of various measures of prenatal PAH exposure on cognitive function, psychomotor function, and behavior problems, but there are conflicting research results. A weight of evidence approach is needed.

Objective: Identify, examine, quantify, and summarize the weight of evidence of prenatal PAH exposure on neurodevelopment outcomes in infants and children.

Methods: We conducted a systematic review to identify eligible studies of peer-reviewed data available for inclusion in a meta-analysis. An *a priori* search strategy included search terms in PubMed, Wed of Science, and Google Scholar. Eligibility criteria included English language primary studies that modeled or measured PAH exposure during pregnancy, or early-life, and at least six months before completion of the reported neurodevelopment assessment. No limits were put on study time period or geographic location. Study screening and full-text review followed PRISMA protocol and was performed by two reviewers working independently using Covidence software. Studies included in the meta-analysis were evaluated using Comprehensive Meta-Analysis software, v3. Risk of bias was evaluated using the Navigation Guide protocol. Of studies identified in the initial search, 26 were eligible for inclusion in the meta-analysis. Neurodevelopment outcomes were grouped into either dichotomous (summary effect measure: odds ratio) or continuous outcomes (summary effect measure standardized mean difference, i.e., Cohen's *d*). Neurodevelopment outcomes examined were cognitive domain (96% in 26 studies), psychomotor domain (35%), and behavior domain (62%). The most common dichotomous neurodevelopment outcome subdomains were attention problems, behavior problems, and anxiety/depression (24%, respectively). For continuous outcomes, the most common were intelligence (40%), psychomotor skills (24%), and attention problems (20%). We report the summary effect size of each neurodevelopment domain and subdomain, along with the 95%CI, and evaluate the source and magnitude of between-study variance.

Results: In meta-analysis, we found a statistically significant ($\alpha = 0.05$) positive association in dichotomous outcomes between prenatal/early-life PAH exposure and anxiety/depression (OR:

1.36; 95%CI: 1.10, 1.68; p =0.005; n_{pooled} = 4,989; I^2 = 73.58%), and in neurodevelopment delay (OR: 1.07; 95%CI: 1.01, 1.14; p =0.028; n_{pooled} = 1,113; I^2 = 30.24%). We found a marginally statistically significant positive association between prenatal/early-life PAH exposure and attention problems (OR: 1.81; 95%CI: 0.96, 3.43; p = 0.068; n_{pooled} = 2,997; I^2 = 86.35%). In continuous outcomes, we found a statistically significant negative association between prenatal/early-life PAH exposure and motor skills (Cohen's d: -0.371, 95%CI: -0.52, -0.22; p < 0.001; n_{pooled} = 1,372; I^2 = 96.74%), and in adaptive behavior (Cohen's d: -0.142, 95%CI: -0.25, -0.00; p = 0.042 n_{pooled} = 1,128; I^2 = 84.27%). We did not find a statistically significant association between prenatal/early-life PAH exposure and intelligence, language skills, social behavior, ADHD, or other behavior problems.

Conclusion: Based on the Navigation Guide protocol, there is limited human evidence to determine that prenatal/early-life PAH exposure reduces motor skills; and increases anxiety/depression, attention problems, and neurodevelopment delay. The human evidence linking prenatal/early-life PAH exposure with other evaluated neurodevelopment outcomes was inconclusive. Between-study variance (heterogeneity) was low to considerable across neurodevelopment outcome assessments, with I^2 ranging from 0 to 96.7%, and this led to downgrading the human evidence from sufficient to limited. However, heterogeneity is expected in observational research, and limited human evidence of adverse neurodevelopment effects associated with prenatal/early-life exposure to a common environmental pollutant is cause for concern.

4.2 Introduction

Studying the development and function of the human brain is one of the most complex fields in biomedical sciences [339]. The adult brain is made up over 100 billion neurons with over 100 trillion neural interconnections [340]. The most dynamic neurodevelopment occurs *in utero*, when complex chemical processes are required for normal development and dependent on critical timing of each developmental process [341–343]. Interference by environmental toxins in this precisely orchestrated process can lead to adverse effects, such as lower intelligence, poor coordination, and behavior problems [275,343]. In their 2006 paper regarding the effects of over 200 environmental toxins on the developing human brain, Grandjean and Landrigan (2006, p. 2168) stated that "*... these [neurodevelopment] processes have to take place within a tightly controlled time frame, in which each developmental stage has to be reached on schedule and in the correct sequence. Because of the extraordinary complexity of human brain development, windows of unique susceptibility to toxic interference arise that have no counterpart in the mature brain, or in any other organ*."[341].

4.2.1 Human Neurodevelopment – A Critical Window of Susceptibility

Human neurodevelopment begins within the second week of gestation, and progresses through adulthood [343]. Differentiation of blastocyst cells to neural progenitor cells (i.e., neural stem cells) is intricately regulated, and begins with chemical signals that initiate or mute gene expression before and during uterine implantation [342,343]. By gestational week three, the progenitor cells form the neural plate, which folds and closes to form the neural tube by week four, proto-neuron formation by week six, and vesicles that will develop into the hindbrain, midbrain, forebrain, and the limbic system by week eight [343]

The hindbrain develops into the spinal column and brain stem [343], and further develops into the pons, cerebellum, and medulla oblongata. [343] Cerebellar, pons, and medullar formation begins in the early second trimester (approximately week 14) [344]. The pons contains nerves that process sound, and regulate balance and coordination [345]. The cerebellum regulates musculoskeletal response to sensory stimuli [345]. The medulla oblongata is where the brain transitions to the spinal cord, and contains nerves that regulate mouth movements, including speech [345].

The midbrain sits at the top of the brain stem, and connects nerve impulse between the hindbrain, forebrain, and limbic system [346]. Structures in the midbrain are responsible for processing audio and visual stimuli, pain stimuli, attention, and involuntary movements [343,346]. The substantia nigra, which begins to form in gestational week eight, is located in the midbrain [346,347]. The substantia nigra produces dopamine, a neurotransmitter involved in behavior modulation (e.g., motivation and reward), cognition, voluntary movement, sleep, dreaming, mood, attention, working memory and learning [346,348,349].

The forebrain develops into the largest region of the brain, the cerebrum and the cerebral cortex [350]. The cerebrum is the area of the brain responsible for language processing, thinking, reasoning, and planning, and continues to develop from early in the second trimester (week 14) and continues through young adulthood [340,350]. The basal ganglia, below the cerebral cortex, regulates executive function, and inhibitory impulse control [351], and processes nerve signals from and to the limbic system, involved in memory, arousal, attention, learning, and behavioral and emotional responses [352].

Cells in the limbic system begins to differentiate at seven weeks gestation [353]. The limbic system is so important to survival that several structures are evolutionarily conserved in all vertebrate life [354–356]. The limbic system is connected to the autonomic nervous system that regulates heart rate, blood pressure, involuntary breathing, and body temperature [352]. Brain structures in the limbic system (and approximate gestational week when they begin to form) include the hippocampus (week 13), the amygdala (week 10), the cingulate gyrus (week 14) , the hypothalamus (week 13), and the aforementioned basal ganglia (week 14) [343,351,353,357]. The hippocampus is responsible for memory storage, and spatial awareness [357]. The amygdala is involved in memory, emotional response, and the fight-or-flight reaction in response to perceived threats [352,357]. The cingulate gyrus is involved in autonomic motor function, and regulating emotions, behavior and pain perception [357]. The hypothalamus' primary functions are maintaining body homeostasis via the endocrine system, and attention when responding to sensory stimuli [357]. It seems clear that the timing of neurotoxic exposure can lead to different presentations of adverse outcomes. If cells that make up the nervous system don't multiply enough, or when they should, or migrate to the location, or form connections when and where they should, there is likely to be a neurodevelopmental deficit.

The occurrence of neurodevelopmental disabilities, such as cognitive impairment, learning disabilities, and attention deficit/hyperactivity disorder (ADHD), are increasing faster than what would be expected from genetic evolution over time, which indicates the influence of environmental factors effecting these trends [275,341]. Subsequent research has substantiated Grandjean and Landrigan's earlier work, including evidence of adverse neurodevelopmental outcomes from prenatal/early-life exposure to flame retardants [358,359], metals, such as lead [360], arsenic [361], and mercury [42,362,363], and common environmental pollutants, such as PAHs [169,364,365]. This study focuses on the association of prenatal and early-life exposure to PAHs and adverse neurodevelopmental outcomes in infants and children.

4.2.2 PAHs as Neurotoxicants

Polycyclic aromatic hydrocarbons (PAHs) are widely dispersed environmental contaminants formed from combustion of organic materials that are associated with human disease [46]. Humans are almost constantly exposed to PAHs [258–260], primarily through inhalation of PAH-containing air pollution, or consuming PAH-contaminated food [46]. Infants and children inhale a greater volume of air per unit of body mass, compared to adults, and their immune systems are not developed as an adult, increasing the susceptibility to airborne environmental toxicants, like PAHs [46,366]. Once inside the body, PAHs are primarily metabolized by the liver and excreted in urine and feces. Urinary PAH metabolites are a common exposure surrogate in biomonitoring studies because it is a non-invasive and repeatable method to assess PAH exposure [257]. Other biomarkers of PAH exposure include blood [92], tissue [305] and breast milk [87].

The epidemiological evidence linking prenatal and early-life PAH exposure to adverse human neurodevelopment in the published peer-reviewed literature has mainly come from a few birth cohorts in New York [367], Poland [175,265], the Czech Republic [323], China [291], and Spain [368]. In a study on 1 year olds in China, Lin, et al., (2021) found a negative association between prenatal PAH exposure and neurodevelopment [369]. Talbott, et al., (2015) modeled emissions data during the entire pregnancy and reported a marginally significant association between prenatal PAHs and autism spectrum disorder (ASD) [370]. In a study on prenatal PAH exposure and the effects on human intelligence at age 5 years in the New York birth cohort, Perera, et al., 2009 found that a one ln(PAH) unit increase was associated with a three point decrease in IQ (n = 249) [192]. In the same cohort, Margolis, et al., (2021) found in children 8-14 years of

age, higher prenatal PAH exposure was associated with lower inhibitory control, and Perera, et al., (2014) found a positive association between prenatal PAH exposure and ADHD at ages 6-18 years (n = 233) [371]. In a cross-sectional study using urinary biomarkers as the exposure measure in U.S. children age 6-15 years, Abid, et al., (2014) found that the high fluorene exposure group had twice the odds of needing special education assistance, compared to the low exposure group [193] (n = 1,257) .

However, there are conflicting results in the epidemiologic evidence. For example, Jedrychowski, et al., (2015) found no association between prenatal PAH exposure and decreased intelligence in a Polish cohort (n = 170) [372]. In a case-control study Kalkbrenner, et al., (2010) modeled air monitoring data during the entire pregnancy in North Carolina (n=2,132) and West Virginia (n=1,073) from 1992-2004, and found no association between prenatal PAHs and ASD [373]. In a 2017 air modeling study in Spain, Mortamais did not find a statistically significant association between prenatal PAH exposure and ADHD in 8-12 year old children [368].

Adverse neurodevelopment outcomes come at a societal cost. In their review on the economic benefit of reducing air pollution, Shea, et al., (2020) estimated the per-case cost (in 2015 U.S. dollars) for loss of one IQ point was approximate $11,000 [279]. Perera et al., (2014) estimated the economic benefit of reducing prenatal PAH exposure by 0.25 ng/m^3 in New York City ambient air would have a societal benefit of approximately $42–214 million (in 2014 U.S. dollars) for the 2002 birth cohort characterized as high risk due to Medicaid enrollment status (n = 63,462) [379]. In terms of the medical and financial costs to the individual, the family, and society, it is therefore important to understand the weight of scientific evidence with regards to prenatal and early-life PAH exposures and neurodevelopment outcomes.

The purpose of this systematic review and meta-analysis is to identify eligible studies that quantified the association between prenatal and early-life PAH exposure and cognitive, psychomotor, and behavioral outcomes, summarize the evidence, and rate the quality and strength of the human evidence. This systematic review and meta-analysis were registered on July 25, 2021, in PROSPERO (CRD42021262771).

4.3 Materials and Methods

4.3.1 Study Population

The study population included pregnant mothers and their infants/children who took part in studies published in peer-reviewed literature prior to December 31, 2021. There were no restrictions on time-period before December 31, 2021, or geographic location of primary studies.

4.3.2 Systematic Review Protocol

The systematic review protocol followed the Navigation Guide methodology [280]. This methodology provides a framework to conduct a systematic review in a scientifically rigorous and transparent manner; to rate the quality and strength of the evidence from primary studies; and provide a grade of overall strength of association. The Navigation Guide also provides a framework to assess the risk of bias in primary studies (RoB). Table B.7 lists criteria to assess the quality of primary studies that were adapted from the Navigation Guide for this review. In reporting results, we also followed the steps recommended by the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [281]. PRISMA is an evidence-based approach that establishes search strategy protocols and reporting items in a flow diagram, and a checklist to ensure transparency in reporting of results.

4.3.2.1 Study Search Strategy

The *a priori* protocol started with development of a search strategy, eligibility criteria, and inclusion and exclusion criteria for the selection of primary studies. Search engines used were PubMed®, Web of Science®, and Google Scholar®. Search terms are listed in Table C.1. The term "PAH" refers to any single parent PAH species or a combination, or total PAHs reported in primary studies. Study eligibility criteria is summarized in Table C.2. Measures of exposure included PAHs detected during pregnancy or early-life from biomarkers, personal air sampling, or modeled exposure. Information reported on analytical methods and quality assurance procedures were considered in assessing study quality and risk of bias. Inclusion and exclusion criteria are listed in Table C.3. Inclusion criteria required that primary studies be available in English and published by a peer-reviewed source. This included peer-reviewed journal articles, text resources, e-books, and print books. Gray literature sources included conference proceedings, government documents and technical reports. Authors of relevant

conference proceedings were contacted to inquire about unpublished studies. Reviews, dissertations, and theses were included in the screening step for citation reviews. Additional records were identified through hand searching and screening of the reference list of included papers which had not been captured through the electronic searches.

4.3.2.2 Study Screening Strategy

Two reviewers working independently screened study titles and abstracts, and completed a full-text review relative to the inclusion criteria, using Covidence® software (Veritas Health Innovation, Melbourne, Australia, www.covidence.org). Potentially eligible studies cited in reviewed studies were added to the title and abstract screening. Each study was rated as "include", "exclude with justification" or "inconclusive". Cohen's kappa coefficient for inter-rater reliability of the title and abstract screening was 0.45, and 0.55 in full-text review (moderate agreement, respectively) [283]. Conflicts in study inclusion status were discussed between the two reviewers until consensus was reached.

4.3.2.3 Data Extraction

Specific data from eligible studies was extracted using Covidence®, following guidance from the PRISMA checklist and the Navigation Guide. Briefly, extracted data included the study name and date, study design, location, study time period, sample size, measure of exposure, PAH species, PAH concentration or adduct level and units, analytical method, neurodevelopment outcome(s), comparator group (if reported), covariates, measure of association, and measure of precision. A risk of bias rating, based on Navigation Guide criteria, was created in Covidence® and this rating was also extracted. Table B.6 describes the data extraction fields.

4.3.3 Exposure Estimation

Studies were limited to those in which prenatal PAH concentration was measured by personal air sampling, or modeled from stationary air monitoring data, emissions data, dietary exposure questionnaires, or occupational exposure questionnaires during pregnancy, or measured in a human biomarker (e.g., cord blood, maternal blood, maternal urine, or placental tissue), during pregnancy or shortly after delivery, to establish temporality between the exposure and the neurodevelopment outcome. Some studies reported subgroups of analysis by

evaluating multiple PAH species, more than one exposure matrix, or more than one neurodevelopment outcome. Each exposure-outcome analysis reported in a primary study was assessed individually [216]. For example, Perera, et al., (2006) measured prenatal PAH exposure via personal air sampling and reported the association with both mental development, and psychomotor development, from the two subscales included in the assessment instrument [169]. In our meta-analysis, each reported PAH/neurodevelopment outcome result was assessed as a separate sub-study. For transparency, we report both the number of studies (k), and the number of sub-studies (k_{sub}) per exposure-outcome analysis.

4.3.4 Outcome Measures

Eligible studies reported a neurodevelopment assessment using a validated assessment instrument administered by a qualified professional (e.g., school psychologist, child psychiatrist, etc.) at least six months after collection of the exposure measure. Several assessment instruments have overlapping primary measures. We consulted a neurodevelopment assessment expert [380] regarding the grouping of assessments reported in primary studies. Based on a review and categorization of each assessment instrument's scales and subscales, we grouped reported neurodevelopment outcomes into cognitive, psychomotor and behavior domains and subdomains, shown in Figure 4.1. Table C.4 lists the neurodevelopment assessments, subscales, assessment instruments, and age at assessment reported in included primary studies, along with the neurodevelopment domains, comparison, and outcome type (continuous/dichotomous).

For continuous outcomes, assessments that evaluated intelligence (mental development, full-scale IQ, verbal IQ, non-verbal IQ, performance IQ, reading skills and comprehension, math skills, processing speed, and language skills) were considered subdomains of cognitive function, although it was recognized that language skill also has a psychomotor component. Motor skills (psychomotor development, fine motor, gross motor, visual-motor function), and measures of reflexes (active tone, passive tone, primary reflexes) were considered subdomains of psychomotor function. Adaptive (adaptive, inhibitory control) and social behavior (personal behavior, social behavior) were grouped as subdomains of behavior.

For dichotomous outcomes, ASD and attention problems not measured with an ADHD assessment instrument, were subdomains of cognitive function. ADHD (ADHD symptoms,

ADHD problems, hyperactivity, impulsivity, or attention problems measured with an ADHD instrument); anxiety/depression (anxiety problems, depressive symptoms, withdrawn/ depression); and behavior problems (aggression, externalizing behavior, conduct disorder problems, rule-breaking behavior) were subdomains of behavior domain. Neurodevelopment delayed included assessment from all domains (mental delayed, language delayed, psychomotor delayed, motor development delayed, and personal/social or adaptive behavior delayed) and was its own subdomain.

4.3.5 Covariates

Figure C.1 show the percentage of covariates reported by primary studies. Reported covariates included maternal characteristics (e.g., age, race/ethnicity, BMI, marital status, measure of socio-economic status, SES, education, occupation), maternal exposures during pregnancy (e.g., tobacco smoke, alcohol consumption, diet), maternal history of pregnancy complications (Hx-PC); infant/child characteristics (gestational age, type of delivery, sex of infant at birth, postnatal tobacco smoke exposure, attending school); and information on maternal residence during pregnancy (location, home heating type, cooking fuel. age of residence). We created dummy variables (i.e., did the primary study adjust for the specific covariate: Y/N) for covariates that can confound the measure of association between prenatal/early-life PAH exposure and neurodevelopment outcomes: tobacco smoke exposure, maternal age, race/ethnicity, education, marital status, diet, alcohol, BMI, SES, parity, Hx-PC, gestational age, sex of infant, type of delivery, child attending school, residential or neighborhood characteristics. Additional covariates created for the meta-analysis included when an exposure measure was collected relative to the pregnancy (approximates exposure period), and time range of study (by decade). Studies that measured PAH exposure in either the first or second trimester were combined due to the low number of studies in these two exposure period categories.

4.3.6 Statistical Analysis

Data from eligible studies was aggregated and analyzed using Comprehensive Meta-Analysis software (CMA, v. 3.3.070, November 20, 2014) to generate a summary effect for each exposure-outcome analysis, a measure of precision, and a measure of between-study dispersion using a random-effects model. Summary effects in continuous outcomes are

reported as the standardized mean difference (Cohen's *d*). Summary effects for dichotomous outcomes are reported in odds ratio (OR). We chose 95%CI as the common measure of sampling precision. Beta coefficients from regression analysis were converted to Pearson's product-moment correlation coefficients (*r*). This method was validated by the technical support staff of CMA for generating a point estimate and a measure of precision [381]. Measures of association reported on the raw scale in primary studies were transformed to natural log scale using methods recommended by Higgins, et al., 2008 [287]. Correlation coefficients, when non-zero, can be skewed [288], so they were transformed to Fisher's *z*' scale to approximate a normal distribution prior to converting to an odds ratio. The prediction interval was calculated using the Prediction Interval software from CMA.

With noted exceptions, results reported are based on the summary effect of at least ten sub-studies in each exposure-outcome analysis to increase the precision of the estimate of the true mean and between-study variation [289]. There were only four sub-studies for ASD, but the sample size was large, so the results are presented in Table 4.1, but further analysis on ASD was not performed. When possible, we used measures of association from adjusted analysis to provide a more conservative estimate of the true mean effect size, as recommended by the Cochrane Handbook [213]. When the exposure comparator was reported in quantiles, we used the result reported for the highest v. lowest quantile. We excluded some observations from sub-analysis, i.e., we did not include results reported in non-smokers when the overall sample population of smokers and non-smokers was available. We also did not include interaction results (i.e., effect modification of neurodevelopment outcome from PAH exposure interacted with tobacco smoke exposure).

4.3.6.1 Statistical Power

Statistical power is calculated after completion of the meta-analysis, as the number of included studies is not known *a priori*. Table C.7 is the power calculations results for this meta-analysis, using Equation 8a in Appendix E [215]. Statistical power was adequate (>0.80) for the meta-analysis on motor skills (continuous outcome), and attention problems, anxiety/depression, and neurodevelopment delay (dichotomous outcomes). The behavior domain (continuous) and the behavior problems subdomain (dichotomous) was moderately underpowered (0.46, respectively). The intelligence, and reflexes subdomains (0.03), and the

ADHD subdomain (0.05) were substantially underpowered. Although the pooled sample sizes of each of these subdomains were adequate, the small effect size (absolute value of 1 – the summary effect), and moderate number of sub-studies weakened the statistical power for these neurodevelopment outcomes.

4.3.6.2 Data Visualization

We generated forest a summary forest plot for each exposure-outcome analysis, along with the summary effect and measure of dispersion. A funnel plot was also generated to visualize the risk of publication bias. We also provide a figure of the geographical location of included studies as a visual queue of the evidence of prenatal PAH exposure and neurodevelopment outcomes, and to highlight a recommendation for future research.

4.3.7 Assumptions

The basic assumption for our meta-analysis is that maternal PAH exposure can lead to an internal dose that can cross the placenta and enter the bloodstream of the fetus, and that infant/child exposure to PAHs is likely to be higher that adult exposure, due to differences in metabolic rates, time-activity patterns, and hand-to-mouth behavior. Our analysis assumed the effect size and variation reported in primary studies was estimated accurately and that log-transformed values followed an approximately normal distribution. We also assumed that Tau, the estimated standard deviation of true effects, is a reasonably precise estimate of the true effect dispersion and that in using Tau to calculate the prediction interval to evaluate how much effect size varies across studies included in the meta-analysis, the estimated prediction interval is also reasonably precise.

4.4 Results

4.4.1 Characteristics of Included Studies

Of the 613 studies retrieved in the initial search, 4 were duplicate studies. Screening titles and abstracts culled 552 studies that did not meet eligibility criteria. Of the remaining 76 studies, 20 additional studies were added from citation reviews in the screening step, and 46 studies were judged to be ineligible and were excluded. First phase data extraction excluded four of the 30 remaining studies, leaving 26 to complete data extraction which were retained for the meta-analysis, with 258 sub-studies. Twenty-three studies were of longitudinal study

design, three were case-control design. Ten studies reported continuous outcomes, 13 studies reported dichotomous outcomes, and three studies reported both. Figure 4.2 is the PRISMA diagram of record selection, and a list of included studies, along with some important study characteristics, are listed in Table C.6 and C.7.

In our meta-analysis, Kalkbrenner, et al., (2010) was study with the earliest enrollment period and assessment (enrolled from 1992 to 1996, assessed at eight years of age) to measure prenatal PAH exposure and a neurodevelopment outcome (autism traits), in two sample populations women/infant dyads; one in North Carolina (n = 1,939), the other in West Virginia (n = 1,335) [373]. Blazkova, et al., (2020) enrolled the last mother/infant dyads (enrolled 2013-2014, assessed at five years of age [382]. Thus, the research included in our meta-analysis spans a 27-year timeframe. The pooled sample size (n_{pooled}) across all included studies was 125,635. The median sample size per sub-study was 250, the mean sample size was 4,832, and the sample size range was from 96 to 109,062.

4.4.2 Overall Analysis

The results by birth outcome are provided in Table 4.1. We found a statistically significant ($\alpha = 0.05$) positive association in dichotomous outcomes between prenatal/early-life PAH exposure and anxiety/depression (OR: 1.36; 95%CI: 1.10, 1.68; p =0.005; n_{pooled} = 4,989; I^2 = 73.58%), and in neurodevelopment delay (OR: 1.07; 95%CI: 1.01, 1.14; p =0.028; n_{pooled} = 1,113; I^2 = 30.24%). We found a marginally statistically significant positive association between prenatal/early-life PAH exposure and attention problems (OR: 1.81; 95%CI: 0.96, 3.43; p = 0.068; n_{pooled} = 2,997; I^2 = 86.35%). In continuous outcomes, we found a statistically significant negative association between prenatal/early-life PAH exposure and motor skills (Cohen's d: -0.371, 95%CI: -0.52, -0.22; $p < 0.001$; n_{pooled} = 1,372; I^2 = 96.74%), and in adaptive behavior (Cohen's d: -0.142, 95%CI: -0.25, -0.00; p = 0.042 n_{pooled} = 1,128; I^2 = 84.27%). We did not find a statistically significant association between prenatal/early-life PAH exposure and intelligence, language skills, social behavior, ADHD, or other behavior problems.

Figure 4.3 is a summary forest plot of continuous, and dichotomous birth outcomes, respectively. Meta-regression results follow the results by neurodevelopment outcomes.

4.4.2.1 Continuous Neurodevelopment Outcomes

Some studies assessed prenatal PAH exposure in multiple exposure matrices, so details about exposure matrices in this section may not equal the total number of studies by neurodevelopment outcome. All studies reporting continuous outcomes either excluded smokers from the sample population, or adjusted for tobacco smoke exposure in regression analysis.

4.4.2.1.1 Cognitive domain and subdomains

Thirteen studies (k_{sub} = 44; n_{pooled} = 2,685) measured exposure to 12 PAHs (including total PAHs) and assessed the effect on cognitive function in sample populations from 1998 to 2020 [92,191,192,367,369,372,382–388]. The summary effect, *M*, was not statistically significant (Cohen's d: 0.45; 95%CI: -0.16, 0.25; p = 0.665; I^2 = 94.7%). From prediction interval, we expect the distribution of the standardized mean difference to be within the range of -0.62 to 0.707 in 95% for all comparable populations. Association of prenatal/early-life PAH exposure with the two cognitive subdomains, intelligence (k_{sub} = 24; n_{pooled} = 1,804), and language skills (k_{sub} = 20; n_{pooled} = 681), were not statistically significant, with results of (Cohen's d: -0.004; 95%CI: -0.31, 0.30; p = 0.980; I^2 = 94.8%) and (Cohen's d: 0.101; 95%CI: -0.18, 0.38; p = 0.478; I^2 = 94.9%), respectively. Six studies were conducted in the U.S. [191,192,367,383,386,387], four in China [369,384,385,388], two in Poland [92,372], and one in the Czech Republic [382].

4.4.2.1.2 Psychomotor Domain and subdomains

Seven studies (k_{sub} = 65; n_{pooled} = 1,732) measured exposure to 11 PAHs (including total PAHs) and assessed the effect on psychomotor function in sample populations from 1998 to 2019 [367,369,382–384,388,389]. The summary effect, *M*, was statistically significant (Cohen's d: -0.371; 95%CI: -0.52, -0.22; p <0.001; I^2 = 96.7%). From the prediction interval (i.e., $M \pm 2T$), we expect the distribution of the standardized mean difference to be within the range of -0.96 to 0.21 in 95% for all comparable populations. The psychomotor subdomain motor skills (k_{sub} = 38; n_{pooled} = 1,125) showed a statistically significant association with a moderate to large effect size (Cohen's d: -0.671; 95%CI: -0.93, -0.41; p <0.001; ; I^2 = 96.7%). The association of prenatal/early-life PAH exposure on the reflexes subdomain (k_{sub} = 27; n_{pooled} = 247) was not statistically significant (Cohen's d: -0.007; 95%CI: -0.06, 0.04; p = 0.774; ; I^2 = 0%). Four

studies were conducted in China [369,384,388,389], two in the U.S. [367,383], and one in the Czech Republic [382].

4.4.2.1.3 Behavior domain and subdomains

Five studies (k_{sub} = 51; n_{pooled} = 1,284) measured exposure to 11 PAHs (including total PAHs) and assessed the effect on behavior in sample populations from 1998 to 2016 [367,369,384,387,388]. The summary effect, *M*, was marginally statistically significant (Cohen's d: -0.147; 95%CI: -0.30, 0.01; p = 0.058; I^2 = 93.6%). With the prediction interval, we expect the distribution of the standardized mean difference to be within the range of -0.68 to 0.38 in 95% for all comparable populations. Association of prenatal/early-life PAH exposure with the adaptive behavior subdomain (k_{sub} = 30; n_{pooled} = 1,128) was statistically significant (Cohen's d: -0.142; 95%CI: -0.25, 0.0; p = 0.042; I^2 = 84.3%). The association between prenatal/early-life PAH exposure the social behavior subdomain (k_{sub} = 21; n_{pooled} = 681) was not statistically significant (Cohen's d: -0.171; 95%CI: -0.51, 0.17; p = 0.170; I^2 = 96.7%). Four studies were conducted in China [369,384,388,389], and one in the U.S. [387].

4.4.2.2 Dichotomous Neurodevelopment Outcomes

An overall result for the cognitive domain and behavior domain is not reported for dichotomous outcomes due to little overlap in subscale assessment intention, and difficulty in mapping subscales in the subdomains. The only psychomotor subdomain is reported under the section on neurodevelopment delay.

4.4.2.2.1 Cognitive subdomains

An overall result for the cognitive domain was not evaluated because one of the subdomains, ASD is a spectrum of cognitive, psychomotor and behavior signs and symptoms that did not map well to any other subdomain. In addition, there were three primary studies conducted in Pennsylvania [372],Tennessee [375], and California [392], respectively, from 1995 to 2013, and with only four exposure-outcome sub-studies for ASD, but the results were not statistically significant (OR: 1.16; 95%CI: 0.87, 1.54; p = 0.314; I^2 = 32.37%). However, due to the large sample size (n_{pooled} =117,205), the meta-analysis results for ASD are presented in Table 4.1 as a reference, and to aid future research. Meta-regression and heterogeneity assessments were not performed on the ASD subdomain.

Six studies (k_{sub} = 10; n_{pooled} = 2,997), assessed the association between prenatal/early-life PAH exposure and the attention problems subdomain from 1998 to 2019 [191,371,374,391–393]. The summary effect, *M*, was marginally statistically significant (OR: 1.81; 95%CI: 0.96, 3.43; p = 0.068; I^2 = 86.4%). The prediction interval was, we expect the distribution of the OR to be within the range of 0.95 to 2.38 in 95% for all comparable populations. Five studies were conducted in the U.S. [191,371,374,391,392], and one in Spain [393].

4.4.2.2.2 Behavior subdomains

The behavior domain consists of three subdomains: ADHD symptoms or clinical diagnosis, anxiety/depression, and behavior problems. Five studies (k_{sub} = 20; n_{pooled} = 2,454) measured exposure to total PAHs and assessed the association with ADHD in sample populations from 1998 to 2015 [191,368,371,374,393]. The summary effect, *M*, was not statistically significant (OR: 1.01; 95%CI: 0.96, 1.06; p = 0.658). Since $Q - df = 0$, T^2 and I^2 are also 0%, meaning any variance in true effects is explained by sampling error. We expect the distribution of the OR to be approximately 1.00 in 95% for all comparable populations

Six studies (k_{sub} = 19; n_{pooled} = 4,989) measured exposure to total PAHs and assessed the association with anxiety/depression in sample populations from 1998 to 2019 [191,374,391,392,394,395]. The summary effect, *M*, was statistically significant (OR: 1.36; 95%CI: 1.10, 1.68; p = 0.005; I^2 = 86.4%). The prediction interval was, we expect the distribution of the standardized mean difference to be within the range of 1.045 to 1.68 in 95% for all comparable populations. Five studies were conducted in the U.S. [191,371,374,391,392], and one in Spain [393].

Six studies (k_{sub} = 17; n_{pooled} = 6,842) measured exposure to five PAHs (including total PAHs) and assessed the association with behavior problems in sample populations from 1998 to 2019 [191,391–393,395,396]. The summary effect, *M*, was not statistically significant (OR: 1.06; 95%CI: 0.94, 1.20; p = 0.324; I^2 = 87.8%). With the prediction interval, we expect the distribution of the standardized mean difference to be within the range of 0.86 to 1.27 in 95% for all comparable populations. Four studies were conducted in the U.S. [191,391,392,396], one in Spain [393], and one reported results from cohorts in Spain and the Netherlands [395].

4.4.2.2.3 Neurodevelopment Delay

The neurodevelopment delay subdomain contains subscale assessments from the cognitive, psychomotor, and behavior domains. Three U.S. studies (k_{sub} = 28; n_{pooled} = 1,113) measured exposure to five PAHs (including total PAHs) and assessed the effect on neurodevelopment delay in sample populations from 1998 to 2014 [367,384,396]. The summary effect, *M*, was statistically significant (OR: 1.07; 95%CI: 1.01, 1.14; p = 0.028; I^2 = 30.2%). With the prediction interval, we expect the distribution of the standardized mean difference to be within the range of 0.99 to 1.15 in 95% for all comparable populations.

4.4.3 Meta-Regression Results

In bivariate analysis, we examined the differences between studies that utilized biomarkers, compared to studies that modeled prenatal PAH exposure. Table 4.2. presents these results by continuous and dichotomous birth outcomes, respectively, with the difference between groups assessed by *z*-test, $\alpha = 0.05$. There were statistically significant differences between exposure matrix groups in the overall psychomotor domain in continuous outcomes ($p < 0.001$), and in anxiety/depression subdomain for dichotomous outcomes ($p = 0.002$). However, this may be a spurious difference and the result of unstable variance estimates, as the number of modeled sub-studies in the continuous psychomotor domain k_{sub} = 4), and the number of biomarker sub-studies in the dichotomous anxiety/depression subdomain (k_{sub} = 9) are less than ten. The sample size difference between the biomarker group (n_{pooled} = 728) and the modeled group (n_{pooled} = 2,454) for the anxiety/depression subdomain may also factor into the difference, as the biomarker sample population is 3-fold smaller than the modeled group.

Table 4.3 contains the univariate analysis results by outcome type (continuous/ dichotomous), and lists the covariates included in final models of primary studies. Table 4.3 also provides the results from bivariate meta-regression analysis between covariates and individual neurodevelopment outcomes that were statistically significant and explained at least part of the variance in the summary effect (i.e., $R^2 > 0$). In univariate meta-regression analysis of the dichotomous outcomes' dataset, the following covariates met the aforementioned criteria: age at assessment, and exposure matrix (R^2 = 0.28, respectively), PAH measure (adducts or concentration), and model adjustment for maternal occupation in the primary study (adj. occupation, R^2 = 0.26, respectively), exposure period, and adjustment for maternal age (R^2 = 0.19), respectively), adjustment for maternal pre-pregnancy BMI (adj. BMI, R^2 = 0.14), and

adjustment for parity (adj. parity, R^2 = 0.13). Adjustment for maternal education (adj. educ., R^2 = 0.05), country (R^2 = 0.03), and PAH congener (R^2 = 0.02) were marginally statistically significant, p = 0.058, 0.091, and 0.069, respectively.

In univariate analysis of the continuous birth outcomes' dataset, covariates that met the aforementioned criteria were exposure matrix (R^2 = 0.09), adj. educ. (R^2 = 0.04), adj. BMI, and PAH measure (R^2 = 0.03, respectively), and adjustment for maternal alcohol consumption during pregnancy (adj. alcohol, R^2 = 0.03). Exposure period and adj. parity were marginally statistically significant (R^2 = 0.03, respectively).

In bivariate meta-regression analysis of dichotomous outcomes (does not include ASD), exposure matrix, exposure period, and PAH measure explained 63% and 89% of the variance in anxiety/depression, and behavior problems subdomains, respectively. Further analysis on the potential source of the variance is discussed in the Heterogeneity Assessment section.

In bivariate meta-regression analysis continuous outcomes, exposure matrix and exposure period, explained 82% of the variance in the motor skills; and country and adj. BMI explained 42% of the variance in the intelligence subdomain. Interestingly, the psychomotor domain was statistically significant ($p < 0.05$) in bivariate analysis with 2-3 ringed PAHs (NAP, FLU, PHE), marginally significant in 4 ringed PAHs (PYR, CHR), but not significant in total PAHs, which included HMW PAHs.

4.4.3.1 Assessment of Heterogeneity

Air modeling was used in seven studies to assess prenatal/early-life PAH exposure and ADHD, ASD, attention problems, anxiety/depression, behavior problems, motor skills and intelligence, in children at ages three to eleven years. Air sampling was collected over the entire pregnancy in three studies [370,390,395], only during the third trimester in one study [382], and during childhood (age at assessment range: 6-11 years) in two studies [393,393]. Studies were conducts in Spain[368,393,395], the Czech Republic [382], the Netherlands [395], and the U.S [370,373,390]. The only covariate included in all primary air modeling studies was maternal education.

Personal air sampling was used in seven studies to assess intelligence, motor skills, adaptive and social behavior, attention problems, anxiety/depression, and behavior problems in children, age at assessment range: 1-15 years. All studies except one conducted in Poland [92], were conducted in the U.S. [191,192,367,374,387,391]. All studies adjusted for tobacco smoke exposure,

maternal age, race/ethnicity, education, Hx-PC, and SES, but only the study in Poland adjusted for maternal BMI.

Cord blood was used in eight studies to assess intelligence, language skills, attention problems, motor skills, adaptive and social behavior, anxiety/depression, and neurodevelopment delay in infants and children (age at assessment range: 1-9 years). All studies but one [369] adjusted for tobacco smoke exposure, maternal age, Hx-PC, and SES, but only one study adjusted for maternal pre-pregnancy BMI [372]. PAH exposure has been linked to higher BMI in adults[397] and children [398] Of the five studies that assessed prenatal PAH exposure using personal air monitoring [92,191,192,367,387] to evaluate child intelligence at one, two, three, seven, and 13-15 years, respectively, only adjusted for BMI [92].

Maternal blood collected during the third trimester [374], or at EOP [379,392] was used in three studies to assess ADHD, attention problems, anxiety/depression, and behavior problems in children, age at assessment range: 3-9 years. All studies adjusted for tobacco smoke exposure, maternal age, race/ethnicity, Hx-PC and SES, but none of the studies adjusted for maternal pre-pregnancy BMI.

Maternal urine was used in two studies[388,396] to assess language skills, motor skills, adaptive and social behavior, and neurodevelopment delay in children age at assessment range: 2-3 years. Both studies adjusted for tobacco all key covariates.

Infant/child urine was used in four studies to assess intelligence, motor skills, adaptive and social behavior, reflexes, ADHD, anxiety/depression, attention problems, and behavior problems in infants and children, age at assessment range: 1-9 years. Collection timing range from the third trimester [389], EOP [382], at one year [369], and at 5 years [191]. All but on study [369] adjusted for tobacco smoke exposure, maternal age, race/ethnicity, HX-PC, and SES. Only one study [389] adjusted for maternal BMI.

4.4.4 Bias Assessment

4.4.4.1 Sensitivity Analysis

We tested for the effect of influential sub-studies by utilizing the "one-study removed" feature in the CMA software. This feature recalculates the mean effect size after removing each sub-study, so that influential sub-studies are more easily identified. Sensitivity analysis was conducted by analyzing the mean effect size with an influential sub-study included and

removed from subgroup analysis and meta-regression models, and were excluded if removing the sub-study changed the mean effect size by 10%. No sub-studies met the exclusion criteria. We also performed meta-regression to identify influential covariates. Each covariate was analyzed in univariate and bivariate analysis with birth outcomes to reduce the risk of collinearity. Finally, we assessed publication bias using the Duvall and Tweedie's Trim and Fill method, which is described below.

4.4.4.2 Publication Bias

Publication bias results when studies relevant to the research question are not published or not made available. Some studies are more likely to be unavailable than others. Large studies (based on sample size, n>100), or long-term studies are likely to be published, regardless the result because of the expense involved in conducting the study [215]. Short-term medium-sized studies ($n \geq 30$, <100) and small studies (n<30) with large effect sizes are also likely be published [215]. However, small studies with small effect sizes or null results are the most likely to be unavailable for meta-analysis [215]. Figures C.2 and C.3 are the publication bias funnel plots for dichotomous and continuous outcomes, respectively. In our meta-analysis, our literature search resulted in only two out of 26 studies with samples sizes less than 100, so we expected publication bias to be low. We used Duval and Tweedie's Trim and Fill method to impute estimates of missing studies under a random effects model. For dichotomous outcomes, this resulted in a smaller predicted summary effect size, based on 19 imputed studies (OR: 1.03; 95%CI: 0.97, 1.10), compared to our overall estimate (OR: 1.13; 95%CI: 1.07, 1.19), which changes the significance of our findings. This means that there is a small likelihood of publication bias, and that the results of unpublished studies could change the summary effect of our analysis in dichotomous outcomes. For continuous outcomes, the estimated with 26 imputed studies was smaller , (Cohen's *d*: -0.39; 95%CI: -0.47, -0.27), compared to our observation (Cohen's *d*: -0.19; 95%CI: -0.28, -0.09), meaning the likelihood unpublished studies would change the direction of our findings is very low.

4.4.4.4 Risk of Bias Assessment

We employed the Risk of Bias (RoB) assessment method outlined in the Navigation Guide [280]. We modified the RoB evaluation criteria published in Lam, et al., 2016 [317] to rate each exposure-outcome analysis in nine domains: 1) study design; 2) source population; 3)

exposure assessment; 4) outcome assessment; 5) confounding and analysis; 6) incomplete outcome data; 7) selective outcome reporting; 8) funding and conflicts of interest; and 9) other sources of bias. Each domain had four RoB categories. These categories are, from lowest to highest: 1) low risk of bias; 2) probably low risk of bias; 3) probably high risk of bias; and 4) high risk of bias. The RoB criteria we used in this meta-analysis is provided in Appendix D.

In a departure from the Navigation Guide protocol, we assigned one point for low RoB; two points for probably low RoB; three points for probably high RoB; and four points for high RoB, for each domain. The lowest theoretical RoB score was nine, and the highest theoretical RoB score was 36. The purpose of this was two-fold: 1) to distinguish studies with lower overall RoB from those with higher RoB; and 2) to assess the strength, precision, and thoroughness of the search strategy, eligibility criteria, and inclusion/exclusion criteria we employed in the systematic review. The results of the RoB analysis from our meta-analysis are presented as a heat map in Table 4.4. The average RoB score for studies included in the meta-analysis was 13.8, with a standard deviation of 0.36. The median was 13.5, and the range was 11-17. Thus, the included studies were determined to have low to probably low RoB overall. There were no instances of high RoB in any domain. The confounding category had the highest overall RoB score (56), representing the range covariates included in models of primary studies in this meta-analysis. The category with the next highest score was selection bias (49), followed by exposure assessment (46), and exposure assessment (44).

4.4.5 Quality and Strength of Evidence.

We used the Navigation Guide criteria to rate the quality and strength of evidence across all included studies, and to determine an overall rating. This information is provided in Table 4.5. The quality of evidence rating scale of low, moderate, or high quality is based on assessment for several factors, including downgrade criteria (risk of bias, indirectness, inconsistency, imprecision, publication bias), and upgrade criteria (magnitude of effect, dose response, all possible confounding would confirm a null result). The quality rating of human evidence begins at ‘moderate’.

We downgraded the evidence included in our meta-analysis for indirectness (-1), as 14 out of 26 studies reported modeled prenatal/early-life exposure, although three studies modeled PAH exposure over the entire pregnancy. We also downgraded the evidence for inconsistency (-1), due to the high level of heterogeneity in the overall analysis, although most sources of

heterogeneity were identified through meta-regression. We upgraded the evidence for dose response (+1). Seven studies reporting results in tertiles, or quartiles all showed a statistically significant (six), or a marginally significant dose response. We also upgraded the evidence for all possible confounding confirming a null result (+1). We evaluated the impact on the summary size on whether studies adjusted for tobacco smoke exposure, maternal age, BMI, diet, education, SES, parity, or Hx-PC and found those studies that did not adjust for these covariates had lower, non-significant summary effects, compared studies that included adjustment for these covariates. Thus, the human evidence quality rating stayed at ***moderate***.

We evaluated the strength of human evidence based on 1) the quality of evidence; 2) directness of effect; 3) the confidence in the effect; and 4) other compelling attributes that may influence certainty. The summary of human evidence is sufficient to determine that prenatal/early-life PAH exposure is associated with adverse effects on the motor skills and adaptive behavior of children, associated with anxiety/depression, and neurodevelopment delay, and marginally associated with attention problems. However, confidence in the estimate is constrained by the heterogeneity (inconsistency) of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion. Based on these factors, we determined there is ***limited evidence of toxicity***.

4.5 Discussion

The primary public health objective of this meta-analysis was to evaluate the weight of epidemiological evidence of prenatal and early-life PAH exposure on neurodevelopment in children. We found a body of evidence with considerable between-study variation for each exposure-outcome analyzed, although between-study heterogeneity led us to downgrade the human evidence in our analysis from sufficient to limited.

We found that prenatal/early-life PAH exposure is linked to several adverse neurodevelopment outcomes, including decreased psychomotor function and adaptive behavior; and increased occurrence of anxiety/depression, and neurodevelopmental delay, and possibly linked to attention problems in children. We did not find an association between prenatal/early-life PAH exposure and intelligence, language skills, psychomotor reflexes,

ADHD, or behavior problems. We evaluated ASD, but due to the small number of eligible studies, the results are reported only as reference for future research.

We initially found 613 peer-reviewed studies in English, but only 76 studies met eligibility criteria, and only 26 met inclusion criteria and were included in the meta-analysis. Enrollment periods across studies spanned from 1992-2014, and exposure-neurodevelopment outcome analysis took place between 1998 and 2018, spanning two decades. A recent PAH exposure trend analysis on non-smokers in the U.S. found that PAH exposure levels changed over time with NAP and PYR increasing, while FLU and PHE decreased from 2001-2014, and this may at least partially due to time spent indoors, natural gas home heating and appliances[325].

We created a time range variable for bivariate meta-regression analysis, but the results were not statistically significant and only explain 3-5% of the variance in either continuous or dichotomous outcomes. The earliest study to investigate the effect of prenatal/early-life PAH exposure on neurodevelopment outcomes was a birth cohort initiated in New York in 1998 that measured prenatal PAHs in personal air monitoring in the second and third trimester, and evaluated mental and physical development in children ages one, two and three years [367]. The last study in our analysis was also on the New York cohort, using PAH-DNA adducts from cord blood to assess behavior in children ages 3-11 years. We also explored the potential source of between-study variance using meta-regression, and uncovered several covariates associated with the variance of the estimates of summary effects, including exposure matrix, exposure period, country, and whether a primary study adjusted for potential confounding variables, such as maternal pre-pregnancy BMI.

While there is growing interest to use systematic reviews and meta-analyses in environmental health, there were not many studies available for comparison with ours. Most of the PAH exposure meta-analyses available focused on cancer or respiratory illnesses in occupational settings. A 2006 meta-analysis investigated prenatal PAH exposure and the effects on genetic damage [399]. We also found a more recent meta-analysis (2020) on PAH exposure and ADHD that also did not find a statistically significant association between PAH exposure and ADHD [400]. That study included a cross-sectional that was ineligible for our meta-analysis, and did not include one the studies conducted in Spain.

The mechanism of action that early-life PAH exposure has on the developing human brain is not well characterized. One hypothesis is that PAHs interfere with endocrine processes through AhR interaction [162,183–185,374], resulting in anti-estrogenic activity, and disrupting the critically-timed endocrine processes necessary for normal fetal development [184]. Frye, et al., (2012) posited that PAHs may directly impact the estrogen receptor as an agonist/antagonist in CYP1A1 [375]. Safe et al., (2003) reported that PAHs have exhibited interference with estrogen signaling through cross-talk with the AhR [376].

Another hypothesis is that free radical-induced oxidative stress contributes directly or indirectly to adverse neurodevelopment [329]. Oxidation is a normal by-product of oxygen metabolism and usually, there are several mechanisms to neutralize reactive oxygen species (ROS) via intracellular antioxidant systems [329]. However, when ROS surpasses neutralizing capacity, it triggers an inflammatory response by reacting with lipids, proteins, and polysaccharides in the cell membrane, as well as nucleic acids, that can lead to altered cellular function [377]. For example, Prenatal PAHs measured in maternal plasma and urine, and placental tissue, have been positively correlated to an increase in biomarkers of oxidative stress and inflammation [378]. ROS in prenatal biomarkers was positively associated with altered fetal programming linked to adult diseases, such as metabolic syndrome [377]. PAH-induced oxidative stress in placental tissue was linked to a decrease trophoblast proliferation, which leads to a decrease available fetal oxygen and nutrition [164].

Our findings indicate PAH exposure in early-life, and especially in the prenatal period, is associated with adverse neurodevelopment outcomes. The strongest association was in the motor skills subdomain, and we were surprised to learn in bivariate analysis, that LMW PAHs had a statistically significant association with this outcome, but HMW PAHs did not. LMW PAHs are found at higher indoor concentrations and more likely to be inhaled. The positive adverse effect of PAH exposure we found on anxiety/depression and behavior problem, and marginally, with attention problems, contrasts with the null effect we found with ADHD, but there may be several contributing factors for this, including the different assessment instruments, different child ages at assessment, and by whom the instrument was completed, the child or the parent/guardian.

4.5.1 Strengths

Systematic reviews are considered to be a more rigorous approach to summarizing the weight of scientific evidence. The *a priori* protocol for a study eligibility and inclusion, the search strategy, search terms, and data extraction criteria, elevate the level of transparency in the methods and the results. A meta-analysis is considered of more value because it provides both magnitude and direction of a summary effect, which can be more informative for a broad audiences, such as clinicians, policymakers.

We followed what is arguably the best available science in conducting systematic reviews and meta-analyses in environmental health, by adhering the PRISMA and Navigation Guide protocols for study design, bias assessment, and reporting. We limited eligible studies to those that assessed prenatal or early-life PAH exposure using validated analytical and assessment methods. Two reviewers working independently in the screening and full-text review of articles had fair to moderate agreement, and consensus was reached through review and discussion. Analytical methods reported in primary studies were assessed for appropriateness, given the exposure measure. We set a threshold of ten sub-studies to increase precision of mean effect estimates, and used the more conservative covariate-adjusted results, when available. We assessed risk of bias in primary studies, using the Navigation Guide protocol, and developed a RoB score to evaluate our study identification and selection strategies, and found the risk of bias in our systematic review was probably low.

4.5.2 Limitations

The validity of a systematic review and meta-analysis is dependent upon the accuracy in primary studies. Space constraints in peer-reviewed journals may lead to trade-offs between detail and parsimony to stay within word count constraints. Unfortunately, this may lead to data essential for conducting a thorough and meaningful meta-analysis may be missing. We contacted several authors with the request for additional information, but didn't receive a response. This could be due to external emails getting caught in spam folders, or changes to corresponding authors' contact information. The end result could lead to publication bias. In our meta-analysis, most studies were of moderate or large sample size, reducing the likelihood of publication bias. Using the Duvall and Tweedie Trim and Fill method, we found the likelihood of publication bias in the continuous outcome dataset was very low. However, there

is a small likelihood of publication bias in the dichotomous outcomes, based on imputation of 19 studies.

The use of biomarkers with relatively short half-lives increases the exposure misclassification and null results. However, this is mitigated somewhat by the fact that PAHS are ubiquitous in the environment, and most human likely are exposed on a daily basis. We rated study quality by choice of exposure measure, and collection timing, relative to the completion of the neurodevelopment assessment. Still, the possibility of unmeasured confounding or undetected bias exists. Another potential limitation is from the creation of neurodevelopment domains that may have diluted the effect size of assessment instrument subscales that overlapped more than domain.

The statistical analysis for the neurodevelopment subdomains of intelligence, reflexes, and ADHD were substantially under-powered due to the small effect size and low number of available studies, increasing the risk of a false negative, i.e., failing to detect an effect when one is present. Thus, a low-powered analysis indicates an underestimation of effect size.

The between-study heterogeneity in our analysis ranged from low to high (I^2: 0 – 96.7). We use meta-regression to explore the potential sources of between-study heterogeneity, and found some studies did not report inclusion of key covariates in regression models. It may be possible the covariates were included, but without evidence, it is only speculation, and does not advance summarizing the weight of available evidence. The null hypothesis test for heterogeneity is that all studies share a common effect size, so heterogeneity across all studies equals zero. However, this is rarely the case in environmental health research.

4.5.3 Gaps in the Literature & Recommendations

Variation in effect size is important in considering the potential utility of potential exposure prevention efforts. While there is a need to bring together environmental health studies from different populations and exposure profiles, there is a gap in the current meta-analytical methods to accommodate between-study variation that is inherent in environmental health research.

Included studies in our prenatal/early-life – neurodevelopment meta-analysis were from China, the Czech Republic, the Netherlands, Poland, Spain, and the U.S., a rather limited geographic representation. We highlight this by showing the number of studies by country on

world map in Figure C.4. For example, if we did not find any eligible studies conducted in Canada, Central or South America, or Asia, with the exception of China. Of the 15 U.S. studies included in our meta-analysis for neurodevelopment outcomes, 14 were conducted east of the Mississippi River. Finally, we recommend primary studies report overall results and quantiles (e.g., tertiles or quartiles) so that dose-response can be summarized in a meta-analysis.

4.6 Conclusion

Based on the Navigation Guide protocol, there is limited human evidence to determine that prenatal/early-life PAH exposure reduces motor skills; and increases anxiety/depression, attention problems, and neurodevelopment delay. The human evidence linking prenatal/early-life PAH exposure with other evaluated neurodevelopment outcomes was inconclusive. Between-study variance (heterogeneity) was low to considerable across neurodevelopment outcome assessments, with I^2 ranging from 0 to 96.7%, and this led to downgrading the human evidence from sufficient to limited. However, to stay true to intent of bring together research from various populations in environmental health, the focus should be on the effect heterogeneity may have on the conclusions drawn. Thus, what is critical to include is enough studies that meet eligibility criteria so that the extent of the between-study variation can be quantified reliably with meta-regression.

4.7 Acknowledgements

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Table 4.1. Summary of overall meta-analysis statistics for neurodevelopment outcomes.

Outcome		k	k_{sub}	n_{pooled}	# PAHs [a]	Summary Effect Size, 95% CI: Summary Effect	95%CI Lower	95%CI Upper	p [b]	Test of Heterogeneity: Q[c]	df	p [c]	I^2 (%)
Continuous Outcomes – Summary Effect Measure: Standardized Mean Difference (Cohen's *d*)													
Cognitive	All	13	44	2,685	12	0.045	-0.16	0.25	0.665	817.30	43	<0.001	94.74
	Intelligence	10	24	1,804	3	-0.004	-0.31	0.30	0.980	440.23	23	<0.001	94.78
	Language Skills	3	20	681	10	0.101	-0.18	0.38	0.478	370.26	19	<0.001	94.87
Psychomotor	All	7	65	1,372	11	-0.371	-0.52	-0.22	**<0.001**	1,235.64	64	<0.001	94.82
	Motor Skills	6	38	1,125	11	-0.672	-0.93	-0.41	**<0.001**	1,134.25	37	<0.001	96.74
	Reflexes [d]	1	27	247	9	-0.007	-0.06	0.04	0.774	16.94	26	0.910	0.00
Behavior [e]	All	5	51	1,284	11	-0.147	-0.30	0.01	0.058	786.19	50	<0.001	93.64
	Adaptive Behavior	4	30	1,128	10	-0.142	-0.25	0.00	**0.042**	184.42	29	<0.001	84.27
	Social Behavior	3	21	681	11	-0.171	-0.51	0.17	0.331	600.43	20	<0.001	96.67
Dichotomous Outcomes – Summary Effect Measure: Odds Ratio													
Cognitive	ASD	3	4	117,205	5	1.16	0.87	1.54	0.314	4.44	3	0.218	32.37
	Attention Problems	6	10	2,997	1	1.81	0.96	3.43	0.068	65.92	9	<0.001	86.35
Behavior	ADHD	5	20	2,454	1	1.01	0.96	1.06	0.658	17.87	19	0.531	0.00
	Anxiety/Depression	6	19	4,989	1	1.36	1.10	1.68	**0.005**	68.13	18	<0.001	73.58
	Behavior Problems	6	17	6,842	5	1.06	0.94	1.20	0.324	130.70	16	<0.001	87.76
All	Neurodevelopment Delay	3	28	1,113	5	1.07	1.01	1.14	**0.028**	38.70	27	0.067	30.24

[a] Includes total PAHs. Some studies evaluated PAH congeners and total PAHs in more than one neurodevelopment outcome.

[b] Significance of hypothesis test that the true summary effect is equal to zero. $\alpha = 0.05$. Bold values: $p < \alpha$.

[c] Test of heterogeneity. Two-tailed test of the null hypothesis that the true mean effect does not vary across studies, i.e., the variation is due to within-study sampling error alone. $\alpha = 0.10$.

[d] One study with two repeated measures on nice PAHs, including total PAHs.

[e] Three studies assessed both social and adaptive behavior.

Table 4.2. Stratified analysis by studies that utilized biomarkers, compared to studies that modeled exposure, to examine prenatal PAH exposure effects on neurodevelopment outcomes.

	Biomarker Only Studies [a]						Modeled Only Studies [b]						
Continuous Outcomes	*k*	k_{sub}	n_{pooled} [c]	Cohen's *d*	95%CI	*p* [c]	*k*	k_{sub}	n_{pooled} [c]	Cohen's *d*	95%CI	*p* [d]	*p* [e]
Cognitive-all	9	30	1,841	0.153	0.090, 0.395	0.217	6	14	1,268	-0.188	-0.575, 0.198	0.34	0.127
C-Intelligence	6	10	1,160	0.264	-0.265, 0.792	0.328	6	14	1,268	-0.188	-0.575, 0.198	0.34	0.173
C-Language Skills	3	20	681	0.101	-0.178,0.381	0.478	--	--	--	--	--	--	--
Psychomotor-all	6	61	1,191	-0.327	-0.469, -0.184	<0.001	3	4	350	-1.324	-2.833, 0.185	0.085	**0.000**
P-Motor Skills	5	34	944	-0.613	-0.869, -0.356	<0.001	3	4	350	-1.324	-2.833, 0.185	0.085	0.363
P-Reflexes	1	27	247	-0.007	-0.055, 0.041	0.774	--	--	--	--	--	--	--
Behavior-all	4	50	928	-0.144	-0.300, 0.012	0.070	1	1	356	-0.297	-0.508, -0.086	0.006	0.279
B-Adaptive	4	29	928	-0.121	-0.248, 0.005	0.061	1	1	356	-0.297	-0.508, -0.086	0.006	0.213
B-Social	3	21	681	-0.171	-0.515, 0.173	0.331	--	--	--	--	--	--	--
Dichotomous Outcomes	*k*	k_{sub}	n_{pooled}	OR	95%CI	*p*	*k*	k_{sub}	n_{pooled}	OR	95%CI	*p*	*p*
Cognitive-ASD	--	--	--	--	--	--	3	4	117,205	1.158	0.870, 1.540	0.314	--
C-Attention Problems	4	6	1,190	2.284	1.113, 4.685	0.024	4	4	2,315	1.278	0.596, 2.738	0.528	0.344
Psychomotor-all	1	2	217	1.928	1.27, 2.925	0.002	1	3	181	1.190	0.655, 2.163	0.568	0.199
B-Anxiety/Depression	4	9	728	2.852	1.929, 4.219	<0.001	4	10	2,454	1.012	0.929, 1.102	0.785	**0.002**
B-Behavior Problems	3	10	1,128	1.159	0.955, 1.407	0.135	4	7	4,431	1.037	0.988, 1.089	0.139	0.388
All-Neurodev Delay [f]	1	4	717	1.391	1.037, 1.865	0.028	1	6	5,098	1.238	0.751, 2.040	0.403	0.693
B-ADHD	3	8	217	1.376	0.897, 2.111	0.143	4	12	181	1.025	0.961, 1.092	0.457	0.290

[a] Biomarker studies measured PAH exposure in maternal blood, cord blood, maternal urine, infant/child urine.

[b] Modeled studies measured PAH exposure based on data from stationary air monitors, or personal air sampling.

[c] Some primary studies measured more than one neurodevelopment outcome.

[d] Significance at each neurodevelopment outcome, $\alpha = 0.05$. Bold values: $p < \alpha$.

[e] Significance of difference between groups tested with a *z*-test, $\alpha = 0.05$. Bold values: $p < \alpha$.

[f] Neurodevelopment delay subdomain included development delay assessment in all domains.

Table 4.3 Meta-regression statistics of statistically significant exposure-neurodevelopment outcome analyses, overall, and by covariate, listed in order of R^2, highest to lowest.

			Meta-Regression Results						
Outcome Type	Covariate [a]	Outcome [b]	Q[c]	df [d]	*p* [e]	I^{2} [f]	T^{2} [g]	R^{2} [h]	Note [i]
Univariate Analysis									
Dichotomous	Age at Assessment	--	213.89	12	0.000	24.26	0.00	0.28	
Dichotomous	Exposure Matrix	--	214.98	5	0.000	20.79	0.00	0.28	
Dichotomous	Adj. Occupation	--	130.32	1	0.000	49.49	0.01	0.26	
Dichotomous	PAH Measure	--	135.50	1	0.000	48.14	0.01	0.26	
Dichotomous	Exposure Period	--	112.52	6	0.000	50.06	0.01	0.19	
Dichotomous	Adj. Maternal Age	--	13.76	1	0.000	69.68	0.09	0.19	
Dichotomous	Adj. BMI	--	13.43	1	0.000	71.17	0.10	0.14	
Dichotomous	Adj. Parity	--	12.39	1	0.000	71.30	0.10	0.13	
Continuous	Exposure Matrix	--	20.11	4	0.000	94.65	3.91	0.09	
Dichotomous	Adj. Educ.	--	3.60	1	0.058	70.98	0.11	0.05	MS
Continuous	Adj. Educ.	--	6.64	1	0.010	94.51	1.26	0.04	
Continuous	Adj. BMI	--	5.48	1	0.019	94.70	1.27	0.03	
Continuous	PAH Measure	--	5.19	1	0.023	94.71	4.19	0.03	
Continuous	Exposure Period	--	8.76	3	0.033	94.57	2.04	0.03	
Dichotomous	Country	--	6.47	3	0.091	71.45	0.11	0.03	MS
Continuous	Adj. Alcohol	--	4.64	1	0.031	94.63	1.28	0.02	
Continuous	Adj. Parity	--	4.23	1	0.040	94.71	1.28	0.02	MS
Dichotomous	PAH Congener	--	8.71	4	0.069	71.80	0.11	0.02	MS
Bivariate Analysis									
Continuous	Exposure Matrix	Psychomotor - All	63.69	4	0.000	92.04	0.72	0.51	
Continuous	Exposure Matrix	P-Motor Skills	29.52	4	0.000	95.47	1.47	0.42	
Dichotomous	Country	ADHD	3.71	1	0.054	0.00	0.00	0.41	MS
Dichotomous	Country	Attention Problems	3.71	1	0.054	0.00	0.00	0.41	MS
Continuous	Exposure Period	P-Motor Skills	24.41	2	0.000	96.08	1.53	0.40	
Continuous	Adj. Parity	P-Motor Skills	21.75	1	0.000	95.19	1.58	0.38	
Continuous	Exposure Period	B-Adaptive	9.95	2	0.007	84.71	0.27	0.33	
Dichotomous	Exposure Matrix	B Problems	120.14	4	0.000	0.00	0.00	0.31	
Continuous	Country	C-Intelligence	11.82	3	0.008	94.12	0.47	0.29	
Continuous	Exposure Matrix	B-Adaptive	9.49	3	0.023	85.52	0.29	0.28	
Dichotomous	Instrument	Anxiety/Depression	3.82	1	0.050	59.10	0.38	0.28	MS
Dichotomous	PAH Measure	Behavior Problems	110.74	1	0.000	1.93	0.00	0.27	
Dichotomous	Exposure Period	Anxiety/Depression	40.33	3	0.000	46.05	0.00	0.26	
Dichotomous	Age at Assessment	Anxiety/Depression	61.47	7	0.000	0.00	0.00	0.24	
Continuous	PAH Measure	B-Adaptive	6.05	1	0.014	75.47	0.31	0.24	
Dichotomous	Exposure Period	Behavior Problems	124.30	5	0.000	0.00	0.00	0.22	
Dichotomous	PAH Measure	Anxiety/Depression	39.77	1	0.000	40.07	0.00	0.21	
Dichotomous	Age at Assessment	Behavior Problems	124.84	6	0.000	0.00	0.00	0.18	
Continuous	Age at Assessment	Psychomotor - All	16.86	4	0.002	94.14	1.23	0.18	
Continuous	Adj. Educ.	P-Motor Skills	9.05	1	0.003	96.52	2.09	0.18	
Continuous	Adj. BMI	B-Adaptive	4.93	1	0.026	87.77	0.33	0.18	
Continuous	Adj. Parity	B-Adaptive	4.93	1	0.026	87.77	0.33	0.18	
Continuous	Adj. Alcohol	P-Motor Skills	9.05	1	0.030	96.52	2.09	0.18	
Dichotomous	Exposure Matrix	Anxiety/Depression	53.23	4	0.000	6.10	0.00	0.16	
Continuous	Adj. Alcohol	Psychomotor - All	11.57	1	0.001	94.31	1.27	0.15	

Table 4.3 – Continued.

Outcome Type	Covariate [a]	Outcome [b]	Q[c]	df [d]	*p* [e]	I^{2} [f]	T^{2} [g]	R^{2} [h]	Note [i]
Continuous	Adj. Educ.	Psychomotor - All	11.25	1	0.001	94.47	1.28	0.14	
Continuous	Adj. BMI	C-Intelligence	4.16	1	0.041	94.57	0.57	0.13	
Continuous	Adj. Diet	P-Motor Skills	5.14	1	0.023	96.07	2.27	0.11	
Continuous	PAH Measure	P-Motor Skills	4.17	1	0.041	96.77	2.36	0.08	
Continuous	Exposure Period	Psychomotor - All	6.78	2	0.034	94.86	1.40	0.06	
Continuous	Adj. SES	P-Motor Skills	3.26	1	0.071	96.64	2.40	0.06	MS
Continuous	Adj. BMI	Cognitive - All	3.75	1	0.053	95.56	1.75	0.05	MS
Continuous	PAH Measure	Psychomotor - All	3.70	1	0.054	94.72	1.44	0.03	MS

[a] Covariates. Exp. Matrix: Exposure Matrix (exposure biomarkers: cord blood, maternal blood, maternal urine, or placental tissue; exposure models: data from stationary air monitoring, or personal air monitoring). Exposure Period: estimation of prenatal/early life PAH exposure, based on when exposure biomarker was collected and half-life, or the length of estimated exposure in modeled data (second trimester; third trimester, entire pregnancy, end of pregnancy, or during childhood). Country: country where primary study was conducted. PAH Congener: individual parent PAH, (i.e., NAP, FLU, BaP, etc., including total PAHs). PAH Measure: PAH-DNA adducts or PAH concentration. Age at Assessment: Age when neurodevelopment outcome was assessed. Instrument: neurodevelopment assessment instrument reported in primary study.

Adj. covariates are binary covariates (Y/N) if primary study adjusted for the covariate in final models. Adj. Hx-PC: history of pregnancy complications. Adj. Maternal Diet: maternal diet during pregnancy. Adj. Smoke Exposure: maternal exposure to tobacco smoke during pregnancy. Adj. Maternal Educ.: highest level of maternal education at time of enrollment. Adj. Maternal Age: maternal age at delivery. Adj. Maternal BMI: maternal pre-pregnancy BMI. Adj. Alcohol: maternal alcohol consumption during pregnancy. Adj. Occupation: maternal occupation during pregnancy or postnatal. Adj. Parity: maternal parity. Adj. SES: maternal or household socioeconomic status.

[b] Outcomes. Continuous outcomes only (Cognitive-All: cognitive function, all sub-scales; Psychomotor-All: psychomotor function, all subscales; Behavior-All: behavior problems, all subscales). ADHD: attention deficit hyperactivity disorder. Attention problems: assessments of attentiveness, but not with neurodevelopment assessment instruments that assessed ADHD. C-Intelligence: cognitive domain, intelligence subdomain. C-Language: cognitive domain, language skills subdomain. P-motor skills: psychomotor domain, motor skills subdomain. B-adaptive: behavior domain, adaptive behavior subdomain. B-social: behavior domain, social behavior subdomain.

[c] *Q*. Weighted sum of primary study squared deviations from the summary effect on a standardized scale.

[d] *df*. Degrees of freedom, the number of studies included in the meta-regression, (k) minus one.

[e] *p*. Two-tailed test of the null hypothesis that the summary effect = 0.

Table 4.3 – Continued.

[f] I^2. Ratio of the total amount of variation in the meta-regression explained by variance in true effects, T^2.

[g] T^2. Variance of true effects, using the restricted maximum likelihood (REML) method to estimate variance.

[h] R^2. Ratio comparing the covariate model with the intercept-only model, and estimate of the amount of variation in the model explained by the covariate.

[i] Note. Results of hypothesis test were marginally significant, $\alpha > 0.050, <0.099$.

Table 4.4. Risk of Bias Heat Map of Included Neurodevelopment Outcome Studies.

Study ID	Study Design	Selection Bias	Exp. Assess.	Outcome Assess.	Con-founding	Incomplete Outcome Data	Selective Outcome Reporting	COI	Other	RoB Score
Alemany 2018	2	2	2	2	2	1	1	2	1	15
Blazkova 2020	1	3	2	2	2	3	1	1	1	16
Cao 2020	2	2	2	1	2	1	2	1	1	14
Edwards 2010	2	2	2	1	2	2	1	1	1	14
Jedrychowski 2015	1	2	1	1	2	1	1	1	1	11
Jorcano 2019	2	2	2	2	2	1	1	1	1	14
Kalkbrenner 2010	3	2	3	1	2	1	1	2	1	16
Lin 2021	1	2	2	2	3	2	2	1	1	16
Margolis 2016	2	2	1	1	2	1	2	1	1	13
Margolis 2021	1	1	2	1	2	1	2	2	1	13
Mortamais 2017	3	2	3	1	2	1	2	2	1	17
Nie 2019	2	1	1	1	2	1	1	1	1	11
Pagliaccio 2020	1	2	1	1	2	1	2	1	1	12
Perera 2006	2	1	2	1	2	1	2	1	1	13
Perera 2007	2	2	1	1	2	1	1	1	1	12
Perera 2008	2	2	1	1	2	1	1	1	1	12
Perera 2009	2	2	2	1	2	1	2	2	1	15
Perera 2011	1	2	1	1	2	1	2	1	1	12
Perera 2012a	2	2	1	1	2	1	2	2	1	14
Perera 2012b	1	2	1	1	2	1	2	1	1	12
Perera 2014	1	2	2	1	2	1	1	1	1	12
Perera 2015	2	2	1	1	2	1	2	1	1	13
Peterson 2015	1	2	1	1	2	1	2	2	1	13
Talbott 2015	2	2	2	2	2	2	1	2	1	16
von Ehrenstein 2014	2	1	3	2	3	2	1	2	1	17
Wallace 2022	3	2	2	2	2	2	1	1	1	16

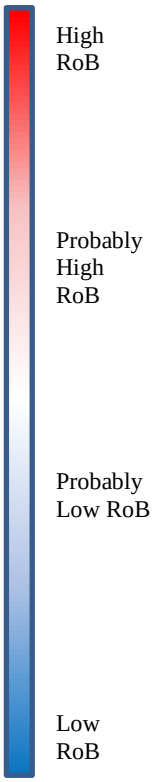


Table 4.5. Quality and Strength of Evidence, and Overall Rating, all included studies, neurodevelopment outcomes [338].

Quality of Evidence	Human evidence begins at "Moderate Quality".	
Downgrade criteria	**Assessment**	**Downgrade**
Risk of Bias	Evidence of probably low risk of bias exists across studies, RoB score range: 10-20. This provides evidence that a priori eligibility criteria and inclusion/exclusion criteria helped to focus on well-conducted relevant research on prenatal PAH exposure and the effect on neurodevelopment outcomes.	0
Indirectness	• Only human studies included and only studies that measured prenatal or early-life PAH exposure included. • Direct measure of outcome using biomarkers (13/26 included studies). • Modeled exposure assessments (16/26 included studies) are an indirect measure of exposure. 3/26 studies used both. • Some biomarkers collected at EOP, and can only indicate recent exposure.	-1
Inconsistency	• Heterogeneity level was low to high across outcomes, but this was expected. • Exposure matrix, exposure period, PAH measure explained 63-89% of variance in dichotomous outcomes, and 42-82% in continuous outcomes. • Whether studies adjusted for maternal BMI, tobacco smoke exposure, alcohol consumption, occupation, or parity explained 34% of the variance.	-1
Imprecision	• The confidence intervals around summary effect of each neurodevelopment outcome are reasonably precise, based on sample size.	0
Publication Bias	• Low probability of publication bias, based on assessment using Duval and Tweedie's Trim and Fill method. • Adequate number of studies with small, moderate, and large sample sizes, with null, and small to moderate effects. • Inclusion criteria of eligible studies available in English may excluded available non-English studies.	0
Upgrade criteria	**Assessment**	**Upgrade**
Large magnitude of effect	• Summary effect was statistically significant for motor skills, adaptive behavior, anxiety/depression, and neurodevelopment delay. Motor skills has a moderate magnitude of effect -0.672. , i.e., a Cohen's $d < -.0.8$ or an OR > 2.00.	0
Dose response	• Of the 7 studies reporting results in tertiles or quartiles, all but one showed a statistically significant dose response. • Highest effect seen in highest exposure matrix. • Most reported exposure was for total PAHs, followed by NAP, PHE, and PYR.	+1
All possible confounding would confirm a null result	• Evaluated impact on results by exposure matrix, exposure period, PAH measure, time range, and if studies adjusted for smoke exposure, maternal age, BMI, diet, education, SES, parity, Hx-PC, and child sex, gestational age, type of delivery. • The statistical significance of adjusted covariates did not change whether studies adjusted for the covariates or not. • Possibility remains of unmeasured confounding.	+1

Table 4.5 – continued.

Final Decision on Overall Quality of Human Evidence

- The quality of evidence was downgraded for:
  - High heterogeneity, although most between-study variation was explained in further analysis (-1).
- The quality of evidence was upgraded for:
  - Evidence of dose response (+1).
  - Evidence that all possible confounding would confirm a null result (+1).

Overall, the meta-analysis is rated as **Moderate to High Quality**.

Strength of Evidence - Considerations	
• Quality of the body of evidence	Moderate
• Directness of effect	Human studies, prenatal exposure, early-life exposure
• Confidence in effect	Moderate confidence in effect
• Other compelling attributes of the data that may influence certainty	Exposure period Adjustment for important covariates Unmeasured confounding
Overall Rating	**Limited human evidence of toxicity.**
Reasoning:	The summary of human evidence is sufficient regarding the exposure-neurodevelopment outcome relationship observed. Evidence is sufficient to determine the effects of the prenatal/early-life PAH exposure on motor skills, anxiety/depression, and neurodevelopment delay, and marginal for attention problems. However, confidence in the estimate is constrained by inconsistency of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion.

Figure 4.1. Mapping of neurodevelopment assessments into domains and subdomains.

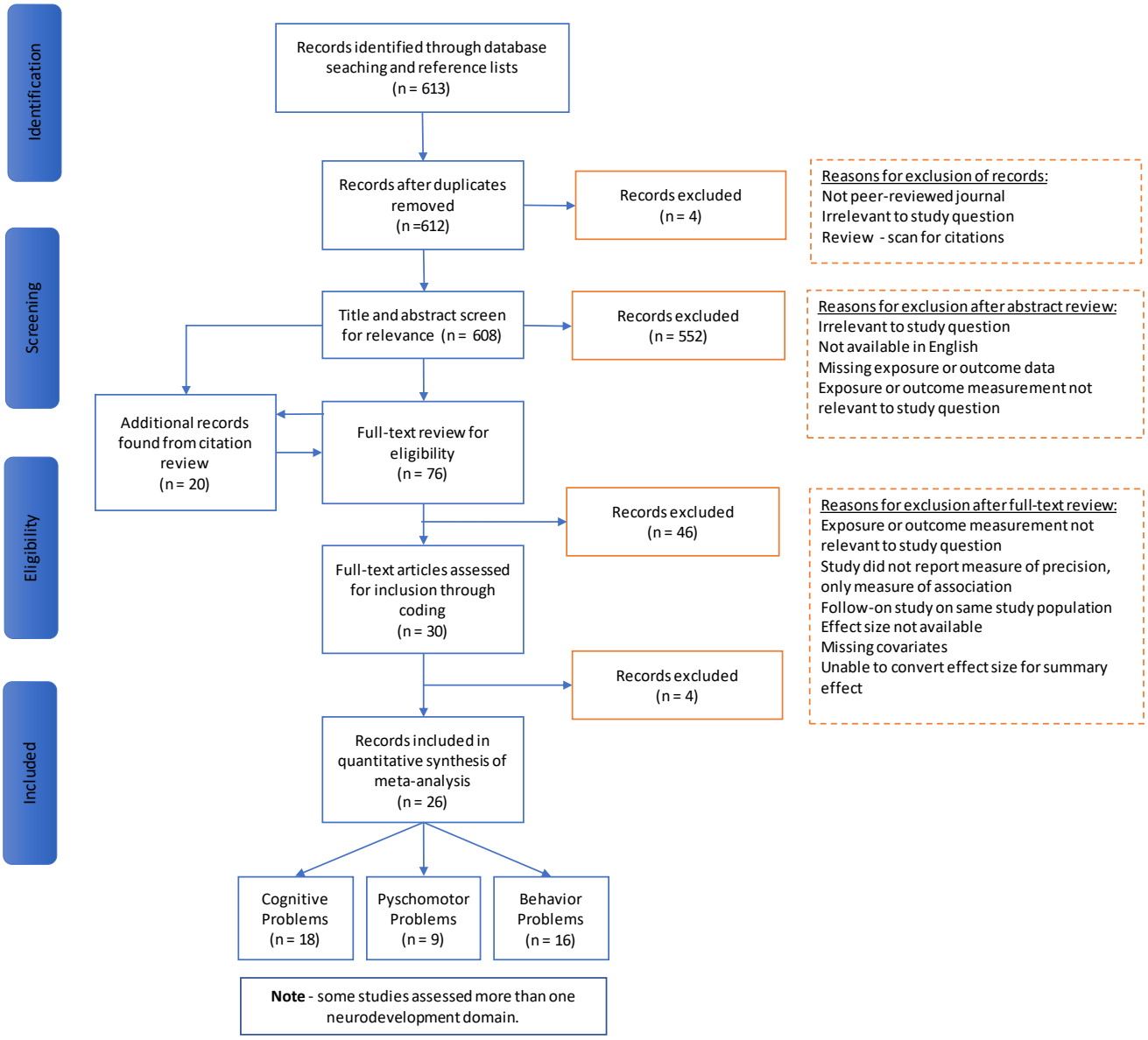
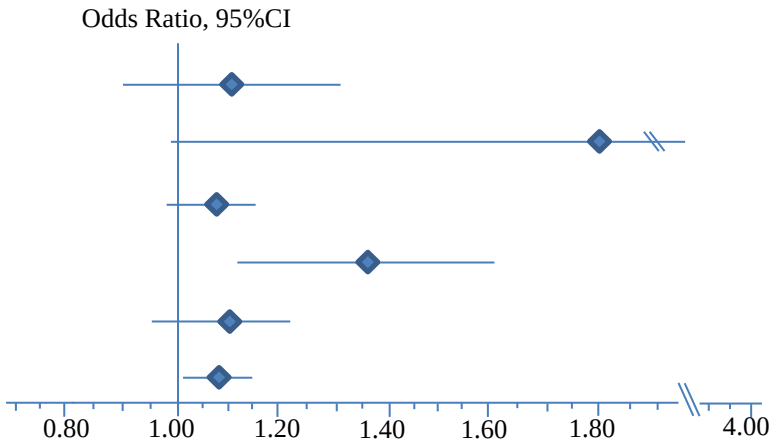


Figure 4.2. PRISMA diagram, neurodevelopment outcomes.

Dichotomous Outcomes

Neurodev. Outcome	Sub-Category	OR	95% Lower	95% Upper	*p*
Cognitive	ASD	1.158	0.870	1.540	0.314
Cognitive	Attention Problems	1.813	0.957	3.435	0.068
Behavior	ADHD	1.011	0.963	1.061	0.658
Behavior	Anxiety/Depression	1.362	1.100	1.685	0.005
Behavior	Behavior Problems	1.064	0.941	1.202	0.324
All	Neurodev. Delay	1.072	1.007	1.138	0.028



Continuous Outcomes

Neurodev. Outcome	Sub-Category	Cohen's *d*	95% Lower	95% Upper	*p*
Cognitive	All	0.045	-0.158	0.248	0.655
Cognitive	Intelligence	-0.004	-0.307	0.299	0.980
Cognitive	Language Skills	0.101	-0.178	0.381	0.478
Psychomotor	All	-0.371	-0.519	-0.223	<0.001
Psychomotor	Motor Skills	-0.672	-0.929	-0.415	<0.001
Psychomotor	Reflexes	-0.007	-0.055	0.041	0.774
Behavior	All	-0.147	-0.299	0.005	0.058
Behavior	Adaptive Behavior	-0.127	-0.250	-0.005	0.042
Behavior	Social Behavior	-0.171	-0.515	0.173	0.331

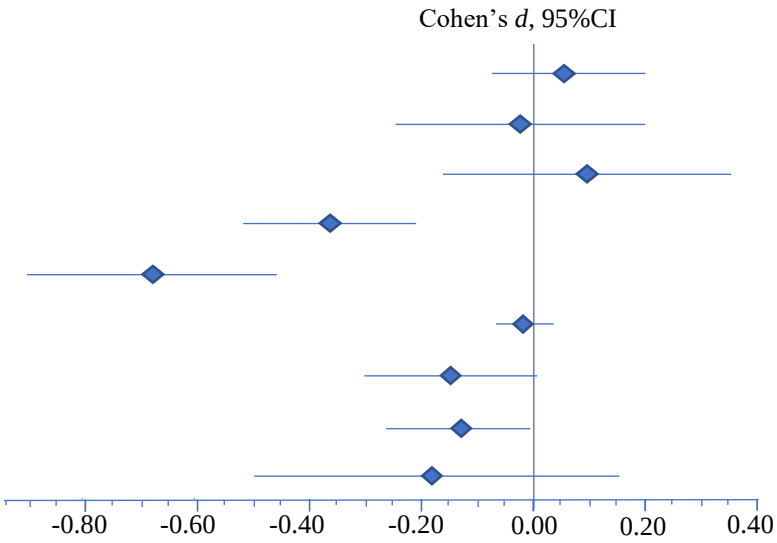


Figure 4.3. Forest plot summaries, by outcome type and neurodevelopment outcome.

Chapter 5 – SUMMARY AND CONCLUSIONS

PAHs are a common environmental pollutant from burning fossil fuels and other organic matter, and humans are almost constantly exposed, posing a public health risk, and especially to vulnerable populations, such as children, minorities, and those with little socioeconomic means. These groups have not benefitted to the same extent from U.S. policies to reduce PAH exposures. Prenatal exposures are of elevated public health concern because even low-dose exposures of environmental toxins during critical windows of human development can have of the substantial effects across a population. The human brain continues to develop through young adulthood, making children more susceptible to the effect of postnatal PAH exposure as well. The exact mechanism that prenatal/early-life effect is still unknown, and needs further study. This research evaluated the PAH exposure trends, and summarized the weight of scientific evidence regarding prenatal and early-life PAH exposure and child development. The conclusions from each proposed specific aim are summarized below.

5.1 Aim 1

The first aim was to evaluate the PAH exposure trends in the U.S. non-smoking population from 2001-2014, using urinary biomarkers. We evaluated the exposure trend in the general population, and investigated effect modification by age, sex, and race/ethnicity. We expected children, females, and Non-Hispanic whites to have lower PAH exposure than adults, males, and other race/ethnicity groups, respectively. Our hypothesis was based on research showing U.S. regulatory policies that reduced PM2.5 and hazardous air pollutants over a 20-year period would lead to decrease in ambient levels of PAHs over time, but that is not what we observed.

We found that Naphthalene and Pyrene exposure actually increased in our sample from 2001 to 2014, while Fluorene and Phenanthrene exposure decreased. When stratified by race/ethnicity, Non-Hispanic Blacks had higher PAH exposure compared to any other racial/ethnic group, and significantly higher compared to Non-Hispanic Whites. Mexican Americans also had significantly higher PAH exposure, compared to Non-Hispanic Whites. Naphthalene was the most abundant urinary PAH, 20-fold higher than Fluorene and Phenanthrene, and over 50-fold higher than Pyrene compared to reference groups. Effect

modification was observed by age (Naphthalene, Pyrene), sex (Fluorene, Pyrene), and race/ethnicity (Naphthalene, Fluorene, Phenanthrene, Pyrene). Our results also showed a changing trend in NAP exposure where children experienced a greater increase in exposure in more recent years, compared to adults.

5.2 Aim 2

The second specific aim evaluated the weight of evidence regarding the association between prenatal PAH exposure and birth outcomes in infants, by conducting a systematic review and meta-analysis. We expected higher levels of prenatal PAH exposure to be associated with adverse birth outcomes.

We found a statistically significant association between prenatal PAH exposure is associated and decreased birth weight and head circumference, and marginally significant association with decreases in birth length. Additionally, we found a statistically significant association between prenatal PAH exposure an increased combined outcome of low birth weight/fetal growth < 85% of normal, an increased combined outcome of small for gestational age/intrauterine growth restriction, and a marginally significant association with preterm birth. We did not find an association between prenatal PAH exposure and gestational age or ponderal index. These finding provide limited evidence of toxicity regarding prenatal PAH exposure and several birth outcomes. Confidence in the evidence is constrained by inconsistency of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion.

5.3 Aim 3

The third specific aim evaluated the weight of evidence regarding the association between prenatal and early-life PAH exposure and neurodevelopment outcomes in children, by conducting a systematic review and meta-analysis. We expected higher levels of prenatal and early-life PAH exposure to be associated with adverse neurodevelopment outcomes.

We found a statistically significant association between prenatal and early-life PAH exposure and decreased psychomotor function, as well as increased anxiety/depression, behavior problems, and neurodevelopment delay in children. Additionally, we found a marginally significant association with increased attention problems. The human evidence linking prenatal/early-life PAH exposure with intelligence, language skills, psychomotor

reflexes, and ADHD was inconclusive. Between-study variance was low to considerable across neurodevelopment outcome assessments, and this led to downgrading the human evidence from sufficient to limited.

5.4 Summary

Our results show that exposure to PAHs can disrupt fetal development and child neurodevelopment. In addition, our revealed a persistent disparity exists in PAH exposure for Non-Hispanic Blacks and Mexican Americans, suggesting these groups have not benefitted to the same extent from U.S. policies to reduce PAH exposures. Our findings provide limited human evidence of adverse fetal development and child neurodevelopment from prenatal and early-life PAH exposure. The evidence is limited due to high heterogeneity across available studies. However, the intent of a systematic review and meta-analysis in environmental epidemiology is to bring together studies that evaluated the exposure-outcome association from diverse populations and conditions. Limited human evidence of adverse fetal developmental, and child neurodevelopmental effects associated with prenatal/early-life exposure to a common environmental pollutant is cause for concern.

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APPENDICES

Appendix A: Supplemental Materials for Chapter 2

Trends in Urinary Metabolites of Polycyclic Aromatic Hydrocarbons (PAHs) in the Non-Smoking U.S. Population, NHANES 2001-2014

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Appendix A: Table of Contents

Table A.1. List of keywords used to identify foods expected to be high in PAHs[a] in the 24-hour dietary recall survey.

Key word	Reference
"Bacon" [b]	Sinha, et al., 2005[402]
"Baked"	Kazerouni, et al., 2001[403]
"Barbecue"	Phillips, 1999[404]
"BBQ"	Phillips, 1999[404]
"Blackened"	Viegas, et al, 2[405]012
"Bologna"	Kazerouni, et al., 2001[403]
"Broil"	Motorykin, et al., 2015[130]
"Burger"	Sinha, et al., 2005[402]
"Charcoal"	Motorykin, et al., 2015[130]
"Charred"	Gorji, et al., 2016[406]
"Cured"	Singh, Varshney & Agarwal, 2016[407]
"Deli"	Singh, Varshney & Agarwal, 2016[407]
"French Fries"	Kazerouni, et al., 2001[403]
"Fried"	Motorykin, et al., 2015[130]
"Hash Browns"	Kazerouni, et al., 2001[403]
"Hot Dog"	Kazerouni, et al., 2001[403]
"Grill"	Motorykin, et al., 2015[130]
"Kebab"	Gorji, et al., 2016[406]
"Lunch Meat"	Singh, Varshney & Agarwal, 2016[407]
"Pork Chop"	Sinha, et al., 2005[402]
"Processed" (c)	Phillips, 1999[404]
"Roasted" (d)	Motorykin, et al., 2015[130]
"Sausage"	Kazerouni, et al., 2001[403]
"Short Ribs"	Kazerouni, et al., 2001[403]
"Smoked"	Motorykin, et al., 2015[130]
"Spare Ribs"	Kazerouni, et al., 2001[403]
"Steak" [d]	Farhadian, et al., 2010[408]
"Toasted" [e]	Motorykin, et al., 2015[130]

(a) Foods expected to be high in PAHs based on presence of a keyword in food description coded as 1. Otherwise, foods coded as 0.

(b) Foods described as "bacon bits", "bacon dressing" or "bacon flavor" coded as 0.

(c) Foods containing the keyword "processed" pertaining to meat products coded as 1. Otherwise, coded as 0.

(d) Foods containing the keyword "roasted" pertaining to meat products or vegetables exposed to open flame coded as 1. Otherwise, coded as 0.

(e) Foods containing the keyword "toasted" pertaining to bread products exposed to open flame or toaster heating element coded as 1. Otherwise, coded as 0.

Table A.2. Limit of Detection (LOD) by NHANES Cycle, and the Maximal LOD, for Each uPAH Analyte.

NHANES Cycle		2001-02	2003-04		2005-06	2007-08		2009-10	2011-12		2013-14		
Author		NA	Sjodin		NA	Sjodin		Calafat	Calafat		Ye		
Method #		NA	09-OD		NA	6703.02		6703.04	6703.04		6705.02		
Date Published or Revised		NA	2006		NA	2012		2013	2013		2016		**Max. LOD**
Unit reported		NA	pg/mL	ug/L	NA	pg/mL	ug/L	pg/mL	pg/mL	ug/L	ng/mL	ug/L	ug/L
Unit converted to ppb		NA	0.001	1	NA	0.001	1	0.001	0.001	1	1	1	1
	1-naphthol	NA	18	0.018	NA	48	0.048	48	48	0.048	0.06	0.06	0.06
	2-naphthol	NA	12	0.012	NA	13	0.013	40	40	0.04	0.09	0.09	0.09
	2-OH-fluorene	NA	4.5	0.0045	NA	5	0.005	10	10	0.01	0.008	0.008	0.01
	3-OH-fluorene	NA	6.9	0.0069	NA	5	0.005	10	10	0.01	0.008	0.008	0.01
	1-OH-phenanthrene	NA	2.6	0.0026	NA	5	0.005	10	10	0.01	0.009	0.009	0.01
	2-OH-phenanthrene	NA	3.8	0.0038	NA	5	0.005	10	10	0.01	--	--	0.01
	3-OH-phenanthrene	NA	2.6	0.0026	NA	5	0.005	10	10	0.01	--	--	0.01
	2&3-OH-phenanthrene	--	--	--	--	--	--	--	11	--	0.01	0.01	0.01
	1-OH-pyrene	NA	4.9	0.0049	NA	5	0.005	10	10	0.01	0.07	0.07	0.07

Table A.3. Characteristics of participants excluded(a) from final sample. Reported as unweighted sample size (and weighted percent).

	Eligible Participants	Final Sample	Missing PAH Data	Weak/ Failing Kidneys	Missing Cotinine Data	Missing BMI Data	Missing PIR Data	Serum Cotinine > 1 ng/mL	*Total Excluded* [(a)]
Overall	19,079	11,053	782	315	1,382	505	1,267	4,008	8,026
Sex									
Males	9,420 (48.7)	5,110 (45.5)	334 (41.0)	158 (46.0)	677 (43.5)	271 (53.1)	619 (46.9)	2,352 (57.3)	4,117 (53.8)
Females	9,659 (51.3)	5,943 (54.5)	448 (59.0)	157 (54.0)	705 (56.5)	234 (46.9)	648 (53.1)	1,656 (42.7)	3,460 (46.2)
Age									
6-17 years	5,801 (18.1)	3,721 (20.1)	255 (17.5)	0	724 (42.4)	129 (15.0)	331 (14.6)	742 (10.3)	1,975 (15.2)
18-29 years	3,209 (18.1)	1,617 (15.3)	118 (18.6)	21 (9.5)	193 (17.5)	82 (16.6)	215 (18.6)	997 (25.7)	1,552 (22.7)
30-49 years	4,210 (30.8)	2,281 (29.7)	132 (25.1)	74 (25.2)	184 (19.5)	122 (33.3)	254 (26.9)	1,191 (37.4)	1,858 (32.9)
50-64 years	2,905 (19.3)	1,626 (19.8)	74 (10.9)	82 (25.2)	137 11.3)	62 (16.2)	234 (21.7)	716 (20.1)	1,212 (18.8)
65+ years	2,951 (13.7)	1,808 (15.1)	203 (27.9)	138 (40.1)	144 (9.4)	110 (18.9)	233 (18.2)	362 (6.5)	979 (10.4)
Race/Ethnicity									
Mexican American	3,924 (9.2)	2,666 (10.4)	122 (5.4)	51 (9.1)	251 (9.1)	91 (10.0)	331 (13.9)	471 (5.7)	1,175 (7.6)
Non-Hispanic White	7,697 (67.1)	4,339 (67.5)	363 (72.8)	146 (64.5)	400 (55.3)	177 (61.1)	372 (56.2)	1,950 (70.9)	3,150 (66.3)
Non-Hispanic Black	4,568 (12.0)	2,309 (10.2)	197 (11.6)	74 (16.1)	522 (22.9)	124 (12.7)	300 (13.5)	1,131 (13.7)	2,165 (14.8)
Other/Multi-Racial	2,890 (11.7)	1,739 (11.9)	100 (10.2)	44 (10.3)	209 (12.7)	113 (16.2)	264 (16.4)	456 (9.7)	1,087 (11.4)
Poverty-to-Income Ratio (PIR)									
PIR < 2.00	9,131 (37.5)	5,167 (31.6)	371 (42.5)	181 (53.7)	654 (41.9)	281 (47.6)	--	2,511 (48.8)	3,738 (47.8)
PIR $\geq$ 2.00	8,562 (62.5)	5,886 (68.4)	326 (57.6)	100 (46.3)	578 (58.1)	182 (52.4)	--	1,497 (51.2)	2,453 (52.2)
Body Mass Index									
Normal weight (includes underweight)	7,714 (40.1)	4,539 (39.1)	296 (38.9)	85 (31.4)	666 (49.9)	--	500 (42.4)	1,691 (40.3)	3,020 (41.9)
Overweight	5,318 (30.1)	3,210 (30.2)	179 (28.8)	93 (29.5)	312 (24.8)	--	393 (32.6)	1,178 (30.7)	1,972 (29.8)
Obese	5,405 (29.9)	3,304 (30.7)	187 (32.9)	120 (30.1)	352 (25.3)	--	332 (25.0)	1,139 (29.1)	1,943 (28.3)
Consumed foods likely to be high in PAHs 24-Hours Prior to Exam									
No	5,297 (26.0)	2,903 (25.1)	352 (36.6)	84 (25.2)	473 (33.9)	174 (33.0)	431 (33.8)	972 (23.4)	2,260 (27.3)
Yes	13,782 (74.0)	8,150 (74.9)	430 (63.4)	231 (74.8)	909 (66.1)	331 (67.0)	836 (66.2)	3,036 (76.6)	5,317 (72.7)
Seasonality									
Nov 1 – Apr. 30	9,185 (42.0)	5,513 (42.5)	344 (40.4)	151 (44 6)	677 (43.5)	223 (40.4)	643 (43.6)	1,742 (40.0)	3,456 (41.1)
May 1 – Oct. 31	9,894 (58.0)	5,540 (57.5)	438 (59.6)	164 (55.4)	705 (56.5)	282 (59.7)	624 (56.4)	2,266 (60.0)	4,121 (58.9)

(a) There were 3 participants with missing urinary creatinine data and 236 excluded participants who had missing data in more than one category.

Table A.4. Estimated weighted aGM and 95%CI of uPAHs[a] at each NHANES cycle. Adjusted for covariates[b], and stratified by 1) age, and 2) sex. See Figures 2.3 and 2.4, respectively, for graphical representation.

	1. Stratified by Age							2. Stratified by Sex, 6+ years						
	Children, 6-17 years			Adults, 18+ years				Males			Females			
	aGM	LCI	UCI	aGM	LCI	UCI	*p* [c]	aGM	LCI	UCI	aGM	LCI	UCI	*p*
uNAP, Overall							*< 0.01*							*0.21*
2001-02	4.02	3.68	4.36	4.23	4.06	4.41		4.35	4.15	4.56	4.06	3.86	4.26	
2003-04	4.94	4.60	5.27	5.22	4.90	5.54		5.40	5.00	5.80	4.98	4.74	5.21	
2005-06	4.82	4.55	5.10	6.22	5.84	6.60		5.86	5.59	6.14	5.90	5.57	6.24	
2007-08	5.51	5.15	5.87	6.50	6.19	6.81		6.52	6.24	6.80	6.14	5.85	6.43	
2009-10	5.70	5.38	6.03	5.95	5.68	6.23		5.96	5.76	6.17	5.86	5.50	6.21	
2011-12	5.85	5.43	6.27	5.84	5.52	6.15		5.89	5.58	6.20	5.78	5.26	6.30	
2013-14	6.48	6.00	6.96	5.92	5.65	6.18		5.91	5.64	6.19	6.12	5.72	6.51	
uNAP, 25th percentile							*< 0.01*							*<0.01*
2001-02	2.31	1.97	2.69	2.39	2.22	2.57		2.77	2.44	3.14	2.20	1.96	2.46	
2003-04	3.15	2.83	3.50	2.92	2.54	3.36		3.51	3.04	4.04	2.54	2.20	2.92	
2005-06	2.94	2.69	3.22	3.72	3.27	4.23		3.76	3.44	4.11	3.30	2.90	3.76	
2007-08	3.29	2.93	3.68	3.58	3.31	3.88		4.11	3.92	4.32	3.01	2.73	3.32	
2009-10	3.33	2.97	3.74	3.24	2.93	3.58		3.80	3.43	4.21	2.86	2.70	3.02	
2011-12	3.17	2.43	4.14	3.12	2.89	3.38		3.47	3.02	3.99	3.00	2.63	3.42	
2013-14	3.28	2.90	3.71	3.08	2.77	3.43		3.12	2.82	3.45	3.04	2.64	3.51	
uNAP, 50th percentile							*< 0.01*							*<0.01*
2001-02	3.74	3.35	4.18	3.95	3.78	4.12		4.23	4.04	4.43	3.64	3.42	3.87	
2003-04	4.76	4.45	5.10	4.92	4.57	5.30		5.04	4.60	5.52	4.76	4.41	5.13	
2005-06	4.32	4.11	4.53	5.79	5.41	6.19		5.44	5.17	5.72	5.38	5.15	5.62	
2007-08	5.00	4.55	5.50	6.20	5.81	6.63		6.16	5.80	6.55	5.56	5.20	5.95	
2009-10	5.07	4.76	5.40	5.45	5.09	5.83		5.67	5.39	5.96	5.16	4.64	5.74	
2011-12	5.46	4.66	6.40	5.40	5.00	5.83		5.78	5.31	6.30	4.98	4.49	5.51	
2013-14	5.57	4.91	6.31	5.22	4.91	5.55		5.52	5.17	5.89	5.11	4.56	5.72	
uNAP, 75th percentile							*< 0.01*							*<0.01*
2001-02	5.31	4.94	5.70	5.55	5.32	5.78		5.63	5.30	5.99	5.42	5.13	5.73	
2003-04	6.52	6.03	7.06	6.85	6.46	7.26		7.08	6.56	7.63	6.68	6.44	6.94	
2005-06	6.06	5.67	6.48	8.07	7.66	8.50		7.49	7.27	7.71	7.70	7.21	8.21	
2007-08	7.28	6.81	7.77	8.66	8.24	9.10		8.46	7.93	9.02	8.11	7.67	8.57	
2009-10	7.58	7.04	8.16	8.01	7.44	8.63		7.81	7.50	8.13	8.13	7.30	9.05	
2011-12	7.67	7.32	8.04	7.81	7.36	8.29		7.85	7.35	8.39	7.91	7.24	8.64	
2013-14	9.04	8.47	9.64	7.96	7.60	8.33		7.94	7.51	8.40	8.37	7.81	8.97	
uNAP, 95th percentile							*< 0.01*							*<0.01*
2001-02	7.82	7.18	8.53	8.61	8.15	9.08		8.08	7.64	8.55	8.69	7.88	9.59	
2003-04	9.55	8.88	10.28	10.30	9.55	11.11		10.36	9.70	11.06	9.96	9.34	10.61	
2005-06	9.70	9.14	10.30	12.33	11.61	13.10		11.50	10.72	12.32	11.96	11.39	12.56	
2007-08	11.24	9.91	12.75	12.91	12.12	13.76		12.00	10.76	13.39	13.25	12.38	14.19	
2009-10	11.49	10.79	12.23	12.62	11.92	13.37		11.53	10.82	12.29	12.77	11.82	13.79	
2011-12	12.39	11.19	13.73	12.25	11.67	12.86		11.32	10.66	12.02	12.90	12.06	13.81	
2013-14	13.92	12.71	15.24	12.98	12.11	13.91		12.96	11.85	14.18	14.38	13.05	15.85	
uFLU, Overall							*0.38*							*<0.01*
2001-02	0.40	0.37	0.43	0.36	0.34	0.38		0.42	0.40	0.44	0.33	0.31	0.35	
2003-04	0.35	0.33	0.37	0.29	0.27	0.31		0.34	0.32	0.37	0.27	0.26	0.28	
2005-06	0.35	0.33	0.38	0.32	0.30	0.34		0.38	0.36	0.39	0.29	0.27	0.30	

Table A.4. Continued.

	1. Stratified by Age							2. Stratified by Sex, 6+ years						
	Children, 6-17 years			Adults, 18+ years				Males			Females			
	aGM	LCI	UCI	aGM	LCI	UCI	*p* [c]	aGM	LCI	UCI	aGM	LCI	UCI	*p*
2007-08	0.35	0.33	0.37	0.31	0.29	0.32		0.36	0.34	0.37	0.28	0.27	0.30	
2009-10	0.31	0.29	0.33	0.27	0.25	0.28		0.30	0.29	0.32	0.25	0.24	0.26	
2011-12	0.30	0.28	0.32	0.26	0.25	0.28		0.31	0.29	0.33	0.24	0.22	0.25	
2013-14	0.23	0.21	0.25	0.21	0.20	0.22		0.23	0.22	0.24	0.20	0.18	0.21	
uFLU, 25th percentile							*<0.01*							*<0.01*
2001-02	0.23	0.21	0.26	0.20	0.19	0.21		0.27	0.24	0.30	0.18	0.16	0.19	
2003-04	0.22	0.20	0.24	0.15	0.13	0.18		0.23	0.19	0.26	0.14	0.12	0.16	
2005-06	0.22	0.20	0.24	0.19	0.17	0.21		0.24	0.22	0.26	0.16	0.13	0.18	
2007-08	0.20	0.19	0.22	0.17	0.15	0.19		0.23	0.21	0.25	0.14	0.12	0.16	
2009-10	0.16	0.15	0.18	0.14	0.13	0.15		0.20	0.18	0.22	0.12	0.12	0.14	
2011-12	0.14	0.11	0.19	0.14	0.13	0.15		0.17	0.15	0.20	0.12	0.11	0.13	
2013-14	0.12	0.10	0.13	0.11	0.10	0.12		0.12	0.11	0.13	0.09	0.08	0.11	
uFLU, 50th percentile							*<0.01*							*<0.01*
2001-02	0.37	0.32	0.44	0.35	0.33	0.36		0.40	0.38	0.43	0.30	0.27	0.32	
2003-04	0.33	0.31	0.36	0.27	0.25	0.30		0.32	0.30	0.36	0.26	0.24	0.28	
2005-06	0.33	0.30	0.36	0.30	0.28	0.32		0.36	0.34	0.38	0.27	0.25	0.30	
2007-08	0.32	0.30	0.35	0.30	0.28	0.31		0.34	0.33	0.36	0.26	0.23	0.29	
2009-10	0.28	0.26	0.30	0.24	0.23	0.26		0.28	0.27	0.29	0.22	0.20	0.23	
2011-12	0.27	0.23	0.31	0.24	0.23	0.25		0.29	0.26	0.32	0.20	0.18	0.23	
2013-14	0.21	0.18	0.24	0.18	0.17	0.20		0.21	0.19	0.23	0.16	0.15	0.18	
uFLU, 75th percentile							*<0.01*							*<0.01*
2001-02	0.52	0.48	0.56	0.48	0.46	0.50		0.55	0.51	0.59	0.44	0.43	0.46	
2003-04	0.46	0.43	0.49	0.40	0.37	0.43		0.44	0.41	0.48	0.37	0.35	0.39	
2005-06	0.48	0.44	0.52	0.42	0.39	0.44		0.48	0.46	0.51	0.37	0.35	0.39	
2007-08	0.44	0.41	0.48	0.42	0.39	0.45		0.46	0.44	0.48	0.38	0.37	0.40	
2009-10	0.40	0.35	0.45	0.36	0.34	0.37		0.39	0.37	0.41	0.34	0.32	0.36	
2011-12	0.41	0.38	0.43	0.36	0.34	0.39		0.41	0.39	0.43	0.32	0.30	0.35	
2013-14	0.34	0.31	0.38	0.28	0.27	0.30		0.31	0.28	0.33	0.27	0.25	0.29	
uFLU, 95th percentile							*<0.01*							*<0.01*
2001-02	0.76	0.70	0.83	0.70	0.65	0.75		0.76	0.71	0.81	0.69	0.64	0.75	
2003-04	0.67	0.63	0.71	0.57	0.52	0.62		0.66	0.62	0.70	0.53	0.50	0.56	
2005-06	0.72	0.63	0.83	0.63	0.59	0.66		0.70	0.68	0.73	0.59	0.55	0.64	
2007-08	0.68	0.60	0.77	0.62	0.58	0.67		0.65	0.60	0.70	0.62	0.57	0.67	
2009-10	0.62	0.54	0.70	0.56	0.52	0.60		0.59	0.55	0.63	0.57	0.54	0.59	
2011-12	0.62	0.57	0.66	0.56	0.53	0.59		0.62	0.56	0.68	0.53	0.49	0.58	
2013-14	0.54	0.49	0.58	0.46	0.41	0.51		0.49	0.45	0.53	0.46	0.41	0.50	
uPHEN, Overall							*0.28*							*0.08*
2001-02	0.31	0.29	0.33	0.33	0.31	0.35		0.35	0.34	0.37	0.30	0.28	0.32	
2003-04	0.33	0.31	0.35	0.31	0.29	0.33		0.34	0.31	0.36	0.29	0.28	0.31	
2005-06	0.30	0.28	0.32	0.32	0.31	0.34		0.35	0.34	0.37	0.29	0.27	0.30	
2007-08	0.30	0.28	0.32	0.30	0.29	0.32		0.33	0.31	0.35	0.28	0.26	0.29	
2009-10	0.28	0.26	0.30	0.28	0.27	0.30		0.30	0.28	0.31	0.27	0.25	0.28	
2011-12	0.25	0.23	0.27	0.26	0.25	0.28		0.29	0.26	0.31	0.24	0.22	0.25	
2013-14	0.21	0.19	0.23	0.22	0.21	0.23		0.23	0.22	0.25	0.20	0.19	0.21	

Table A.4. Continued

	1. Stratified by Age							2. Stratified by Sex, 6+ years						
	Children, 6-17 years			Adults, 18+ years				Males			Females			
	aGM	LCI	UCI	aGM	LCI	UCI	*p* [(c)]	aGM	LCI	UCI	aGM	LCI	UCI	*p*
uPHEN, 25th percentile							*<0.01*							*<0.01*
2001-02	0.19	0.17	0.21	0.19	0.17	0.20		0.23	0.21	0.25	0.17	0.15	0.18	
2003-04	0.21	0.19	0.24	0.17	0.15	0.21		0.22	0.19	0.26	0.16	0.14	0.19	
2005-06	0.18	0.17	0.20	0.20	0.18	0.22		0.23	0.21	0.25	0.17	0.14	0.20	
2007-08	0.18	0.16	0.20	0.17	0.16	0.19		0.21	0.21	0.22	0.15	0.13	0.17	
2009-10	0.15	0.14	0.17	0.16	0.15	0.18		0.19	0.17	0.21	0.14	0.13	0.15	
2011-12	0.13	0.10	0.16	0.14	0.13	0.15		0.17	0.15	0.19	0.13	0.11	0.14	
2013-14	0.11	0.10	0.13	0.11	0.10	0.13		0.13	0.12	0.13	0.10	0.09	0.12	
uPHEN, 50th percentile							*<0.01*							*<0.01*
2001-02	0.29	0.25	0.34	0.32	0.30	0.34		0.35	0.33	0.37	0.27	0.25	0.29	
2003-04	0.32	0.30	0.34	0.30	0.27	0.33		0.32	0.29	0.36	0.27	0.25	0.30	
2005-06	0.28	0.25	0.30	0.31	0.29	0.33		0.34	0.32	0.35	0.27	0.26	0.29	
2007-08	0.29	0.26	0.31	0.29	0.27	0.32		0.32	0.30	0.34	0.25	0.23	0.27	
2009-10	0.26	0.24	0.28	0.26	0.25	0.28		0.28	0.26	0.30	0.24	0.22	0.26	
2011-12	0.23	0.20	0.26	0.24	0.23	0.26		0.27	0.25	0.30	0.21	0.18	0.24	
2013-14	0.18	0.16	0.20	0.19	0.18	0.21		0.21	0.20	0.23	0.17	0.16	0.18	
uPHEN, 75th percentile							*<0.01*							*<0.01*
2001-02	0.41	0.39	0.44	0.43	0.41	0.45		0.46	0.42	0.49	0.40	0.38	0.43	
2003-04	0.44	0.41	0.46	0.41	0.39	0.44		0.44	0.41	0.48	0.41	0.38	0.44	
2005-06	0.38	0.35	0.41	0.42	0.41	0.43		0.46	0.44	0.48	0.38	0.37	0.40	
2007-08	0.40	0.37	0.44	0.41	0.38	0.43		0.43	0.40	0.46	0.37	0.35	0.40	
2009-10	0.38	0.34	0.42	0.38	0.36	0.40		0.39	0.37	0.42	0.37	0.35	0.39	
2011-12	0.37	0.32	0.42	0.36	0.34	0.39		0.39	0.36	0.43	0.32	0.30	0.33	
2013-14	0.30	0.25	0.34	0.29	0.27	0.31		0.31	0.29	0.33	0.28	0.25	0.30	
uPHEN, 95th percentile							*<0.01*							*<0.01*
2001-02	0.59	0.55	0.64	0.63	0.58	0.67		0.62	0.57	0.68	0.61	0.53	0.69	
2003-04	0.63	0.58	0.69	0.59	0.57	0.61		0.60	0.56	0.65	0.59	0.55	0.62	
2005-06	0.59	0.52	0.65	0.60	0.57	0.63		0.66	0.62	0.71	0.56	0.53	0.59	
2007-08	0.64	0.56	0.73	0.60	0.57	0.64		0.63	0.60	0.66	0.60	0.55	0.65	
2009-10	0.59	0.51	0.69	0.56	0.51	0.62		0.57	0.51	0.64	0.58	0.54	0.63	
2011-12	0.53	0.48	0.60	0.53	0.49	0.57		0.53	0.45	0.61	0.50	0.46	0.55	
2013-14	0.44	0.41	0.48	0.45	0.40	0.51		0.46	0.43	0.49	0.43	0.38	0.49	
uPYR, Overall							*<0.01*							*<0.01*
2001-02	0.06	0.05	0.06	0.04	0.04	0.04		0.05	0.05	0.05	0.04	0.04	0.04	
2003-04	0.12	0.11	0.13	0.07	0.06	0.07		0.09	0.08	0.10	0.07	0.07	0.07	
2005-06	0.12	0.11	0.12	0.08	0.07	0.08		0.10	0.09	0.10	0.08	0.08	0.09	
2007-08	0.15	0.14	0.16	0.10	0.10	0.11		0.12	0.11	0.12	0.11	0.10	0.11	
2009-10	0.16	0.15	0.17	0.10	0.10	0.11		0.12	0.11	0.12	0.11	0.11	0.12	
2011-12	0.14	0.13	0.15	0.10	0.09	0.10		0.12	0.11	0.12	0.10	0.09	0.11	
2013-14	0.16	0.15	0.17	0.12	0.12	0.13		0.13	0.12	0.13	0.13	0.12	0.14	
uPYR, 25th percentile [(d)]							*<0.01*							*<0.01*
2001-02	0.04	0.03	0.04	0.02	0.02	0.03		0.03	0.03	0.04	0.02	0.02	0.02	
2003-04	0.08	0.08	0.09	0.04	0.03	0.04		0.06	0.05	0.07	0.04	0.03	0.04	
2005-06	0.07	0.07	0.08	0.05	0.04	0.06		0.06	0.06	0.07	0.04	0.04	0.05	
2007-08	0.10	0.09	0.11	0.06	0.05	0.07		0.08	0.07	0.08	0.05	0.05	0.06	
2009-10	0.10	0.09	0.11	0.06	0.06	0.07		0.08	0.07	0.08	0.06	0.05	0.06	
2011-12	0.08	0.06	0.10	0.06	0.05	0.06		0.07	0.06	0.08	0.05	0.05	0.06	
2013-14	0.09	0.08	0.10	0.07	0.06	0.07		0.07	0.07	0.08	0.07	0.06	0.07	

Table A.4. Continued

	1. Stratified by Age							2. Stratified by Sex, 6+ years						
	Children, 6-17 years			Adults, 18+ years				Males			Females			
	aGM	LCI	UCI	aGM	LCI	UCI	*p* [c]	aGM	LCI	UCI	aGM	LCI	UCI	*p*
uPYR, 50th percentile [d]							*0.01*							*0.01*
2001-02	0.06	0.05	0.06	0.04	0.04	0.04		0.05	0.05	0.05	0.04	0.03	0.04	
2003-04	0.12	0.11	0.12	0.07	0.06	0.07		0.08	0.08	0.09	0.06	0.06	0.07	
2005-06	0.11	0.10	0.12	0.07	0.07	0.08		0.09	0.09	0.09	0.07	0.07	0.08	
2007-08	0.14	0.13	0.15	0.10	0.09	0.10		0.11	0.11	0.12	0.10	0.09	0.10	
2009-10	0.15	0.14	0.16	0.10	0.09	0.10		0.11	0.10	0.12	0.10	0.09	0.11	
2011-12	0.13	0.11	0.15	0.09	0.09	0.10		0.11	0.10	0.12	0.09	0.08	0.09	
2013-14	0.14	0.12	0.16	0.11	0.10	0.12		0.12	0.11	0.12	0.11	0.10	0.12	
uPYR, 75th percentile							*<0.01*							*<0.01*
2001-02	0.08	0.07	0.08	0.05	0.05	0.06		0.06	0.06	0.07	0.05	0.05	0.06	
2003-04	0.15	0.14	0.16	0.09	0.08	0.09		0.12	0.11	0.13	0.09	0.09	0.10	
2005-06	0.15	0.14	0.16	0.10	0.10	0.11		0.13	0.12	0.13	0.11	0.10	0.11	
2007-08	0.19	0.18	0.20	0.13	0.13	0.14		0.15	0.14	0.16	0.14	0.13	0.15	
2009-10	0.22	0.20	0.24	0.14	0.13	0.14		0.15	0.15	0.16	0.15	0.14	0.16	
2011-12	0.19	0.18	0.20	0.13	0.13	0.14		0.15	0.14	0.16	0.14	0.12	0.15	
2013-14	0.22	0.20	0.24	0.16	0.15	0.17		0.17	0.16	0.18	0.17	0.16	0.18	
uPYR, 95th percentile							*<0.01*							*<0.01*
2001-02	0.11	0.10	0.12	0.08	0.07	0.09		0.10	0.09	0.10	0.09	0.08	0.09	
2003-04	0.22	0.20	0.24	0.12	0.12	0.13		0.17	0.16	0.18	0.14	0.14	0.15	
2005-06	0.22	0.19	0.24	0.14	0.14	0.15		0.18	0.16	0.19	0.17	0.16	0.18	
2007-08	0.29	0.26	0.31	0.19	0.18	0.20		0.20	0.19	0.22	0.23	0.21	0.26	
2009-10	0.32	0.30	0.35	0.20	0.19	0.21		0.23	0.21	0.26	0.26	0.24	0.29	
2011-12	0.28	0.26	0.30	0.20	0.18	0.21		0.22	0.20	0.24	0.23	0.22	0.25	
2013-14	0.33	0.31	0.36	0.25	0.23	0.27		0.27	0.25	0.30	0.32	0.29	0.35	

Table A.4. Continued. Estimated weighted aGM and 95%CI of uPAHs[(a)] at each NHANES cycle. Adjusted for covariates[(b)], and stratified by at reproductive age (18-49 years). See Figure 2.5 for a graphical representation.

Stratified by Reproductive Age (18-49 Years)						
Men			Women			
aGM	LCI	UCI	aGM	LCI	UCI	*p*
uNAP, Overall						*<0.01*
4.36	4.09	4.63	3.91	3.68	4.15	
5.64	5.04	6.24	4.93	4.67	5.20	
5.61	5.27	5.95	6.36	5.80	6.92	
7.13	6.52	7.74	5.73	5.37	6.10	
5.64	5.34	5.94	6.23	5.71	6.75	
5.91	5.39	6.44	6.28	5.43	7.13	
5.62	5.18	6.06	7.05	6.51	7.58	
uNAP, 25th percentile						*<0.01*
3.03	2.64	3.48	2.09	1.75	2.49	
3.85	3.31	4.49	2.53	2.00	3.20	
3.61	2.98	4.38	3.98	3.25	4.87	
5.10	4.17	6.23	3.06	2.35	3.98	
3.75	3.05	4.61	2.97	2.57	3.44	
3.44	2.69	4.40	3.07	2.57	3.66	
3.01	2.46	3.67	3.42	2.93	3.99	
uNAP, 50th percentile						*<0.01*
4.24	4.02	4.46	3.60	3.14	4.12	
5.02	4.36	5.78	4.83	4.21	5.54	
5.74	5.33	6.17	5.96	5.63	6.31	
6.89	6.30	7.52	5.37	5.02	5.74	
5.53	4.99	6.14	5.35	4.60	6.23	
5.56	4.65	6.65	4.88	3.91	6.07	
5.12	4.47	5.87	5.83	5.04	6.74	
uNAP, 75th percentile						*<0.01*
5.69	5.22	6.21	5.10	4.82	5.40	
7.51	6.71	8.40	6.67	6.30	7.06	
7.23	6.85	7.63	8.28	7.81	8.77	
9.28	8.43	10.22	7.42	6.65	8.28	
7.40	6.95	7.88	8.93	8.23	9.70	
8.10	7.55	8.68	9.12	7.79	10.68	
7.28	6.46	8.20	9.54	8.76	10.40	
uNAP, 95th percentile						*<0.01*
7.99	7.63	8.36	7.81	7.26	8.40	
10.64	9.14	12.38	9.58	8.70	10.55	
10.37	9.52	11.31	12.30	11.43	13.23	
11.65	11.16	12.16	11.97	10.82	13.25	
10.27	9.48	11.12	13.89	12.58	15.33	
10.79	9.87	11.81	14.24	13.21	15.35	
12.04	10.83	13.38	15.71	14.00	17.64	
uFLU, Overall						*<0.01*
0.46	0.43	0.50	0.33	0.30	0.35	
0.37	0.32	0.41	0.28	0.26	0.30	
0.39	0.37	0.41	0.29	0.26	0.32	

Table A.4. Continued.

Stratified by Reproductive Age (18-49 Years)						
Men			Women			
aGM	LCI	UCI	aGM	LCI	UCI	*p*
0.40	0.37	0.43	0.29	0.27	0.31	
0.30	0.29	0.32	0.27	0.25	0.29	
0.33	0.30	0.36	0.25	0.22	0.29	
0.23	0.22	0.24	0.23	0.21	0.24	
uFLU, 25th percentile						*<0.01*
0.31	0.25	0.37	0.18	0.15	0.21	
0.26	0.22	0.31	0.14	0.12	0.18	
0.25	0.20	0.31	0.18	0.13	0.25	
0.27	0.23	0.31	0.16	0.13	0.20	
0.20	0.18	0.23	0.13	0.12	0.15	
0.19	0.14	0.25	0.12	0.10	0.14	
0.12	0.10	0.14	0.10	0.09	0.13	
uFLU, 50th percentile						*<0.01*
0.46	0.43	0.49	0.31	0.28	0.35	
0.34	0.29	0.40	0.27	0.23	0.31	
0.39	0.37	0.42	0.27	0.26	0.30	
0.39	0.35	0.43	0.28	0.26	0.30	
0.27	0.25	0.31	0.23	0.21	0.27	
0.32	0.27	0.37	0.20	0.16	0.25	
0.22	0.19	0.25	0.19	0.16	0.21	
uFLU, 75th percentile						*<0.01*
0.60	0.56	0.66	0.44	0.42	0.46	
0.48	0.42	0.55	0.38	0.35	0.41	
0.50	0.47	0.54	0.38	0.35	0.41	
0.52	0.47	0.57	0.39	0.36	0.42	
0.39	0.36	0.43	0.39	0.36	0.41	
0.45	0.41	0.48	0.37	0.32	0.42	
0.31	0.29	0.33	0.33	0.30	0.36	
uFLU, 95th percentile						*<0.01*
0.83	0.76	0.91	0.62	0.56	0.70	
0.68	0.58	0.81	0.55	0.53	0.58	
0.66	0.61	0.72	0.59	0.54	0.64	
0.69	0.60	0.79	0.62	0.55	0.70	
0.59	0.53	0.65	0.61	0.53	0.71	
0.60	0.53	0.69	0.59	0.53	0.65	
0.46	0.43	0.50	0.56	0.47	0.68	
uPHEN, Overall						*<0.01*
0.38	0.35	0.41	0.30	0.28	0.32	
0.37	0.32	0.41	0.30	0.27	0.33	
0.35	0.34	0.37	0.30	0.27	0.32	
0.36	0.33	0.39	0.29	0.27	0.31	
0.30	0.28	0.31	0.29	0.27	0.31	
0.30	0.27	0.33	0.26	0.23	0.29	
0.23	0.22	0.24	0.22	0.21	0.24	
uPHEN, 25th percentile						*<0.01*
0.24	0.20	0.29	0.16	0.14	0.19	
0.26	0.20	0.33	0.16	0.13	0.20	

Table A.4. Continued.

Stratified by Reproductive Age (18-49 Years)						
Men			Women			
aGM	LCI	UCI	aGM	LCI	UCI	*p*
0.23	0.19	0.27	0.20	0.16	0.24	
0.25	0.23	0.27	0.15	0.12	0.19	
0.21	0.18	0.24	0.14	0.12	0.16	
0.17	0.13	0.23	0.13	0.12	0.15	
0.11	0.10	0.13	0.10	0.09	0.12	
uPHEN, 50th percentile						*<0.01*
0.38	0.36	0.40	0.29	0.25	0.32	
0.36	0.31	0.41	0.29	0.26	0.33	
0.36	0.33	0.39	0.29	0.25	0.32	
0.35	0.32	0.39	0.28	0.25	0.32	
0.27	0.24	0.29	0.25	0.23	0.28	
0.28	0.24	0.32	0.22	0.18	0.26	
0.21	0.19	0.24	0.18	0.16	0.20	
uPHEN, 75th percentile						*<0.01*
0.48	0.43	0.54	0.40	0.37	0.43	
0.47	0.41	0.55	0.40	0.35	0.45	
0.46	0.44	0.48	0.38	0.36	0.41	
0.46	0.42	0.52	0.38	0.35	0.41	
0.39	0.36	0.42	0.40	0.38	0.43	
0.40	0.37	0.44	0.36	0.31	0.42	
0.31	0.28	0.34	0.32	0.28	0.36	
uPHEN, 95th percentile						*<0.01*
0.67	0.63	0.71	0.58	0.53	0.63	
0.64	0.55	0.75	0.64	0.59	0.68	
0.59	0.55	0.64	0.59	0.51	0.67	
0.66	0.57	0.76	0.61	0.53	0.69	
0.58	0.50	0.66	0.66	0.57	0.76	
0.56	0.49	0.63	0.58	0.52	0.66	
0.46	0.40	0.54	0.51	0.41	0.62	
uPYR, Overall						*<0.01*
0.05	0.05	0.06	0.04	0.04	0.04	
0.09	0.08	0.10	0.07	0.06	0.07	
0.10	0.09	0.10	0.09	0.08	0.10	
0.13	0.12	0.14	0.11	0.10	0.12	
0.12	0.12	0.13	0.13	0.12	0.14	
0.12	0.11	0.13	0.11	0.10	0.13	
0.13	0.12	0.13	0.14	0.13	0.15	
uPYR, 25th percentile [(d)]						*<0.01*
0.04	0.03	0.05	0.02	0.02	0.03	
0.07	0.05	0.08	0.04	0.03	0.04	
0.06	0.05	0.07	0.06	0.05	0.07	
0.10	0.09	0.11	0.06	0.05	0.08	
0.09	0.07	0.11	0.07	0.06	0.07	
0.07	0.06	0.09	0.06	0.05	0.07	
0.07	0.06	0.08	0.07	0.06	0.08	

Table A.4. Continued.

Stratified by Reproductive Age (18-49 Years)						
Men			Women			
aGM	LCI	UCI	aGM	LCI	UCI	*p*
uPYR, 50th percentile [d]						*<0.01*
0.05	0.05	0.06	0.04	0.04	0.04	
0.09	0.08	0.10	0.07	0.06	0.08	
0.09	0.09	0.10	0.08	0.07	0.09	
0.13	0.12	0.14	0.11	0.10	0.12	
0.11	0.11	0.12	0.11	0.10	0.13	
0.12	0.10	0.13	0.09	0.08	0.12	
0.12	0.11	0.13	0.12	0.11	0.14	
uPYR, 75th percentile						*<0.01*
0.07	0.06	0.07	0.05	0.05	0.06	
0.11	0.10	0.13	0.10	0.09	0.10	
0.12	0.12	0.12	0.11	0.10	0.13	
0.17	0.16	0.19	0.15	0.14	0.16	
0.16	0.15	0.17	0.18	0.17	0.19	
0.16	0.15	0.17	0.16	0.14	0.19	
0.17	0.15	0.18	0.20	0.18	0.22	
uPYR, 95th percentile						*<0.01*
0.09	0.08	0.10	0.08	0.07	0.09	
0.17	0.15	0.19	0.13	0.12	0.14	
0.16	0.14	0.18	0.17	0.15	0.19	
0.22	0.19	0.25	0.23	0.21	0.26	
0.23	0.20	0.25	0.28	0.25	0.31	
0.22	0.21	0.24	0.25	0.22	0.30	
0.25	0.23	0.27	0.33	0.27	0.41	

[a] uNAP; sum of urinary Naphthalene metabolites (ug/L). uFLU: sum of urinary Fluorene metabolites (ug/L). uPHEN: sum of urinary Phenanthrene metabolites (ug/L). UPYR: urinary Pyrene metabolites (ug/L).

[b] Model for age: adjusted for urinary creatinine, sex, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##age. Model for sex 6+years: adjusted for urinary creatinine, age, race/ethnicity, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##sex. Model for sex at reproductive age: same as model for sex, but age restricted to 18-49 years.

[c] *p*-value for the overall trend in weighted aGM between groups across NHANES cycles was assessed by the adjusted Wald test, $\alpha = 0.05$.

[d] The delta in trend values between 2001-02 and 2013-14 are within the maximal analytical error for urinary Pyrene metabolite (0.07 ug/L).

Table A.5. Estimated weighted aGM (95%CI) of uPAHs[a] at each NHANES cycle. Adjusted for covariates[b], and stratified by race/ethnicity. Non-Hispanic White (NHW) is the reference group, and compared to Mexican American (MA), Non-Hispanic Black (NHB), and Other/Multi-Racial (Other/Multi.) group, respectively.

	NHW			**MA**				**NHB**				**Other/Multi.**			
	aGM	Lower 95%CI	Upper 95%CI	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*
uNAP, Overall															
2001-02	3.81	3.65	3.97	4.96	4.59	5.32	*<0.01*	5.78	5.37	6.18	*<0.01*	4.98	4.45	5.51	*<0.01*
2003-04	4.85	4.55	5.14	5.62	5.29	5.96		7.35	6.92	7.78		4.49	4.04	4.94	
2005-06	5.32	4.98	5.66	6.54	6.06	7.03		8.13	7.65	8.60		6.49	5.72	7.25	
2007-08	6.03	5.74	6.31	7.15	6.77	7.53		7.08	6.51	7.65		6.20	5.32	7.08	
2009-10	5.46	5.23	5.68	7.23	6.64	7.83		7.73	6.88	8.58		5.78	5.33	6.24	
2011-12	4.98	4.75	5.22	7.90	7.41	8.40		9.19	8.53	9.84		6.58	5.59	7.57	
2013-14	5.41	5.10	5.72	8.05	7.40	8.70		8.70	8.05	9.34		5.66	5.27	6.05	
uNAP, 25th percentile							*<0.01*				*<0.01*				*0.01*
2001-02	2.19	2.01	2.39	3.16	2.92	3.41		3.40	3.02	3.83		3.20	2.54	4.04	
2003-04	2.68	2.28	3.14	3.55	3.34	3.78		4.55	4.22	4.90		2.55	1.88	3.45	
2005-06	3.18	2.77	3.65	4.09	3.65	4.58		5.29	5.02	5.58		4.43	3.41	5.77	
2007-08	3.37	3.10	3.66	4.56	4.10	5.08		4.31	3.89	4.78		3.22	2.70	3.84	
2009-10	2.88	2.71	3.07	4.34	3.96	4.77		4.91	4.48	5.38		3.43	2.62	4.49	
2011-12	2.71	2.46	2.99	4.56	4.02	5.17		6.10	5.07	7.34		3.23	2.67	3.92	
2013-14	2.69	2.35	3.08	4.07	3.53	4.69		5.94	5.38	6.56		2.85	2.61	3.12	
uNAP, 50th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	3.58	3.32	3.87	4.68	4.21	5.20		5.64	5.10	6.24		4.63	4.16	5.16	
2003-04	4.58	4.23	4.97	5.42	4.84	6.07		7.06	6.54	7.62		4.47	3.80	5.25	
2005-06	5.05	4.77	5.35	6.13	5.58	6.73		7.74	7.34	8.16		6.64	5.73	7.70	
2007-08	5.72	5.34	6.13	7.08	6.55	7.66		6.34	5.91	6.81		5.68	4.68	6.89	
2009-10	4.95	4.58	5.35	6.81	6.30	7.37		7.36	6.47	8.37		5.07	4.39	5.85	
2011-12	4.61	4.26	5.00	7.02	5.97	8.26		8.88	8.19	9.62		5.86	4.56	7.52	
2013-14	4.63	4.20	5.10	7.08	6.36	7.87		8.12	7.78	8.47		5.01	4.59	5.48	
uNAP, 75th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	5.07	4.97	5.18	6.76	6.24	7.32		7.42	6.75	8.16		6.66	5.82	7.61	
2003-04	6.60	6.32	6.90	7.57	6.92	8.28		9.20	8.77	9.66		5.91	5.31	6.58	
2005-06	6.98	6.55	7.44	8.53	8.01	9.08		10.70	9.91	11.55		8.27	7.43	9.20	
2007-08	7.99	7.65	8.34	9.71	9.39	10.04		9.18	8.09	10.41		8.22	7.23	9.36	
2009-10	7.49	7.17	7.82	9.47	8.68	10.33		9.68	8.66	10.82		7.73	6.97	8.58	
2011-12	6.92	6.58	7.27	10.19	9.64	10.78		11.74	11.10	12.43		9.25	8.04	10.65	

Table A.5. Continued.

	NHW			MA				NHB				Other/Multi.			
	aGM	Lower 95%CI	Upper 95%CI	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*
2013-14	7.49	7.13	7.86	11.33	10.70	11.99		11.08	10.10	12.15		7.34	6.81	7.90	
uNAP, 95th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	7.40	6.90	7.93	9.47	8.57	10.46		11.01	9.49	12.79		8.73	8.13	9.37	
2003-04	9.32	8.81	9.86	10.32	9.68	11.01		15.12	12.68	18.02		8.56	7.12	10.29	
2005-06	10.70	9.69	11.80	12.20	11.31	13.15		14.74	13.51	16.08		11.96	10.09	14.18	
2007-08	12.11	11.66	12.59	12.89	11.17	14.88		14.26	12.61	16.12		12.74	10.70	15.16	
2009-10	11.24	10.71	11.80	14.69	12.77	16.88		14.90	13.17	16.85		11.85	10.43	13.46	
2011-12	9.89	9.27	10.55	16.42	14.65	18.41		16.57	14.97	18.34		14.13	12.43	16.06	
2013-14	11.98	10.91	13.15	16.08	13.42	19.27		16.18	14.76	17.75		12.40	11.37	13.53	
uFLU, Overall							*0.01*				*<0.01*				*0.10*
2001-02	0.36	0.34	0.37	0.37	0.33	0.41		0.51	0.47	0.55		0.35	0.30	0.41	
2003-04	0.29	0.27	0.31	0.29	0.27	0.31		0.46	0.43	0.48		0.25	0.23	0.27	
2005-06	0.32	0.31	0.34	0.28	0.25	0.31		0.43	0.39	0.46		0.29	0.26	0.33	
2007-08	0.31	0.29	0.33	0.32	0.30	0.34		0.38	0.35	0.41		0.29	0.25	0.33	
2009-10	0.26	0.25	0.27	0.28	0.26	0.30		0.39	0.35	0.43		0.26	0.23	0.28	
2011-12	0.24	0.23	0.26	0.29	0.26	0.31		0.40	0.37	0.43		0.29	0.24	0.33	
2013-14	0.20	0.19	0.22	0.23	0.21	0.25		0.29	0.26	0.31		0.19	0.17	0.20	
uFLU, 25th percentile							*<0.01*				*<0.01*				*0.68*
2001-02	0.20	0.18	0.22	0.22	0.20	0.24		0.31	0.28	0.36		0.21	0.17	0.25	
2003-04	0.15	0.12	0.18	0.19	0.17	0.21		0.27	0.24	0.30		0.14	0.09	0.22	
2005-06	0.19	0.16	0.22	0.18	0.15	0.20		0.27	0.25	0.28		0.18	0.14	0.23	
2007-08	0.17	0.16	0.19	0.20	0.17	0.23		0.25	0.21	0.29		0.15	0.11	0.19	
2009-10	0.14	0.12	0.15	0.16	0.15	0.17		0.24	0.21	0.28		0.15	0.13	0.19	
2011-12	0.13	0.12	0.14	0.15	0.13	0.18		0.25	0.22	0.28		0.14	0.10	0.18	
2013-14	0.10	0.09	0.12	0.11	0.10	0.13		0.20	0.18	0.22		0.10	0.08	0.11	
uFLU, 50th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	0.34	0.32	0.36	0.35	0.31	0.40		0.48	0.44	0.53		0.34	0.27	0.42	
2003-04	0.28	0.26	0.31	0.27	0.26	0.29		0.43	0.40	0.45		0.24	0.22	0.27	
2005-06	0.31	0.29	0.32	0.25	0.23	0.28		0.39	0.36	0.43		0.30	0.25	0.36	
2007-08	0.30	0.27	0.33	0.32	0.29	0.34		0.35	0.32	0.39		0.26	0.22	0.32	
2009-10	0.24	0.22	0.25	0.26	0.24	0.28		0.36	0.32	0.40		0.23	0.20	0.26	
2011-12	0.22	0.21	0.23	0.27	0.24	0.31		0.38	0.35	0.41		0.24	0.20	0.29	
2013-14	0.17	0.16	0.19	0.20	0.18	0.23		0.27	0.25	0.30		0.16	0.14	0.17	

Table A.5. Continued.

	NHW			MA				NHB				Other/Multi.			
	aGM	Lower 95%CI	Upper 95%CI	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*
uFLU, 75th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	0.47	0.45	0.49	0.50	0.46	0.55		0.69	0.66	0.72		0.48	0.38	0.61	
2003-04	0.40	0.37	0.43	0.38	0.35	0.40		0.59	0.56	0.63		0.32	0.30	0.35	
2005-06	0.42	0.40	0.44	0.36	0.33	0.38		0.57	0.53	0.61		0.38	0.33	0.44	
2007-08	0.42	0.39	0.45	0.43	0.40	0.45		0.48	0.44	0.53		0.39	0.34	0.45	
2009-10	0.36	0.34	0.38	0.37	0.34	0.40		0.51	0.44	0.60		0.34	0.30	0.39	
2011-12	0.34	0.31	0.38	0.37	0.35	0.40		0.52	0.50	0.54		0.39	0.34	0.44	
2013-14	0.28	0.26	0.30	0.31	0.28	0.34		0.35	0.32	0.37		0.25	0.23	0.27	
uFLU, 95th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	0.71	0.66	0.76	0.72	0.66	0.79		0.96	0.86	1.06		0.62	0.56	0.69	
2003-04	0.54	0.50	0.60	0.51	0.45	0.57		0.89	0.81	0.99		0.51	0.45	0.58	
2005-06	0.62	0.58	0.66	0.55	0.46	0.66		0.79	0.64	0.98		0.56	0.47	0.67	
2007-08	0.64	0.60	0.68	0.58	0.52	0.65		0.78	0.71	0.85		0.62	0.56	0.70	
2009-10	0.56	0.52	0.61	0.54	0.50	0.58		0.79	0.70	0.88		0.54	0.48	0.60	
2011-12	0.51	0.48	0.56	0.59	0.48	0.72		0.78	0.67	0.91		0.64	0.55	0.74	
2013-14	0.47	0.42	0.53	0.48	0.42	0.55		0.55	0.51	0.59		0.43	0.39	0.48	
uPHEN, Overall							*0.17*				*<0.01*				*0.22*
2001-02	0.33	0.32	0.34	0.28	0.25	0.31		0.36	0.33	0.4		0.31	0.26	0.36	
2003-04	0.31	0.29	0.33	0.28	0.26	0.30		0.41	0.38	0.44		0.27	0.24	0.29	
2005-06	0.32	0.31	0.34	0.26	0.23	0.29		0.36	0.33	0.39		0.28	0.25	0.32	
2007-08	0.30	0.29	0.32	0.27	0.25	0.29		0.33	0.30	0.36		0.29	0.25	0.32	
2009-10	0.29	0.28	0.30	0.25	0.23	0.26		0.33	0.29	0.36		0.25	0.23	0.28	
2011-12	0.25	0.24	0.26	0.24	0.21	0.26		0.33	0.31	0.36		0.27	0.23	0.30	
2013-14	0.21	0.20	0.23	0.20	0.18	0.22		0.27	0.25	0.29		0.20	0.19	0.21	
uPHEN, 25th percentile							*<0.01*				*<0.01*				*0.60*
2001-02	0.19	0.17	0.20	0.17	0.16	0.19		0.22	0.19	0.26		0.18	0.15	0.22	
2003-04	0.18	0.14	0.21	0.18	0.16	0.19		0.25	0.24	0.27		0.16	0.12	0.21	
2005-06	0.18	0.16	0.21	0.17	0.15	0.19		0.22	0.21	0.24		0.20	0.16	0.25	
2007-08	0.17	0.16	0.19	0.17	0.15	0.19		0.21	0.18	0.25		0.15	0.11	0.19	
2009-10	0.16	0.14	0.17	0.15	0.14	0.16		0.21	0.19	0.23		0.15	0.12	0.20	
2011-12	0.13	0.12	0.15	0.13	0.12	0.14		0.21	0.19	0.24		0.13	0.10	0.17	
2013-14	0.11	0.10	0.12	0.10	0.09	0.11		0.18	0.16	0.20		0.10	0.09	0.12	

Table A.5. Continued.

	NHW			MA				NHB				Other/Multi.			
	aGM	Lower 95%CI	Upper 95%CI	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*
uPHEN, 50th percentile							*<0.01*				*<0.01*				*0.01*
2001-02	0.32	0.29	0.34	0.26	0.23	0.29		0.34	0.31	0.38		0.30	0.25	0.36	
2003-04	0.31	0.28	0.34	0.26	0.24	0.28		0.38	0.36	0.40		0.26	0.24	0.29	
2005-06	0.31	0.29	0.33	0.24	0.21	0.27		0.34	0.30	0.39		0.28	0.22	0.34	
2007-08	0.29	0.27	0.33	0.27	0.25	0.29		0.30	0.27	0.34		0.26	0.22	0.31	
2009-10	0.26	0.25	0.28	0.23	0.21	0.25		0.31	0.27	0.35		0.23	0.21	0.26	
2011-12	0.23	0.22	0.24	0.22	0.19	0.25		0.31	0.29	0.34		0.24	0.20	0.29	
2013-14	0.19	0.17	0.21	0.18	0.16	0.21		0.26	0.24	0.28		0.17	0.15	0.19	
uPHEN, 75th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	0.43	0.41	0.45	0.38	0.34	0.42		0.47	0.42	0.53		0.42	0.34	0.53	
2003-04	0.42	0.40	0.45	0.36	0.34	0.39		0.53	0.50	0.56		0.35	0.32	0.39	
2005-06	0.42	0.40	0.43	0.34	0.31	0.38		0.47	0.44	0.51		0.36	0.33	0.40	
2007-08	0.41	0.38	0.43	0.36	0.34	0.38		0.43	0.39	0.47		0.38	0.32	0.45	
2009-10	0.39	0.38	0.41	0.32	0.30	0.35		0.41	0.36	0.47		0.33	0.30	0.37	
2011-12	0.35	0.32	0.39	0.31	0.28	0.34		0.42	0.40	0.44		0.37	0.33	0.41	
2013-14	0.30	0.27	0.33	0.27	0.25	0.30		0.33	0.30	0.36		0.26	0.24	0.29	
uPHEN, 95th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	0.62	0.57	0.67	0.56	0.47	0.66		0.68	0.61	0.76		0.53	0.51	0.55	
2003-04	0.58	0.55	0.61	0.50	0.42	0.60		0.78	0.70	0.87		0.55	0.46	0.65	
2005-06	0.60	0.57	0.64	0.50	0.42	0.60		0.66	0.55	0.79		0.52	0.44	0.62	
2007-08	0.61	0.59	0.63	0.50	0.47	0.54		0.69	0.62	0.76		0.59	0.52	0.66	
2009-10	0.59	0.53	0.65	0.48	0.44	0.53		0.61	0.51	0.73		0.52	0.45	0.61	
2011-12	0.50	0.44	0.55	0.48	0.38	0.61		0.64	0.57	0.73		0.58	0.51	0.67	
2013-14	0.47	0.42	0.52	0.43	0.37	0.49		0.47	0.43	0.52		0.45	0.41	0.50	
uPYR, Overall							*<0.01*				*<0.01*				*0.11*
2001-02	0.04	0.04	0.04	0.05	0.05	0.06		0.06	0.05	0.06		0.06	0.05	0.07	
2003-04	0.07	0.07	0.08	0.08	0.08	0.09		0.11	0.11	0.12		0.08	0.07	0.09	
2005-06	0.08	0.08	0.09	0.09	0.08	0.10		0.10	0.10	0.11		0.09	0.08	0.10	
2007-08	0.11	0.10	0.11	0.12	0.11	0.13		0.12	0.11	0.13		0.12	0.10	0.13	
2009-10	0.10	0.10	0.11	0.14	0.13	0.15		0.16	0.14	0.17		0.13	0.12	0.14	
2011-12	0.10	0.09	0.10	0.13	0.12	0.14		0.15	0.14	0.15		0.12	0.10	0.13	
2013-14	0.12	0.12	0.13	0.14	0.13	0.15		0.15	0.14	0.16		0.13	0.12	0.14	

Table A.5. Continued.

	NHW			MA				NHB				Other/Multi.			
	aGM	Lower 95%CI	Upper 95%CI	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*	aGM	Lower 95%CI	Upper 95%CI	*p*
uPYR, 25th percentile [(d)]							*<0.01*				*<0.01*				*<0.01*
2001-02	0.02	0.02	0.03	0.03	0.03	0.03		0.04	0.03	0.04		0.03	0.03	0.04	
2003-04	0.04	0.03	0.05	0.06	0.05	0.06		0.07	0.06	0.07		0.05	0.04	0.08	
2005-06	0.05	0.04	0.06	0.06	0.05	0.07		0.06	0.06	0.07		0.06	0.05	0.07	
2007-08	0.06	0.05	0.06	0.08	0.07	0.09		0.08	0.07	0.09		0.06	0.05	0.09	
2009-10	0.06	0.05	0.06	0.09	0.08	0.10		0.10	0.09	0.11		0.08	0.07	0.10	
2011-12	0.05	0.05	0.06	0.07	0.06	0.09		0.09	0.08	0.10		0.06	0.05	0.08	
2013-14	0.07	0.06	0.07	0.08	0.06	0.09		0.11	0.10	0.12		0.07	0.06	0.07	
uPYR, 50th percentile [(d)]							*<0.01*				*<0.01*				*<0.01*
2001-02	0.04	0.04	0.04	0.05	0.04	0.06		0.05	0.05	0.06		0.05	0.04	0.06	
2003-04	0.07	0.06	0.08	0.08	0.08	0.09		0.10	0.09	0.11		0.07	0.07	0.08	
2005-06	0.08	0.07	0.08	0.08	0.08	0.09		0.10	0.09	0.10		0.09	0.07	0.10	
2007-08	0.10	0.09	0.11	0.12	0.10	0.13		0.11	0.10	0.13		0.10	0.09	0.12	
2009-10	0.09	0.09	0.10	0.14	0.12	0.15		0.14	0.13	0.15		0.12	0.10	0.13	
2011-12	0.09	0.08	0.09	0.12	0.11	0.14		0.14	0.13	0.15		0.10	0.09	0.12	
2013-14	0.11	0.10	0.12	0.13	0.11	0.15		0.14	0.13	0.15		0.11	0.10	0.12	
uPYR, 75th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	0.06	0.05	0.06	0.07	0.06	0.07		0.07	0.07	0.08		0.08	0.06	0.10	
2003-04	0.09	0.09	0.10	0.11	0.10	0.12		0.14	0.14	0.15		0.10	0.09	0.11	
2005-06	0.11	0.11	0.11	0.12	0.10	0.13		0.13	0.12	0.14		0.11	0.09	0.13	
2007-08	0.14	0.13	0.15	0.16	0.15	0.17		0.15	0.14	0.16		0.14	0.12	0.18	
2009-10	0.14	0.13	0.14	0.18	0.17	0.19		0.20	0.17	0.24		0.17	0.15	0.19	
2011-12	0.13	0.12	0.14	0.17	0.16	0.19		0.19	0.18	0.20		0.16	0.14	0.18	
2013-14	0.16	0.15	0.18	0.19	0.17	0.21		0.19	0.17	0.21		0.17	0.15	0.18	
uPYR, 95th percentile							*<0.01*				*<0.01*				*<0.01*
2001-02	0.08	0.08	0.08	0.09	0.08	0.11		0.10	0.09	0.11		0.11	0.10	0.12	
2003-04	0.14	0.14	0.15	0.15	0.14	0.16		0.23	0.21	0.25		0.17	0.16	0.19	
2005-06	0.16	0.15	0.16	0.17	0.15	0.18		0.20	0.17	0.24		0.16	0.13	0.19	
2007-08	0.21	0.19	0.22	0.23	0.22	0.24		0.24	0.21	0.28		0.24	0.20	0.31	
2009-10	0.22	0.20	0.24	0.28	0.25	0.31		0.31	0.26	0.38		0.27	0.24	0.30	
2011-12	0.21	0.20	0.21	0.27	0.24	0.30		0.29	0.26	0.32		0.26	0.21	0.33	
2013-14	0.29	0.26	0.32	0.29	0.25	0.34		0.30	0.28	0.33		0.28	0.26	0.31	

Table A.5 – Continued.

[a] uNAP; sum of urinary Naphthalene metabolites (ug/L). uFLU: sum of urinary Fluorene metabolites (ug/L). uPHEN: sum of urinary Phenanthrene metabolites (ug/L). UPYR: urinary Pyrene metabolites (ug/L).

[b] Adjusted for urinary creatinine, age, sex, BMI, dietary sources of PAHs, PIR, and seasonality. Interaction term is NHANES cycle##race/ethnicity.

[c] p-value for the overall trend in weighted aGM between groups across NHANES cycles was assessed by the adjusted Wald test, $\alpha = 0.05$.

[d] The delta in trend values between 2001-02 and 2013-14 are within the maximal analytical error for urinary Pyrene metabolite (0.07 ug/L).

Table A.6. Sensitivity analysis – work characteristics. uPAH biomarkers[a] in ug/L, reported as estimated weighted and adjusted[b] geometric mean (aGM) and 95%CI at each NHANES cycle that data was publicly available.

	n	2001-02 aGM (95%CI)	2003-04 aGM (95%CI)	2005-06 aGM (95%CI)	2007-08 aGM (95%CI)	2009-10 aGM (95%CI)	2011-12 aGM (95%CI)	2013-14 aGM (95%CI)	*p*[c]
Work status 1 week prior to exam[d]									
uNAP	7,880	4.30 (4.13, 4.47)	5.20 (4.92, 5.49)	6.01 (5.66, 6.35)	6.43 (6.15, 6.70)	6.05 (5.76, 6.34)	5.96 (5.64, 6.28)	6.15 (5.86, 6.44)	0.99
uFLU	7,852	0.37 (0.35, 0.39)	0.29 (0.27, 0.31)	0.32 (0.31, 0.34)	0.32 (0.30, 0.33)	0.27 (0.26, 0.28)	0.27 (0.25, 0.28)	0.21 (0.20, 0.22)	0.24
uPHEN	7,866	0.33 (0.31, 0.35)	0.31 (0.29, 0.34)	0.32 (0.30, 0.33)	0.31 (0.29, 0.32)	0.29 (0.27, 0.30)	0.26 (0.25, 0.28)	0.22 (0.21, 0.23)	0.44
uPYR	7,820	0.04 (0.04, 0.04)	0.07 (0.07, 0.08)	0.08 (0.08, 0.09)	0.11 (0.10, 0.11)	0.11 (0.10, 0.11)	0.10 (0.10, 0.11)	0.12 (0.12, 0.13)	0.26
Reason for Not Working[e]									
uNAP	3,336	4.28 (4.12, 4.44)	5.10 (4.62, 5.57)	6.06 (5.78, 6.34)	6.12 (5.64, 6.60)	6.31 (5.91, 6.70)	5.81 (5.36, 6.25)	6.38 (5.95, 6.81)	0.17
uFLU	3,326	0.34 (0.32, 0.36)	0.27 (0.25, 0.30)	0.31 (0.29, 0.32)	0.29 (0.26, 0.31)	0.27 (0.25, 0.28)	0.25 (0.23, 0.26)	0.21 (0.19, 0.22)	<0.01
uPHEN	3,327	0.31 (0.30, 0.33)	0.30 (0.27, 0.32)	0.31 (0.30, 0.33)	0.29 (0.26, 0.31)	0.29 (0.27, 0.30)	0.25 (0.23, 0.26)	0.22 (0.21, 0.24)	0.01
uPYR	3,303	0.04 (0.04, 0.04)	0.06 (0.06, 0.07)	0.08 (0.07, 0.08)	0.10 (0.09, 0.11)	0.10 (0.10, 0.11)	0.09 (0.09, 0.10)	0.12 (0.11, 0.13)	0.26
Industry[f]									
uNAP	3,668	4.30 (4.07, 4.54)	5.25 (4.98, 5.52)	5.98 (5.54, 6.43)	6.56 (6.20, 6.92)	5.92 (5.53, 6.30)	6.08 (5.67, 6.49)	--	0.39
uFLU	3,648	0.38 (0.36, 0.40)	0.30 (0.28, 0.33)	0.33 (0.31, 0.35)	0.33 (0.31, 0.35)	0.27 (0.26, 0.29)	0.28 (0.26, 0.30)	--	0.40
uPHEN	3,661	0.34 (0.32, 0.36)	0.32 (0.30, 0.35)	0.32 (0.30, 0.34)	0.32 (0.30, 0.34)	0.29 (0.27, 0.30)	0.27 (0.26, 0.29)	--	0.35
uPYR	3,640	0.04 (0.04, 0.05)	0.07 (0.07, 0.08)	0.08 (0.08, 0.09)	0.11 (0.10, 0.12)	0.11 (0.10, 0.12)	0.11 (0.10, 0.11)	--	0.10

Table A.6. Continued.

	n	2001-02 aGM (95%CI)	2003-04 aGM (95%CI)	2005-06 aGM (95%CI)	2007-08 aGM (95%CI)	2009-10 aGM (95%CI)	2011-12 aGM (95%CI)	2013-14 aGM (95%CI)	$p^{(c)}$
Occupation [(g)]									
uNAP	3,667	4.32 (4.08, 4.55)	5.25 (4.98, 5.52)	5.98 (5.54, 6.43)	6.56 (6.20, 6.92)	5.92 (5.53, 6.30)	6.07 (5.66, 6.48)	--	0.43
uFLU	3,647	0.38 (0.36, 0.40)	0.30 (0.28, 0.33)	0.33 (0.31, 0.35)	0.33 (0.31, 0.35)	0.27 (0.26, 0.29)	0.28 (0.26, 0.30)	--	0.42
uPHEN	3,660	0.34 (0.32, 0.36)	0.32 (0.30, 0.35)	0.32 (0.30, 0.34)	0.32 (0.30, 0.34)	0.29 (0.27, 0.30)	0.27 (0.26, 0.29)	--	0.39
uPYR	3,639	0.04 (0.04, 0.05)	0.07 (0.07, 0.08)	0.08 (0.08, 0.09)	0.11 (0.10, 0.12)	0.11 (0.10, 0.12)	0.11 (0.10, 0.11)	--	0.13

(a) Naphthalene metabolites (uNAP): sum of 1- & 2-hydroxynaphthalene. Fluorene metabolites (uFLU): sum of 2- & 3-hydroxyfluorene. Phenanthrene metabolites (uPHEN): sum of 1-, 2- & 3-hyroxyphenathrene. Pyrene metabolites (uPYR): 1-hydroxypyrene.

(b) Linear regression for the log-transformed uPAH, after LOD correction, adjusted for urinary creatinine, age, sex, race/ethnicity, BMI, dietary sources of PAHs, PIR, work-related characteristic, and seasonality. Some work characteristic data was not available for every NHANES cycle of interest, denoted by "--".

(c) *p*-value for sensitivity analysis was assessed by the adjusted Wald test, $\alpha = 0.05$, comparing Model 1: estimated weighted aGM and 95%CI of the main effects models (Table 2.1), to Model 1-W, with the respective work-related characteristics added to the main effects model.

(d) From occupational questionnaire, variable OCD150: *type of work done last week*. Restricted to participants 16+ years of age.

(e) From occupational questionnaire, variable OCQ380: *main reason did not work last week*. Restricted to participants 16+ years of age.

(f) From occupational questionnaire, variable OCD230/OCD231: *industry group code: current job*. Codes assigned by NHANES using U.S. Bureau of the Census Industrial & Occupational Classification coding system.[233] Restricted to participants 16+ years of age.

Table A.6 – Continued.

(g) From occupational questionnaire, variable OCD240/OCD241: *occupation group code: current job*. Codes assigned by NHANES using U.S. Bureau of the Census Industrial & Occupational Classification coding system.[233] Restricted to participants 16+ years of age.

Table A.7. Sensitivity analysis – housing characteristics. uPAH biomarkers[(a)] in ug/L, reported as estimated weighted and adjusted[(b)] geometric mean (aGM) and 95%CI at each NHANES cycle.

	n	2001-02 aGM (95%CI)	2003-04 aGM (95%CI)	2005-06 aGM (95%CI)	2007-08 aGM (95%CI)	2009-10 aGM (95%CI)	2011-12 aGM (95%CI)	2013-14 aGM (95%CI)	$p^{(c)}$
Type of Home									
uNAP	4,846	4.19 (4.05, 4.34)	5.17 (4.94, 5.40)	5.89 (5.61, 6.17)	--	--	--	--	0.40
uFLU	4,786	0.37 (0.36, 0.38)	0.30 (0.29, 0.32)	0.33 (0.31, 0.34)	--	--	--	--	0.47
uPHEN	4,809	0.32 (0.31, 0.34)	0.31 (0.30, 0.33)	0.32 (0.30, 0.33)	--	--	--	--	0.78
uPYR	4,766	0.04 (0.04, 0.05)	0.08 (0.07, 0.08)	0.09 (0.08, 0.09)	--	--	--	--	0.40
When Home was Built									
uNAP	6,376	4.09 3.93, 4.26)	5.02 (4.78, 5.27)	5.72 (5.43, 6.02)	6.22 (5.97, 6.47)	5.77 (5.53, 6.02)	--	--	0.37
uFLU	6,337	0.36 (0.35, 0.38)	0.30 (0.28, 0.31)	0.32 (0.31, 0.34)	0.31 (0.30, 0.33)	0.27 (0.26, 0.28)	--	--	0.97
uPHEN	6,356	0.32 (0.31, 0.34)	0.31 (0.29, 0.33)	0.31 (0.30, 0.33)	0.30 (0.29, 0.32)	0.28 (0.27, 0.29)	--	--	0.93
uPYR	6,311	0.04 (0.04, 0.05)	0.08 (0.07, 0.08)	0.09 (0.08, 0.09)	0.11 (0.10, 0.11)	0.11 (0.11, 0.12)	--	--	0.03
Home Owned, Rented, Other Arrangement									
uNAP	11,024	4.19 (4.05, 4.34)	5.17 (4.94, 5.40)	5.89 (5.61, 6.17)	6.31 (6.07, 6.54)	5.93 (5.68, 6.17)	5.87 (5.59, 6.14)	6.04 (5.78, 6.30)	0.21
uFLU	10.985	0.37 (0.36, 0.38)	0.30 (0.29, 0.32)	0.33 (0.31, 0.34)	0.32 (0.30, 0.33)	0.27 (0.26, 0.28)	0.27 (0.26, 0.28)	0.21 (0.20, 0.22)	0.21
uPHEN	11,008	0.33 (0.31, 0.34)	0.31 (0.30, 0.33)	0.32 (0.30, 0.33)	0.30 (0.29, 0.32)	0.28 (0.27, 0.29)	0.26 (0.25, 0.27)	0.22 (0.21, 0.23)	0.55
uPYR	10,951	0.04 (0.04, 0.05)	0.08 (0.07, 0.08)	0.09 (0.08, 0.09)	0.11 (0.11, 0.12)	0.12 (0.11, 0.12)	0.11 (0.10, 0.11)	0.13 (0.12, 0.13)	0.24

(a) Naphthalene metabolites (uNAP): sum of 1- & 2-hydroxynaphthalene. Fluorene metabolites (uFLU): sum of 2- & 3-hydroxyfluorene. Phenanthrene metabolites (uPHEN): sum of 1-, 2- & 3-hyroxyphenathrene. Pyrene metabolites (uPYR): 1-hydroxypyrene.

Table A.7. Continued.

(b) Linear regression for the log-transformed uPAH biomarker, after LOD correction, adjusted for urinary creatinine, age, sex, race/ethnicity, BMI, dietary sources of PAHs, PIR, housing characteristic, and seasonality. Some housing characteristic data was not available for every NHANES cycle of interest, denoted by "--".

(c) *p*-value for sensitivity analysis was assessed by the adjusted Wald test, $\alpha = 0.05$, comparing Model 1: estimated weighted aGM and 95%CI of the main effects models (Table 1), to Model 1-H, with the respective housing-related characteristics added to the main effects model.

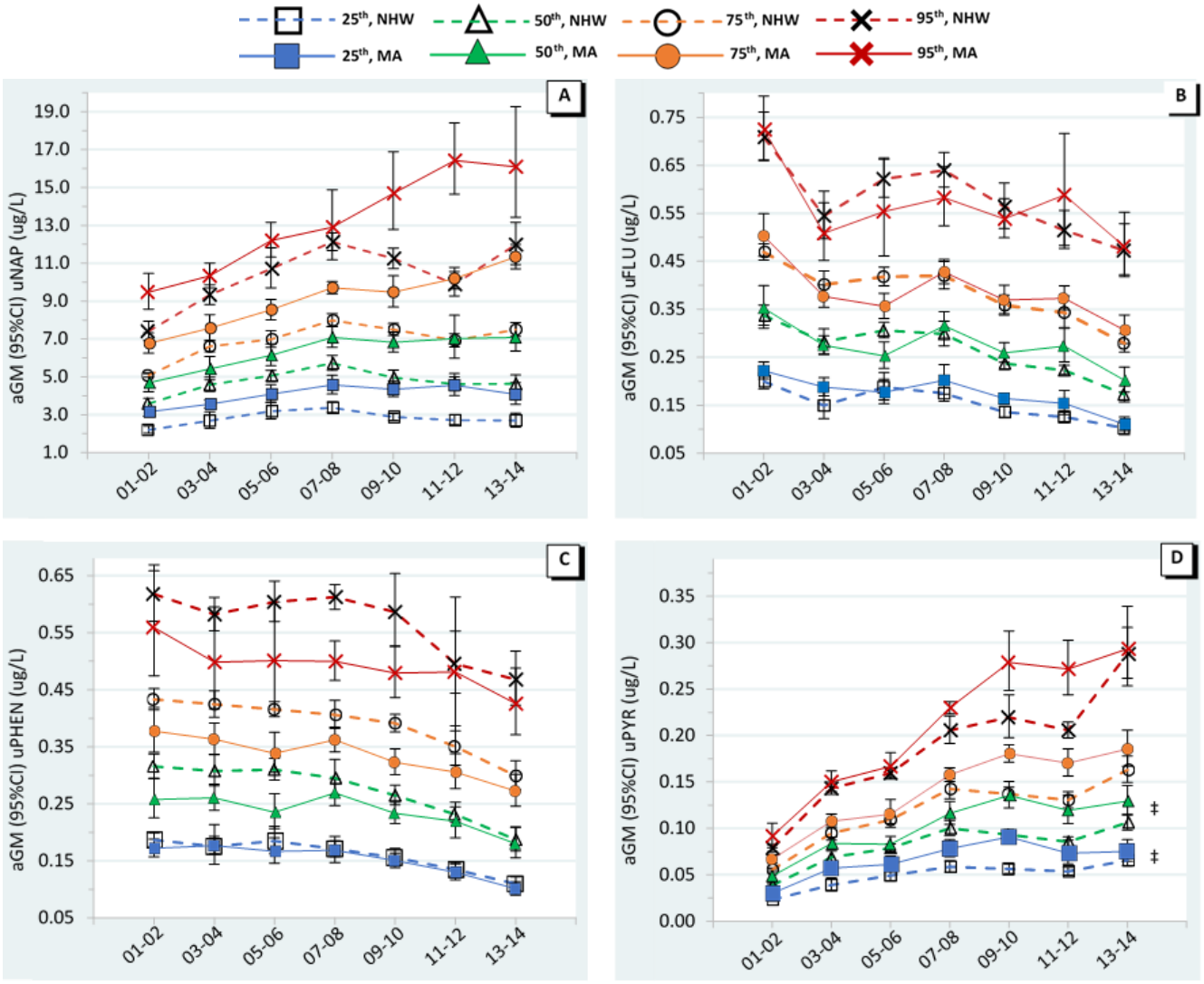

Figure A.1. Trends in uPAHs in ug/L, in the U.S. non-smoking Mexican Americans (MA), compared to Non-Hispanic Whites (NHW, reference) participants, age 6+ years, by 25th, 50th 75th and 95th percentile, 2001-2014. Weighted aGM and 95%CI for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, age, sex, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##race/ethnicity. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol), n = 11,028. (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene), n = 10989. (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene), n = 11,012. (D) uPYR: urinary Pyrene metabolites, n = 10,955. See Table A.5 to view these results in tabular form.

(‡) The delta in trend values between 2001-02 and 2013-14 are within the maximal analytical error for urinary Pyrene metabolites (0.07 ug/L).

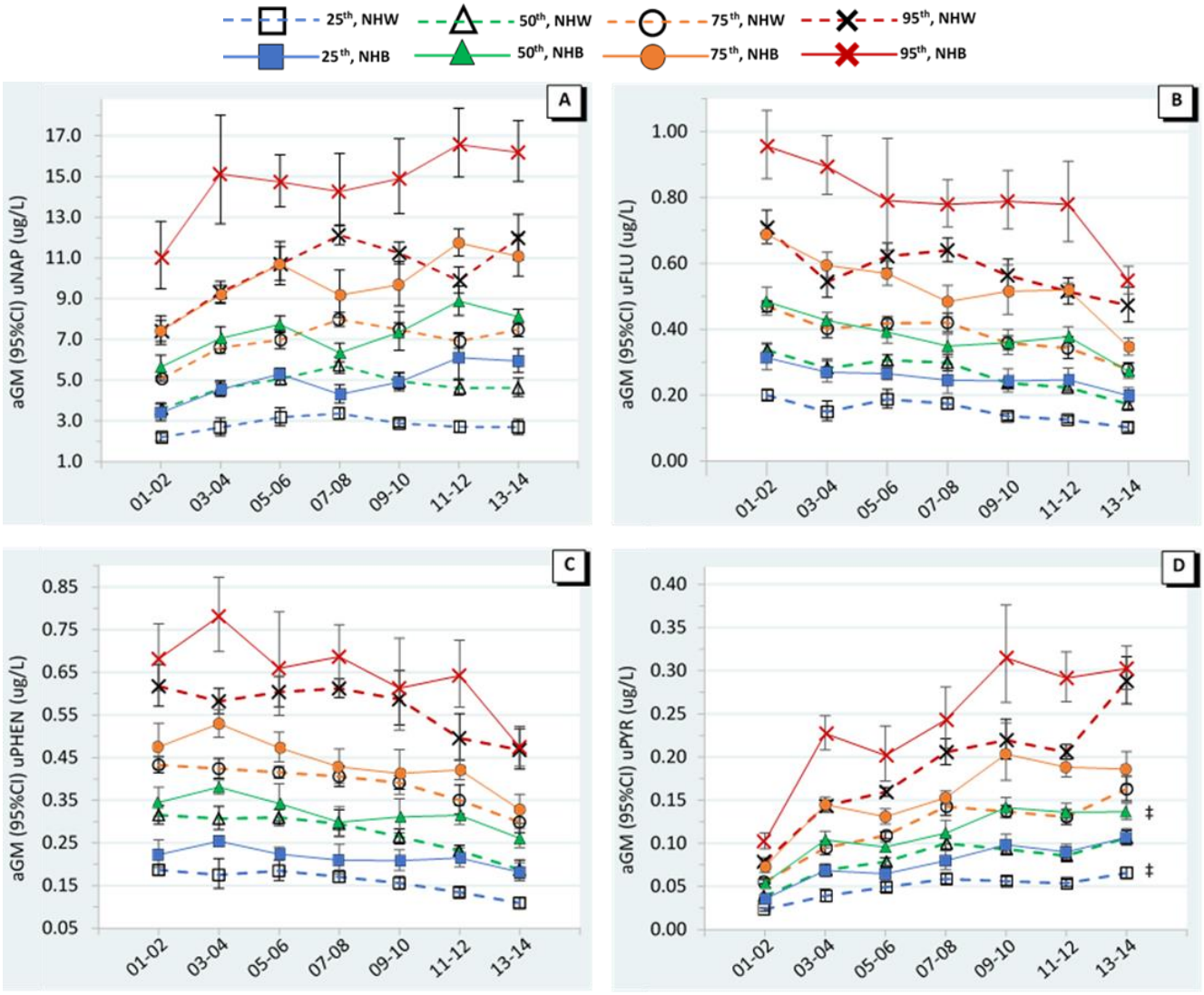

Figure A.2. Trends in uPAHs in ug/L, in the U.S. non-smoking Non-Hispanic Blacks (NHB), compared to Non-Hispanic Whites (NHW, reference), age 6+ years, by 25th, 50th 75th and 95th percentile, 2001-2014. Weighted aGM and 95%CI for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, age, sex, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##race/ethnicity. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol), n = 11,028. (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene), n = 10989. (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene), n = 11,012. (D) uPYR: urinary Pyrene metabolites, n = 10,955. See Table A.5 to view these results in tabular form.

(‡) The delta in trend values between 2001-02 and 2013-14 are within the maximal analytical error for urinary Pyrene metabolites (0.07 ug/L).

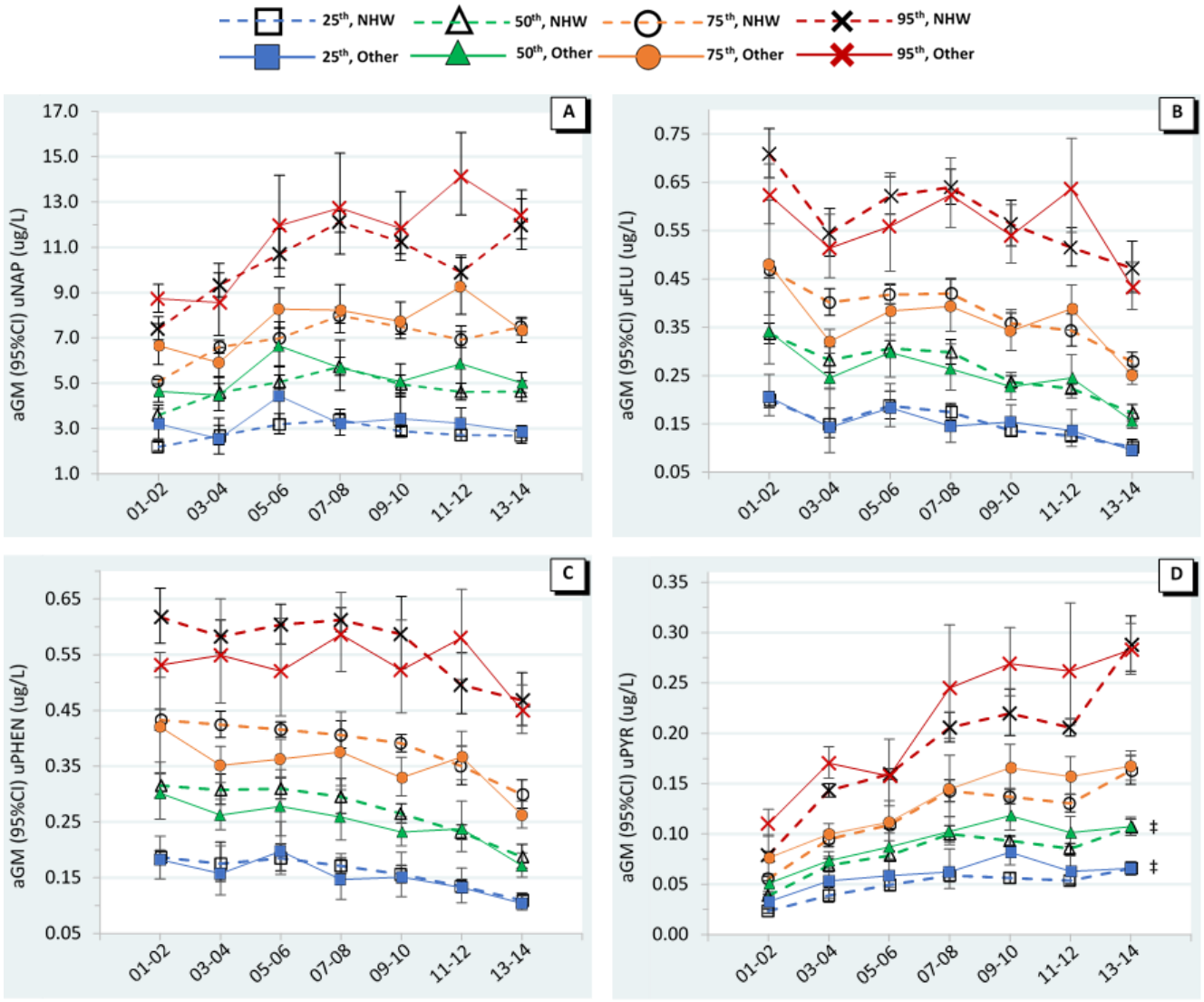

Figure A.3. Trends in uPAHs in ug/L, in the U.S. non-smoking Other/Multi-Racial participants, compared to Non-Hispanic Whites (NHW, reference), age 6+ years, by 25th, 50th 75th and 95th percentile, 2001-2014. Weighted aGM and 95%CI for each NHANES cycle estimated from linear regression models adjusted for urinary creatinine, age, sex, BMI, dietary sources of PAHs, PIR, and seasonality; interaction term is NHANES cycle##race/ethnicity. (A) uNAP: sum of urinary Naphthalene metabolites (1- & 2-naphthol), n = 11,028. (B) uFLU: sum of urinary Fluorene metabolites (2- & 3-fluorene), n = 10989. (C) uPHEN: sum of urinary Phenanthrene metabolites (1-, 2- & 3-phenanthrene), n = 11,012. (D) uPYR: urinary Pyrene metabolites, n = 10,955. See Table A.5 to view these results in tabular form.

(‡) The delta in trend values between 2001-02 and 2013-14 are within the maximal analytical error for urinary Pyrene metabolites (0.07 ug/L).

Appendix B: Supplemental Materials for Chapter 3

Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Birth Outcomes in Infants, A Systematic Review and Meta-Analysis

Barbara Hudson-Hanley, Ellen Smit, Adam Branscum, Perry Hystad, Molly L. Kile

Appendix B: Table of Contents

Table B.1. Characteristics of Included studies – Birth Outcomes.

Study, year	Study Design	Data collection time period	Location	Study population	Sample size
Agarwal, et al., 2018 [262]	Case-control	2016-2017	Agra, India	Pregnant women, age 18-40 years of age, seeking antenatal care at the S.N. Medical College.	84
Agarwal, et al., 2020 [305]	Cross-sectional	2017-2018	Agra, India	Non-smoking pregnant women 18-40 years old attending antenatal care at S.N. Medical College, Agra, India	110
Al-Saleh 2013 [174]	Cross-sectional	2005-2006	Al-Kharj, Saudi Arabia	Pregnant non-smoking women, 16-50 years of age, admitted to King Khalid Hospital for labor and delivery.	1,543
Cabrera-Rodriguez, et al., 2019 [296]	Cross-sectional	2015-2016	La Palma, Canary Islands	Pregnant women delivering at La Palma hospital who agreed to participate in the study upon enrollment.	447
Chen, et al., 2014 [306]	Cross-sectional	2010	Beijing, Lanzhou, Taiyuan, Xiamen, China	Randomly selected pregnant non-smoking women hospitalized for labor and delivery at 4 hospitals in China.	81
Choi, et al., 2006 [297]	Cohort	Krakow: 2000-2003 New York: 1997(?)-2004	Krakow, Poland, New York City, New York	Both cohorts: non-smoking pregnant women, 18+ years of age, registered for prenatal care < 20th week gestation; living at present address at least one year prior to delivery; no history of pregnancy-related complications.	Krakow: 340 NYC: 380
Choi, et al., 2008 [271]	Case-control	not reported, assume 1998.	New York City	Non-smoking, pregnant African American or Dominican women recruited <20th week gestation; residing in Washington Heights, Harlem, or South Bronx at least 1 year prior to delivery; age 18-35 years.	616
Dejmek, et al., 2000 [164]	Cohort	1994-1998	Teplice, Prachatice, Czech Republic	Pregnant women who delivered their single infants at hospitals in either Teplice or Prachatice	4,854
Duarte-Salles, et al., 2012 [409]	Cohort	2004-2006	Sabadell (Barcelona), Spain	INMA (Environment and Childhood) Project: Non-smoking pregnant women seeking prenatal care in 1st trimester in participating study hospitals in Spain.	574
Duarte-Salles, et al., 2013 [264]	Cohort	1999-2008	Norway	Norwegian Mother and Child Cohort Study (MoBA): Pregnant women seeking prenatal care in Norway; ultrasound in 17-18th week gestation, singleton deliveries.	46,420
Ghosh, et al., 2012 [102]	Case-control	2000-2006	Los Angeles County, California	Live term singleton births born to women residing in select areas of LA County; living < 5 miles of air monitoring stations, major population centers, roadways.	283,303
Gong, et al., 2018 [311]	Case-control	1996-2008	Texas	Live singleton births	470,530
Guo, et al., 2012 [274]	Cross-sectional	2008 - 2009	Guiyu, Chaonan, China	Healthy pregnant women seeking prenatal care from hospitals in Guiyu and Chaonan	183

Table B.1. Continued.

Study, year	Study Design	Data collection time period	Location	Study population	Sample size
Huang, et al., 2020 [267]	Cross-sectional	2016-2017	Guiyu and Haojiang, China	Pregnant women from Guiyu and Haojiang seeking prenatal care at local hospitals.	163
Huo, et al., 2019 [298]	Cross-sectional	2011-2012	Guiyu, Haojiang, China	Healthy pregnant women living in Guiyu (e-waste area) and Haojiang (no e-waste operations),	257
Kumar, et al., 2020 [312]	Case-control	not reported	Assam, India	Pregnant women attending antenatal clinic of Assam Medical College who delivered term births	175
Lamichhane, et al., 2016 [299]	Cohort	2006-2011	South Korea	Mothers and Children's Environmental Health (MOCEH) birth cohort: Pregnant women between 12-28 weeks gestation, with not-at-risk pregnancies, seeking prenatal care in Seoul, Ulsan, and Cheonan, Korea.	778
Langlois, et al., 2014 [313]	Case-control	1997-2002	AR, CA, GA, IA, MA, NJ, NY. TX.	Control infants (no birth defects) from the National Birth Defects Prevention Study were live-born and selected at random from birth certificates or medical records.	2,803
Maxwell, et al., 1994 [295]	Cross-sec.	1989-1990	Ibadan, Nigeria	Pregnant women delivering at two participating hospitals.	607
Maypole-Keenan, et al., 2016 [272]	Case-control	2005-2007	El Paso County, Texas	Pregnant women residing in El Paso County and delivering singleton births without birth defects in County hospitals	30,783
Nie, et al., 2018 [273]	Cross-sectional	not reported	Taiyuan, China	Non-smoking pregnant women, 18+ years of age, residing for at least 1 year in Taiyuan, who delivered a singleton infant.	263
Norlen, et al., 2019 [310]	Cohort	1994-2012	Sweden	Working (full or part-time) pregnant women, as reported by the 10th week of pregnancy, living in Sweden during study period delivering singleton births.	995,843
Padula, et al., 2014 [96]	Cohort	2001-2006	Fresno, California	Study of Air pollution, Genetics and Early life events (SAGE) retrospective cohort study: Pregnant women living in the Fresno area < 20 km of EPA monitoring station; singleton births; 20-42 wks. gestation.	42,904
Pedersen, et al., 2013 [263]	Cross-sectional	2006-2010	Denmark, England, Greece, Norway, Spain	NewGeneris (Newborns and Genotoxic exposure risks) cohort: Pregnant women, live term births.	612
Perera, et al., 1998 [189]	Cross-sectional	1992	Krakow, Limanowa, Poland	Pregnant women with vaginal deliveries; lived in study area at least 1 year prior to delivery.	135
Perera, et al., 2003 [88]	Cohort	1997-2001	New York City, New York	Non-smoking, pregnant African American or Dominican women recruited <20th week gestation; residing in Washington Heights, Harlem, or South Bronx at least 1 year prior to delivery; age 18-35 years.	261

Table B.1. Continued.

Study, year	Study Design	Data collection time period	Location	Study population	Sample size
Perera, et al., 2004 [300]	Cohort	not reported, assume 1997-2001.	New York City, New York	Non-smoking, pregnant African American or Dominican women recruited <20th week gestation; residing in Washington Heights, Harlem, or South Bronx at least 1 year prior to delivery; age 18-35 years.	214
Perera, et al., 2005 [225]	Cohort	2001-2002	New York City, New York	Non-smoking women pregnant on 09/11/2001; age 18-39 years; admitted at 3 NYC hospitals in proximity to the WTC; singleton full term delivery; no pregnancy complications, HIV/AIDS, illegal drug use.	186
Polanska, et al., 2010 [265]	Cohort	2007-2010	Poland	Polish Mother and Child (REPRO_PL) Cohort Study: Non-smoking pregnant women; no history of occupational PAH exposure, recruited at 8-12 weeks gestation; singleton births.	423
Polanska, et al., 2014 [301]	Cohort	2007-2011	Poland	Polish Mother and Child (REPRO_PL) Cohort Study: Non-smoking pregnant women; no history of occupational PAH exposure, recruited at 8-12 weeks gestation; singleton births.	104
Porter, et al., 2014 [269]	Cohort	1991-2010	Alabama	Live, singleton births recorded in the Birth records.	412,973
Snijder, et al., 2012 [302]	Cohort	2002-2006	Rotterdam, The Netherlands	Generation R Study: pregnant women who had expected delivery date between 04/2002 and 01/2006.	4,680
Sram, et al., 2006 [307]	Case-control	1994-1995	Teplice, Prachatice, Prague, Czech Republic	Pregnant women residing at least 1 year in district; primiparous births with low birth weight (<2500g), premature births (<37 weeks gestation) and controls.	199
Suter, et al., 2019 [308]	Cross-sectional	not reported	Harris County, TX	PeriBank Project: Non-smoking pregnant women; live singleton births.	104
Suzuki, et al., 2010 [303]	Cohort	2005-2008	Tokyo, Japan	Pregnant women seeking prenatal care.	128
Tang, et al., 2014 [304]	Cross-sectional	2002-2003, and 2005-2006	Tongliang, China	Both cohorts: non-smoking pregnant women, 20+ years of age, residence within 2.5 km of power plant.	251
Vassilev, et al., 2001a [410]	Cohort	1990-1991	New Jersey	Singleton live births.	199,474
Vassilev, et al., 2001b [309]	Cohort	1990-1991	New Jersey	Singleton live births.	215,869
Wilhelm, et al., 2011 [270]	Case-control	2004-2006	Los Angeles County, CA	Pregnant women residing in LA County; live singleton births; living < 5 miles of an air monitoring station.	111,203
Yang, et al., 2018 [266]	Cross-sectional	2011-2012	Wuhan, Xiaogan, Hubei Province, China	Non-smoking, pregnant women, age 18+ years; residing at least 1 year prior to delivery; live singleton births.	106

Table B.2 Additional Characteristics of Included studies [a] – Birth Outcomes.

Study, year	Exposure Matrix	PAHs Assessed [a]	Exposure Measure Collection Timing [b]	Birth Outcome(s) [c]
Agarwal, et al., 2018 [262]	placental tissue	EPA16: and Total PAHs	EOP	PTB
Agarwal, et al., 2020 [305]	placental tissue	EPA16:	EOP	BW
Al-Saleh 2013 [174]	urine, placental tissue	BaP, PYR, Total PAHs	EOP	BL, BW, HC, PI
Cabrera-Rodriguez, et al., 2019 [296]	cord blood	EPA16:	EOP	SGA
Chen, et al., 2014 [306]	cord blood, maternal blood	ANT, BaP, BbF, BghiP, BkF, DahA, FLA, PYR	EOP	BW
Choi, et al., 2006 [297]	personal air sampling	sum of 8 c-PAHs: BaA, BaP, BbF, BghiP, BkF, CHR, DahA, IcdP	3rd trimester	BL, BW, HC
Choi, et al., 2008 [271]	personal air sampling	8 c-PAHs: BaA, BaP, BbF, BghiP, BkF, CHR, DahA, IcdP	3rd trimester	GA, PTB, FG< 85%, SGA
Dejmek, et al., 2000 [164]	modeling - air	8 c-PAHs: BaA, BaP, BbF, BghiP, BkF, CHR, DahA, IcdP, Total PAHs	9 months	IUGR
Duarte-Salles, et al., 2012 [409]	modeling -diet	Dietary sources of B(a)P	1st trimester	SGA
Duarte-Salles, et al., 2013 [264]	modeling - diet	BaP	2nd trimester	BL, BW
Ghosh, et al., 2012 [102]	modeling - air	BaP, BghiP, and total PAHs	9 months	LBW
Gong, et al., 2018 [311]	modeling - air	NAP, BghiP	9 months	LBW
Guo, et al., 2012 [274]	cord blood	7 c-PAHs: BaA, BaP, BbF, BbkF, BkF, CHR, DahA, and Total cPAHs	EOP	BL, BW, GA
Huang, et al., 2020 [267]	urine	FLU, NAP, PHE, PYR	EOP	BL, BW, GA, HC
Huo, et al., 2019 [298]	urine	NAP, PHE	EOP	BL, BW, HC
Kumar, et al., 2020 [312]	maternal blood, cord blood	DahA, FLA, FLU, PYR	EOP	LBW
Lamichhane, et al., 2016 [299]	modeling - diet	NAP, PYR, Total PAHs	1st trimester	BL, BW, HC
Langlois, et al., 2014 [313]	modeling - occupation	Total PAHs	9 months	SGA
Maxwell, et al., 1994 [295]	cord blood	NAP	EOP	BW
Maypole-Keenan, et al., 2016 [272]	modeling - air	7 c-PAHs: BaA, BaP, BbF, BkF, CHR, DahA, IcdP, and NAP	9 months	SGA
Nie, et al., 2018 [273]	urine	FLU, NAP, PHE, PYR, and Total PAHs.	EOP	BL, BW, HC, PI
Norlen, et al., 2019 [310]	modeling - occupation	Total PAHs	9 months	LBW, PTB, SGA

Table B.2. Continued.

Study, year	Exposure Matrix	PAHs Assessed [a]	Exposure Measure Collection Timing [b]	Birth Outcome(s) [c]
Padula, et al., 2014 [96]	modeling - air	Airborne semi-volatile (4, 5 or 6 rings) PAHs: BaA, BaP, BbF, BghiP, BkF, CHR, DahA, FLA, IcdP	9 months	PTB
Pedersen, et al., 2013 [263]	cord blood	PAH-DNA adducts in cord blood	EOP	BW
Perera, et al., 1998 [189]	cord blood	PAH-DNA adducts in cord blood	EOP	BL, BW, HC
Perera, et al., 2003 [88]	personal air sampling	8 c-PAHs: BaA, BaP, BbF, BghiP, BkF, CHR, DahA, IcdP	3rd trimester	BL, BW, HC
Perera, et al., 2004 [300]	maternal blood	BaP-DNA adducts in maternal blood	EOP	BL, BW, HC
Perera, et al., 2005 [225]	cord blood	BaP-DNA adducts in cord blood	EOP	BL, BW, HC
Polanska, et al., 2010 [265]	urine	PYR	2nd trimester	BW, PI
Polanska, et al., 2014 [301]	urine	PHE, PYR	2nd trimester	BL, BW, HC, PI
Porter, et al., 2014 [269]	modeling - emissions	Total PAHs	9 months	PTB
Snijder, et al., 2012 [302]	modeling - occupation	Total PAHs	9 months	BW, HC
Sram, et al., 2006 [307]	placental tissue	PAH-DNA adducts in placental tissue.	EOP	BW
Suter, et al., 2019 [308]	placental tissue	BaP, BbF, DBA	EOP	GA
Suzuki, et al., 2010 [303]	urine	PYR	9^{th} - 40^{th} week	BL, BW, GA, HC
Tang, et al., 2014 [304]	maternal blood, cord blood	BaP-DNA adducts	EOP	BL, BW, HC
Vassilev, et al., 2001a [410]	modeling - emissions	POM	9 months	SGA
Vassilev, et al., 2001b [309]	modeling - emissions	POM	9 months	BL, LBW, PTB
Wilhelm, et al., 2011 [270]	modeling - air	Total PAHs	9 months	PTB
Yang, et al., 2018 [266]	urine	FLU, NAP, PHE, PYR	EOP	BL, BW, GA

[a] See abbreviations and acronyms section for description of PAH abbreviations.
[b] Exposure measure collection timing. EOP: end of pregnancy. 9 months: entire pregnancy.
[c] Birth outcomes. BL: birth length. BW: birth weight. FG<85% fetal growth < 85% of normal. GA: gestational age. IUGR: intrauterine growth restriction. HC: head circumference. LBW: low birth weight. PI: ponderal index. PTB: preterm birth. SGA: small for gestational age.

Table B-3. Search Terms – Birth Outcomes (showing query, search details and results from PubMed).

Search #	Query	Search Details	Results
1	((((((((((polycyclic aromatic hydrocarbon*) AND ("PAH") OR ("polynuclear aromatic hydrocarbon") AND ("PAH")) OR ("polycyclic organic matter") AND ("POM")) OR ("naphthalene")) OR ("fluorene")) OR ("phenanthrene")) OR ("anthracene")) OR ("pyrene")) OR (benz*)) OR ("chrysene")) OR ("perylene"))	((((((("polycyclic"[All Fields] OR "polycyclics"[All Fields]) AND ("aromatic"[All Fields] OR "aromatics"[All Fields]) AND "hydrocarbon*"[All Fields] OR "hydrocarbons"[All Fields]) AND "PAH"[All Fields]) OR "polycyclic aromatic hydrocarbon"[All Fields] OR "polycyclic aromatic hydrocarbons"[All Fields] AND "PAH"[All Fields]) OR "polynuclear aromatic hydrocarbon"[All Fields] OR "polynuclear aromatic hydrocarbons"[All Fields]) AND "PAH"[All Fields]) OR "polyaromatic hydrocarbon"[All Fields] OR "polyaromatic hydrocarbons"[All Fields] AND "PAH"[All Fields]) OR "polycyclic organic matter"[All Fields]) AND "POM"[All Fields]) OR "naphthalene"[All Fields] OR "fluorene"[All Fields] OR "phenanthrene"[All Fields] OR "anthracene"[All Fields] OR "pyrene"[All Fields] OR "benz*"[All Fields] OR "chrysene"[All Fields] OR "perylene"[All Fields]	487,150
2	(((((((("infant") OR ("fetal")) OR ("prenatal")) OR (reproduct*))) OR ("pregnancy outcome")) OR ("birth outcome")) OR (gestation*)	"infant"[All Fields] OR "fetal"[All Fields] OR "prenatal"[All Fields] OR "reproduct*"[All Fields] OR "pregnancy outcome"[All Fields] OR "birth outcome"[All Fields] OR "gestation*"[All Fields]	2,219,173
3	((((("preterm birth") OR ("intrauterine growth restriction")) OR ("birth weight")) OR ("birth length")) OR ("head circumference")	"preterm birth"[All Fields] OR "intrauterine growth restriction"[All Fields] OR "birth weight"[All Fields] OR "birth length"[All Fields] OR "head circumference"[All Fields]	113,521
4	#1 AND #3		20,087
5	#2 AND #4		444
6	#1 AND #4 AND #5		412

Table B.4. Study search strategy: eligibility criteria for prenatal PAH exposure and birth outcomes.

Study Element	**Eligibility Criteria**
Type of Studies	Observational (Epidemiologic)
Study Participants	• Birth cohort, case-control, or cross-sectional studies: ○ Pregnant women and their infants living and/or working in the study location during the study time-period.
Measure of Exposure	• PAH in biomarker collected during pregnancy, or within 24-hours of the end of pregnancy. • Airborne PAH detected in personal air sampling. • Modeled PAH exposure from air monitoring or emissions data. • Modeled PAH exposure from questionnaire data. • Modeled exposure from electronic medical records and/or Census data.
Outcome	• Birth outcomes reported in eligible studies (examples: gestational age, birth weight, birth length, head circumference).
Measure of Association	• Risk Ratio with Standard Deviation, Confidence Interval, or *p*-value. • Odds Ratio with Standard Deviation, Confidence Interval, or *p*-value. • Correlation with Standard Deviation or Confidence Interval, or *p*-value. • Mean or Mean Difference with Standard Deviation, Confidence Interval, or *p*-value. • Regression coefficient, β with Standard Deviation, Confidence Interval, or *p*-value.
Measure of Dispersion	• Standard deviation • Standard error • Confidence interval based on a reported alpha • *p*-value
Response Variable	Continuous, Categorical or Binary
Time-Period	Any
Geographic Location	Any
Analytical Method	Information reported in study regarding: • Sample collection, storage, and preparation. • Instrument model and manufacturer. • Quality assurance/quality control procedures. • Limit of detection (LOD).

Table B.5. Primary study inclusion and Exclusion criteria – Birth Outcomes.

Inclusion Criteria	**Exclusion Criteria**

Study Criteria
• Study participants are pregnant or recently post-partum women and their infants.
• Study design: cohort, case-control, cross-sectional that measured PAH exposure during pregnancy or shortly after delivery.
• Exposure Matrix: data collected from:
  o appropriate biomarkers (blood, urine, feces, genetic markers),
  o personal air sampling,
  o modeled exposure (i.e., air, emissions, occupation, diet).
• Birth outcomes reported (i.e., gestational age, birth weight, head circumference, etc.).
• Measure of association reported.
• Measure of dispersion reported.
• Measures of association and dispersion reported can be combined with data from other studies in a meta-analysis to produce a mean effect.
 	
Study in English language
 	
Published peer-reviewed literature sources:
• Journal articles
• Text resources
• E-books
• Print books
• Reviews-for citations only
 	
"Gray" Literature Sources:
• Conference proceedings
• Government documents
• Technical reports
• Theses and dissertations – for citations only
	Study Criteria
	• Studies that did not measure prenatal PAH exposure.
	• Nested studies on a population already covered under another study.
	• Birth outcomes:
	  o Fetal death
	  o Neural tube defects
	  o Birth defects
	Literature Sources
	• Reference entries
	• Newspaper articles
	• Patents
	• E-Audio and e-Video
	• Microform
	• Maps
	• Journals
	• Blogs
	• CD or DVD-ROM

Table B.6 Data extraction fields and description.

Heading	Field	Field Type	Instructions
General Information	Author(s)	Text field	List last name and first initial of authors
General Information	Year	Text field	Insert year of study publication.
General Information	Citation	Text field	Insert citation.
General Information	Study Design	Single choice list	Study Design: Choose the study design type from the dropdown list.
General Information	Purpose of Study	Text field	Briefly describe purpose of study. Optional for MK.
General Information	Location(s) of Study	Text field	Enter the study location(s). Include city, state, country, if data is available.
General Information	Time Period of Study	Text field	Enter time period of study in either yyyy to yyyy, or mm/yyyy to mm/yyyy format, depending on data available.
General Information	Source of Funding	Text field	Indicate the source of funding for this study. Use acronyms of government funding sources, but not grant numbers.
General Information	Does the author report a COI or financial disclosure?	Single choice list	Indicate if authors report a conflict of interest (COI) and/or financial disclosure.
General Information	COI and/or Financial Disclosure Details	Text field	Enter details about the COI and financial disclosure, if reported by the authors.
Study Population	Demographic Description	Text field	Describe the demographics of study population: age, Race/Ethnicity, occupation, residence, co-morbidities, smoking status, etc. Case-control: describe demographic data on both cases and controls. Cohort: Enter the official name of the cohort or another brief description of the population studied (e.g., distinguishing feature, job occupation, type of clinical population, or work site).
Study Population	Demographic Information Source	Text field	Enter source(s) of demographic information.

Table B.6. Continued.

Heading	Field	Field Type	Instructions
Study Population	Assessment of Control/Reference Population Matching	Text field	Describe how the control/reference population demographic statistics were assessed to ensure control/reference population demographics matched the exposed population demographics.
Study Population	Enrollment Period	Text Field	Enter the start month/year and end month/year.
Study Population	Exclusion Criteria	Text field	Describe criteria used to exclude subjects in the study population. If not specified in the paper, type "Not specified".
Study Population	Sample size – start (number eligible to participate)	Text field	Enter the size of the study population eligible to participate in the study, if provided. For example, a cohort study might have a total population of 10,000 members although only a subset of the population was invited to participate in the specific study.
Study Population	Sample size – Controls/ Reference	Text field	Enter the size of the reference or control population eligible to participate in the study, if provided.
Study Population	Sample size - Final	Text field	Enter the size of the final sample population eligible to participate in the study, if provided.
Study Population	Description of Losses in Selection and Recruitment Process	Text field	If the health status of subjects was followed but subjects were lost from the study, explain how this loss to follow-up was addressed in the statistical analysis. Example: "29 subjects lost to follow-up because they moved out of the region; excluded from statistical tests since health outcome could not be determined."
Study Population	Evaluation of Selection/Recruitment Process	Text field	Enter any additional details related to study design or to the population selection.
Exposure Measurement	Chemicals Evaluated	Text field	Enter the chemicals evaluated in the study.
Exposure Measurement	Exposure Surrogate	Single choice list	Specify whether the exposure data during pregnancy are from biomarkers, environmental monitoring (include matrix in detail), emissions-based models (include specific model in detail), questionnaire (include specific determinant of exposure in details), or other (specify in detail).
Exposure Measurement	Timing of Exposure Measurement Collection	Single choice list	Exposure measurement timing: Select the stage of pregnancy when exposure occurred, if specified. Use "multiple time points" if exposure measurement collection was repeated during pregnancy, including immediately after pregnancy ended.
Exposure Measurement	Location of Exposure Data in Study	Text field	Enter the table(s) or figure(s) (or text field) from which the exposure category and level data was extracted. Example: "Table 6, upper portion". Example: "Text field, page 667, second paragraph"
Exposure Measurement	Analytical Method Reported	Single choice list	Choose whether the exposure assessment method was reported in the study or not, or if it is cited from another study
Exposure Measurement	Analytical Method, Cited in Another Study	Text field	If analytical method is cited from another study, cite the study describing the analytical method.

Table B.6. Continued.

Heading	Field	Field Type	Instructions
Exposure Measurement	Analytical Method Description	Text field	Describe the exposure assessment analytical method, if reported. Include type of instrument used (i.e., "HPLC with fluorescence detector", "GC/MS with electron ionization). Examples: PAH-DNA adducts: indicate if an enzyme-linked immunoassay (ELISA) method was used. Urinary biomarker: describe whether PAH concentration is creatinine-corrected or not. Stationary air monitoring data: describe if EPA method used. Personal air sampling: identify instrument, flow rate, filter type, and length of time in use.
Exposure Measurement	Analytical Method – QA/QC	Text field	Describe the exposure assessment analytical QA/QC methods, if reported.
Exposure Measurement	Limit of Detection (LOD) Reported	Single choice list	Indicate if the limit of detection was reported for each chemical analyzed or not.
Exposure Measurement	Limit of Detection Value	Text field	If LOD reported, provide the LOD value for each chemical analyzed.
Exposure Measurement	Observations under the LOD	Single choice list	If LOD reported, indicate how observations under the LOD were handled.
Outcome Measurement	Primary Outcome Measure	Single choice list	Choose the primary birth outcome. If primary birth outcome not in choice list, choose "Other" and describe in the following text box.
Outcome Measurement	Secondary Outcome Measure, if applicable	Single choice list	Choose the secondary birth outcome, if applicable. If secondary birth outcome not in choice list, choose "Other" and describe in the following text box.
Outcome Measurement	Additional Outcome Measure(s), if applicable	Text field	Identify additional birth outcomes, if applicable.
Outcome Measurement	Diagnostic Description	Text field	Method of birth outcome assessment: Include detail about the method used and conclusions about how reliable the method was compared with other available methods. Example: "From electronic health records, method established by hospital".
Outcome Measurement	Evaluation of Outcome Measure	Text field	Number of subjects analyzed and number of missing participants: Include information about how many subjects were analyzed for each outcome and how many were missing.
Confounding and Analysis	Comparator	Text field	Describe the comparator. Examples: Longitudinal study: describe the outcome in the exposed compared to the unexposed. Case-control study: describe the exposure in cases compared to controls.
Confounding and Analysis	Significance Level	Text field	Describe the significance level if it is different than $p < 0.05$.

Table B.6. Continued.

Heading	Field	Field Type	Instructions
Confounding and Analysis	Description of Control/Reference Population	Text field	Provide information on how the reference population was selected or recruited. If lowest exposure group selected as the reference group, describe, and note any possible issues. Example if no issues: "all subjects recruited in same manner and group with air monitoring concentrations <10 ug/m3 used as reference group." Example if potential issues: "all subjects recruited in same manner; reference group consisted of subjects exposed to <10 ug/m3, however, group significantly younger than other exposure groups and age not adjusted for" For case-control study (one with exposed and unexposed individuals), how were controls or unexposed groups selected? Example: "controls randomly selected to frequency match the cases by age and sex."
Confounding and Analysis	Covariates Considered	Text field	List all covariates included in the study design. This is different than the confounders that were eventually included in the statistical analysis. These covariates are ones considered when choosing either the target population (the whole population considered for the study) or the study population (those that eventually participated in the study).
Confounding and Analysis	Covariates Included in Model Adjustment(s)	Text field	Indicate which covariates were included in model adjustments, and whether confounder is dichotomous, categorical, or continuous.
Confounding and Analysis	Reason for Excluding Adjustment Factors in Final Model(s)	Text field	If some covariates in the "considered" list did not make it into the final "included" list, enter a description of why they were excluded.
Confounding and Analysis	Other Comments on Covariates	Text field	Enter any additional comments on covariates (e.g., if the study is evaluating an occupational exposure, indicate any co-exposures that may have occurred.)
Confounding and Analysis	Covariate Information Location in Study	Text field	Enter the location in the study where the statistical conclusion information can be found; Table X, Page Y in the study reference or section in Text field (section number/title, page number)
Confounding and Analysis	Primary Statistical Analysis	Single choice list	Choose the primary statistical analysis used for the comparator.
Confounding and Analysis	Additional Information on Statistical Analysis	Text field	Enter any additional information on the statistical analysis, including additional statistical analysis performed, that would be relevant to assessing the reliability of the statistical method.
Confounding and Analysis	Statistical Software	Text field	Identify the statistical software used.
Confounding and Analysis	Measure of Association	Single choice list	Choose the primary measure of association to analyze the birth outcome in the exposed, compared to the control/reference group.
Confounding and Analysis	Additional Information on Measure of Assoc.	Text field	Indicate if additional measures of association were reported.

Table B.6. Continued.

Heading	Field	Field Type	Instructions
Confounding and Analysis	Measure of Dispersion	Single choice list	Choose the primary measure of dispersion to analyze the birth outcome in the exposed, compared to the control/reference group.
Confounding and Analysis	Additional Information on Measure of Dispersion	Text field	Indicate if additional measures of dispersion were reported.
Confounding and Analysis	Significance Level	Text field	Describe Significance Level if different than $p < 0.05$.
Confounding and Analysis	Other Method Notes	Text field	Enter any other information from the study (other than covariates, matching, outcome/exposure timing, missing data, co-exposures, exposure assessment, and outcome assessment) that may introduce bias into the study and how the bias was accounted for.
Confounding and Analysis	Evaluation of Statistical and Analytical Approaches	Text field	Evaluate the statistical and analytical approaches.
Results	Overall Results	Text field	Describe the main findings. Include measure of association value and measure(s) of dispersion value(s) Example: birth weight decreased 100-g (95%CI: 90-110) per 10 ug/m3 PAH in ambient air. Example: preterm birth in exposed group was 10% (SE: 0.03) higher compared to control/reference group. Example: aOR for low birth weight was 1.57 (95%CI: 1.26, 1.91) in highest exposure tertile, compared to lowest tertile.
Results	Direction of Effect	Single choice list	Choose the direction of measure of association effect. An effect is positive if the statistical test indicates that exposure led to an increase in risk of a health outcome.
Results	Number of Exposed with Outcome, or Number of Cases with Exposure	Text field	Number of people in exposure group with outcome, or if case-control study, number of cases with exposure; leave blank if not available.
Results	Number of Exposed without Outcome, or Number of Controls with Exposure	Text field	Number of people in exposure group without outcome, or, if case-control study, number of controls with exposure; leave blank if not available.
Results	Additional Information	Memo	Miscellaneous comments by reviewer regarding data analysis: Use phrases separated by semicolons (;) to make note of any observations pertaining to a single exposure group.
Conclusions	Data Extractor Observations	Single choice list	If the authors did not provide conclusions on the trend, select the option that best describes the statistical results. Note any of your own conclusions that are not necessarily reported by the author.
Conclusions	Study Quality Assessment (from Quality Assess. Tool)	Single choice list	Choose the overall study quality based on the Quality Assessment Tool.
Conclusions	Include in Meta-Analysis?	Single choice list	Choose whether the study should be included in the meta-analysis or not.

Table B.7. Study characteristics for quality rating, based on Navigation Guide principles [411].

Criteria	Criteria of Study Quality	Rating
Source of study	Published, peer-reviewed, scientific journal	High
	Published, peer-reviewed, government report	High
	Published, peer-reviewed, text source (book, e-book, etc.)	High
	Published, peer-reviewed, technical reports	High
	Unpublished, peer-reviewed, scientific journal (in press)	Moderate
	Unpublished, peer-reviewed, draft government report	Moderate
	Published conference proceeding	Low
	Any source, not peer-reviewed	Excluded
Study design	Longitudinal birth cohort (prenatal exposure), biomarker, adjusted for known confounders (i.e., tobacco smoke, diet, etc.)	High
	Longitudinal – modeled prenatal exposure, entire pregnancy	Moderate
	Case-control	Moderate
	Cross-sectional – biomarker collected at end of pregnancy/early-life	Low
Study population	Target and comparator sample populations are similar in characteristics, except for exposure of interest	High
	Target and comparator sample populations differ slightly in non-exposure characteristics, such as age or income level	Moderate
	Target and comparator sample populations are very different in non-exposure characteristics, such as age or income level	Low
PAH exposure	Multiple samples of prenatal biomarker sample (i.e., maternal blood or urine)	High
	Perinatal biomarker sample with personal air sampling, or modeling over entire pregnancy	High
	Personal Air Monitoring	Moderate
	Modeled air exposure, entire pregnancy	Moderate
	Modeled occupational exposure, entire pregnancy	Moderate
	Modeled diet exposure, entire pregnancy	Moderate
	Modeled emissions exposure, entire pregnancy	Low to Moderate
Sample size	Statistical power is 0.80 or greater	High
	Statistical power is 0.5 to 0.79	Moderate
	Statistical power is less than 0.49	Low
Analytical methods	Follows appropriate OECD or EPA method; reports QA/QC protocol, LOD of instrument	High
	Follow appropriate OECD or EPA method; reporting of QA/QC protocol and/or instrument type and LOD is incomplete	Moderate
	Did not report appropriate following OECD or EPA method or did not report instrument type	Low
Risk of Bias (RoB)	1. Study Design 2. Source Population 3. Exposure Assessment 4. Outcome Assessment 5. Confounding Analysis 6. Incomplete Outcome(s) 7. Selective Outcome Reporting 8. Funding and Conflict(s) of Interest 9. Other Risks of Bias	High RoB; Probably High RoB; Probably Low RoB: Low RoB;

Table B.8. Statistical power by birth outcome.

	Q-df [a]	Heterogeneity Level [b]	Summary Effect	Effect size [c]	k_{sub}	n_{pooled}	Power [e]
Continuous Outcomes, Summary Effect: Cohen's *d*							
Birth Length	2,039.89	high	-0.161	0.161	49	39,857	1.00
Birth Weight	2,332.04	high	-0.160	0.160	84	41,493	1.00
Gestational Age	70.37	moderate	0.061	0.061	18	1,189	0.18
Head Circumference	88.29	high	-0.091	0.091	37	5,772	0.93
Ponderal Index	15.76	low	-0.002	0.002	10	2,304	0.03
Dichotomous Outcomes, Summary Effect: Odds Ratio							
LBW + FG<85%	49.81	moderate	1.07	0.07	16	545,587	1.00
Preterm Birth	102.36	high	1.09	0.09	30	92,310	1.00
SGA + IUGR	74.38	moderate	1.19	0.19	11	226,096	1.00

[a] Between-study variance.

[b] Heterogeneity level based on the effect size, average number of subjects per group, and ksub. See Equation 8a in Appendix E. Low: 0 - 25%. Moderate: >25% - 75%. High: > 75%. [217]

[c] Effect size is calculated as the absolute value of 1 – summary effect.

[d] Precision is the difference between the upper and lower 95%CI.

[e] Probability of a 1-β err, α = 0.05.

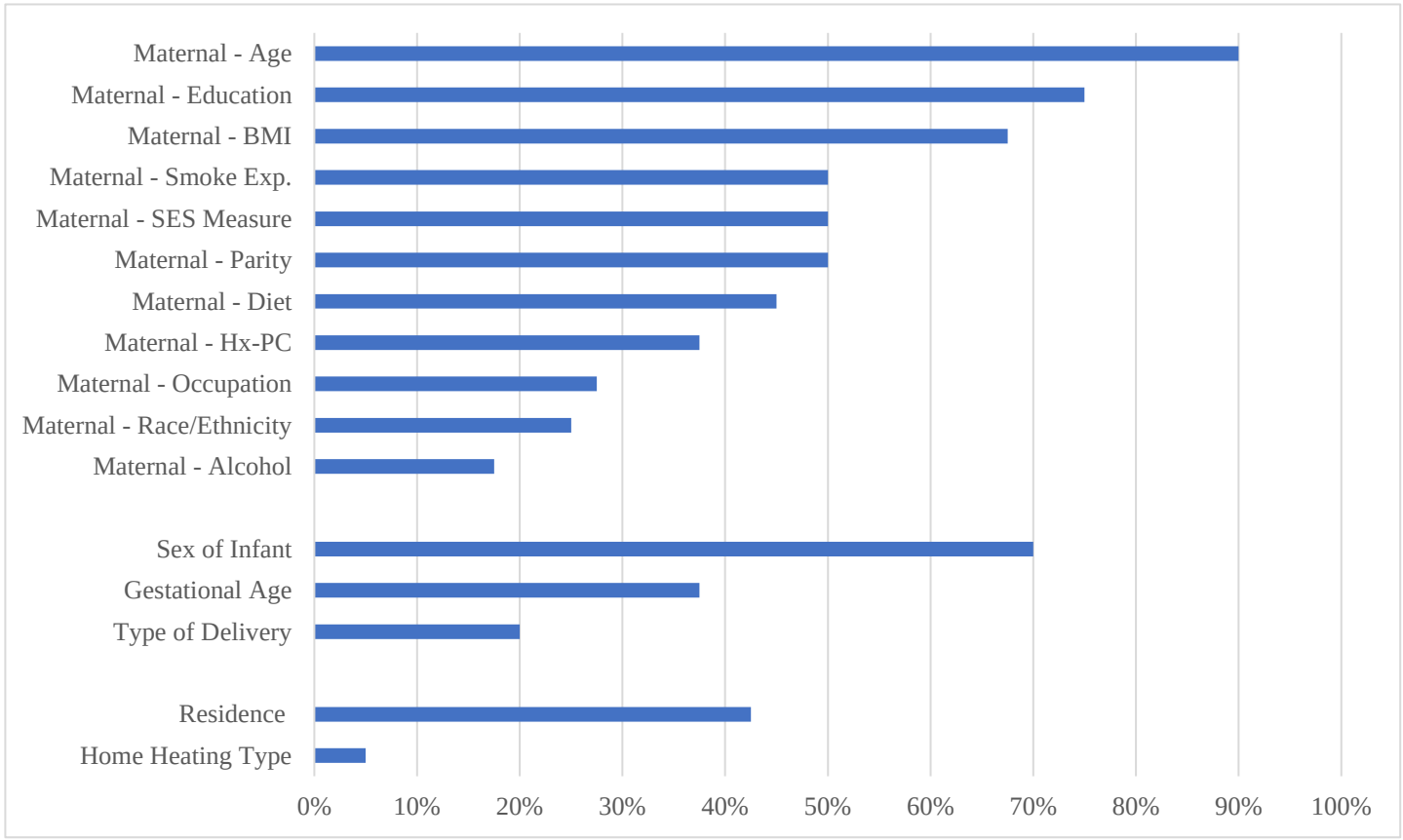

Figure B.1. Covariates reported in primary birth outcome studies, as a percent of total (n = 40).

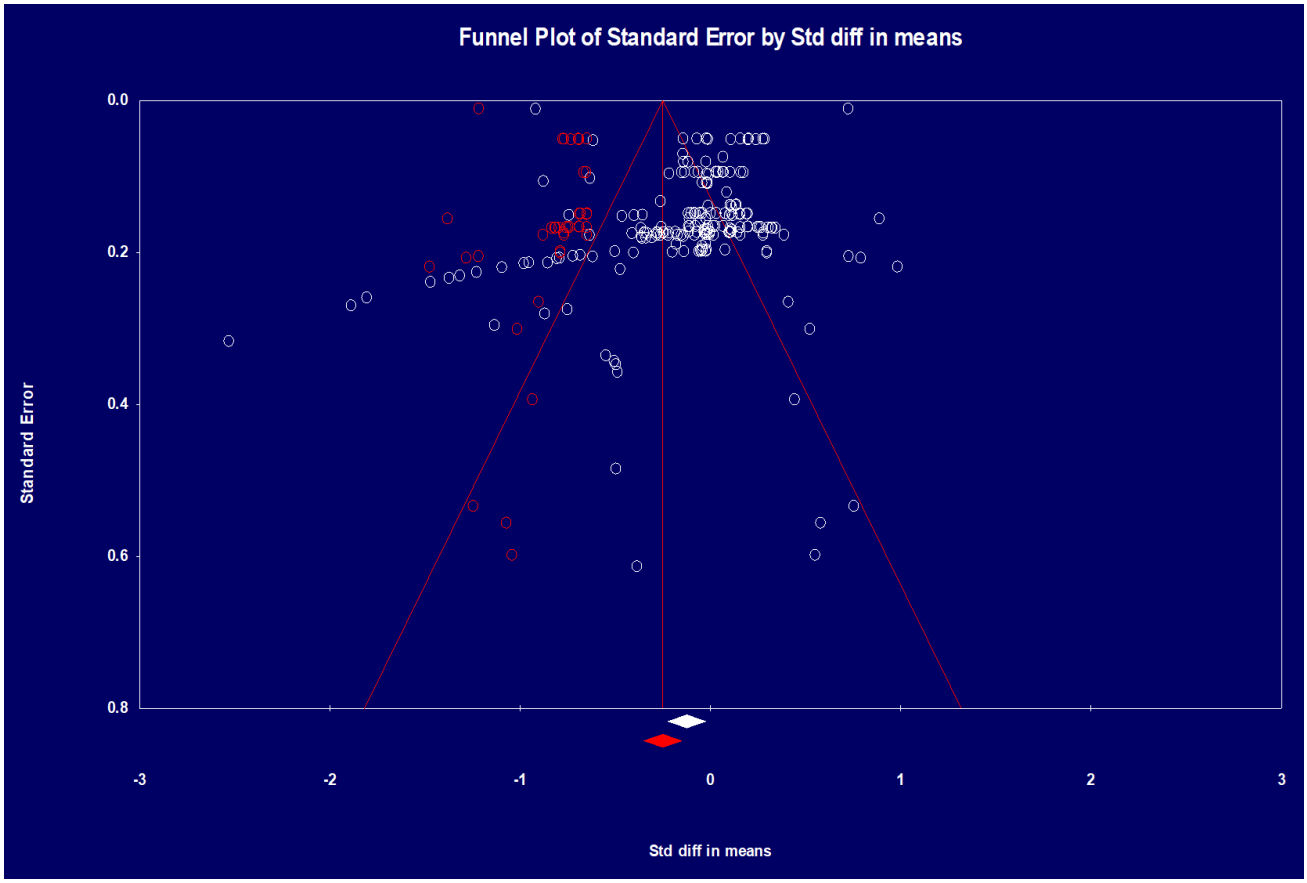

Figure B.2. Publication Bias Analysis Funnel Plot of Continuous Outcomes.[a]

[a] Publication bias in continuous outcomes assessed with Duval and Tweedie's Trim and Fill method. The CMA software imputed estimates of 43 missing studies under a random effects model. For continuous outcomes, this resulted in a smaller predicted summary effect size (Cohen's d: -0.250; 95%CI: -0.349, -0.151), compared to our overall estimate (Cohen's d: -0.124; 95%CI: -0.223, -0.025). The likelihood that unpublished studies would change the direction of our findings for continuous outcomes is very low.

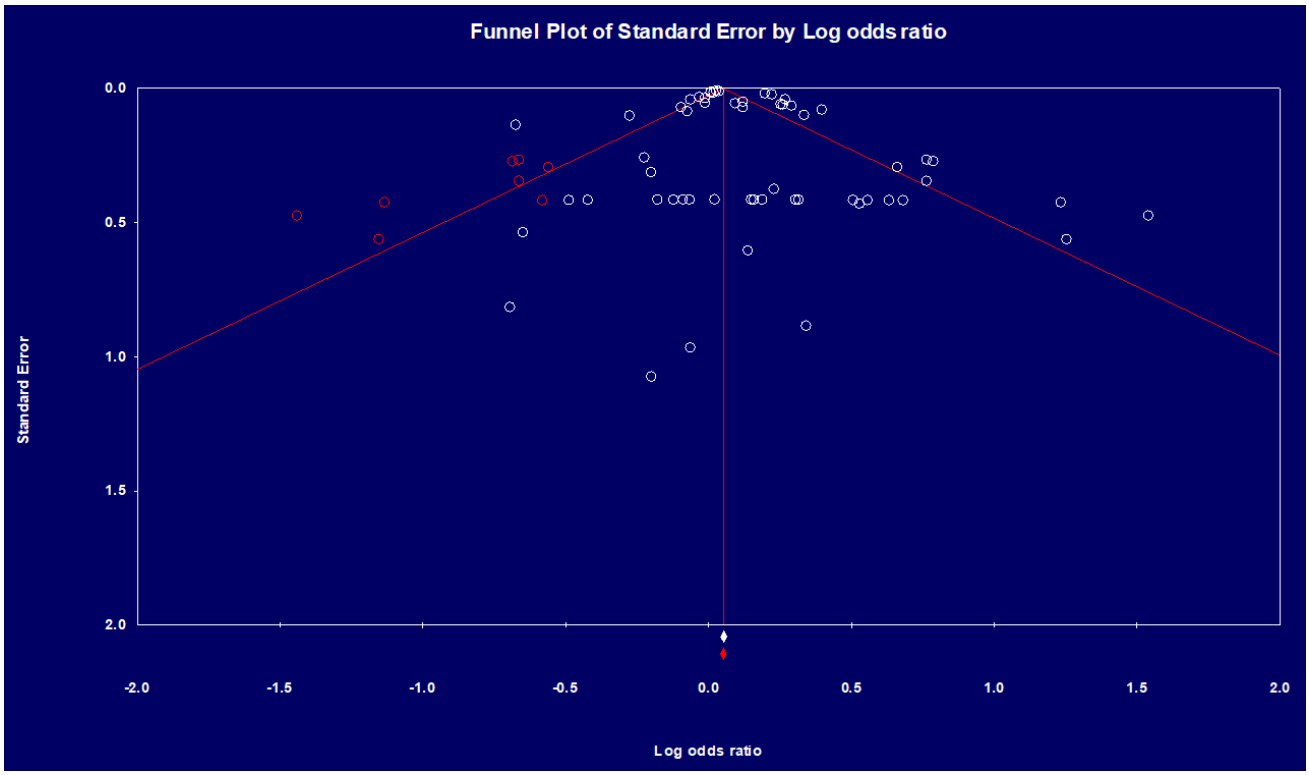

Figure B.3. Publication Bias Analysis Funnel Plot of Dichotomous Outcomes.[a]

[a] Publication bias in dichotomous outcomes assessed with Duval and Tweedie's Trim and Fill method. The CMA software imputed estimates of eight missing studies under a random effects model. The eight imputed estimate was slightly smaller (OR: 1.075; 95%CI: 1.030, 1.122), compared to our overall estimate (OR: 1.100; 95%CI: 1.056, 1.147), but did not change the significance of our findings. The likelihood that unpublished studies would change the direction of our findings for dichotomous outcomes is low.

Figure B.4. Locations of studies included in meta-analysis – Birth Outcomes [412,413].

Appendix C: Supplemental Materials for Chapter 4

Prenatal and Early-Life PAH Exposure and Neurodevelopment Outcomes in Children, A Systematic Review and Meta-Analysis

Barbara Hudson-Hanley, Ellen Smit, Adam Branscum, Perry Hystad, Molly L. Kile

Appendix C: Table of Contents

Table C-1. Search Terms – Neurodevelopment Outcomes (showing query, search details and results from PubMed).

Search #	Query	Search Details	Results
1	((((((((((((((((polycyclic aromatic hydrocarbon*) AND ("PAH") OR ("polynuclear aromatic hydrocarbon") AND ("PAH")) OR ("polyaromatic hydrocarbon") AND ("PAH")) OR ("polycyclic organic matter") AND ("POM")) OR ("naphthalene")) OR ("fluorene")) OR ("phenanthrene")) OR ("anthracene")) OR ("pyrene")) OR (benz*)) OR ("chrysene")) OR ("perylene")) AND ((((((infant) OR (fetal)) OR (prenatal)) OR (perinatal)) OR (child)) OR (children)) AND ((((((((((((((neurodevelopment) OR (neurodevelopment)) AND (cognitive)) OR (neurodevelopment)) AND (intelligence)) OR (neurodevelopment)) AND (motor)) OR (neurodevelopment))) AND (behav*)) OR (neuro*)) AND (cognitive)) OR (neuro*)) AND (motor)) OR (neuro*)) AND (behav*))))) NOT (bisphenol*[Title])) NOT (BPA[Title])) NOT (phthalate*[Title]) NOT (benzodiazepine[All Fields])	((((((((((("polycycle"[All Fields] OR "polycycles"[All Fields] OR "polycyclic"[All Fields] OR "polycyclics"[All Fields] OR "polycyclization"[All Fields] OR "polycyclizations"[All Fields]) AND ("aromatic"[All Fields] OR "aromatically"[All Fields] OR "aromaticities"[All Fields] OR "aromaticity"[All Fields] OR "aromatics"[All Fields] OR "aromatization"[All Fields] OR "aromatizations"[All Fields] OR "aromatize"[All Fields] OR "aromatized"[All Fields] OR "aromatizes"[All Fields] OR "aromatizing"[All Fields]) AND "hydrocarbon*"[All Fields] AND "PAH"[All Fields]) OR "polynuclear aromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polyaromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polycyclic organic matter"[All Fields]) AND "POM"[All Fields]) OR "naphthalene"[All Fields] OR "fluorene"[All Fields] OR "phenanthrene"[All Fields] OR "anthracene"[All Fields] OR "pyrene"[All Fields] OR "benz*"[All Fields] OR "chrysene"[All Fields] OR "perylene"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields] OR ("fetale"[All Fields] OR "fetally"[All Fields] OR "fetals"[All Fields] OR "fetus"[MeSH Terms] OR "fetus"[All Fields] OR "fetal"[All Fields] OR "foetal"[All Fields]) OR ("prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields]) OR ("perinatal"[All Fields] OR "perinatally"[All Fields] OR "perinatals"[All Fields]) OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields])) AND ((((((((((((("neurodevelopment"[All Fields] OR "neurodevelopment"[All Fields]) AND ("cognition"[MeSH Terms] OR "cognition"[All Fields] OR "cognitions"[All Fields] OR "cognitive"[All Fields] OR "cognitively"[All Fields] OR "cognitives"[All Fields])) OR "neurodevelopment"[All Fields]) AND ("intelligence"[MeSH Terms] OR "intelligence"[All Fields] OR "intelligences"[All Fields] OR "intelligent"[All Fields] OR "intelligently"[All Fields] OR "intelligibilities"[All Fields] OR "intelligibility"[All Fields] OR "intelligible"[All Fields])) OR "neurodevelopment"[All Fields]) AND ("motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR "motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields])) OR "neurodevelopment"[All Fields]) AND "behav*"[All Fields]) OR "neuro*"[All Fields]) AND ("cognition"[MeSH Terms] OR "cognition"[All Fields] OR "cognitions"[All Fields] OR "cognitive"[All Fields] OR "cognitively"[All Fields] OR "cognitives"[All Fields])) OR "neuro*"[All Fields]) AND ("motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR "motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields])) OR "neuro*"[All Fields]) AND "behav*"[All Fields])) NOT "bisphenol*"[Title]) NOT "BPA"[Title]) NOT "phthalate*"[Title]) NOT ("benzodiazepin"[All Fields] OR "benzodiazepines"[MeSH Terms] OR "benzodiazepines"[All Fields] OR "benzodiazepine"[All Fields] OR "benzodiazepinic"[All Fields] OR "benzodiazepins"[All Fields])	488

Table C.1. Continued.

Search #	Query	Search Details	Results
2	((((((((("infant") OR ("fetal")) OR ("prenatal")) OR ("perinatal")) ("postnatal")) (child*)))	"infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields] OR "fetale"[All Fields] OR "fetally"[All Fields] OR "fetals"[All Fields] OR "fetus"[MeSH Terms] OR "fetus"[All Fields] OR "fetal"[All Fields] OR "foetal"[All Fields] OR "prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields] OR "perinatal"[All Fields] OR "perinatally"[All Fields] OR "perinatals"[All Fields] OR "child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields] OR "child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]	3,627,929
3	((((((((((((((neurodevelopment) OR (neurodevelopment)) AND (cognitive)) OR (neurodevelopment)) AND (intelligence)) OR (neurodevelopment)) AND (motor)) OR (neurodevelopment))) AND (behav*)) OR (neuro*)) AND (cognitive)) OR (neuro*)) AND (motor)) OR (neuro*)) AND (behav*)	((((((((((((("neurodevelopment"[All Fields] OR "neurodevelopment"[All Fields]) AND ("cognition"[MeSH Terms] OR "cognition"[All Fields] OR "cognitions"[All Fields] OR "cognitive"[All Fields] OR "cognitively"[All Fields] OR "cognitives"[All Fields])) OR "neurodevelopment"[All Fields]) AND ("intelligence"[MeSH Terms] OR "intelligence"[All Fields] OR "intelligences"[All Fields] OR "intelligent"[All Fields] OR "intelligently"[All Fields] OR "intelligibilities"[All Fields] OR "intelligibility"[All Fields] OR "intelligible"[All Fields])) OR "neurodevelopment"[All Fields]) AND ("motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR "motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields])) OR "neurodevelopment"[All Fields]) AND "behav*"[All Fields]) OR "neuro*"[All Fields]) AND ("cognition"[MeSH Terms] OR "cognition"[All Fields] OR "cognitions"[All Fields] OR "cognitive"[All Fields] OR "cognitively"[All Fields] OR "cognitives"[All Fields])) OR "neuro*"[All Fields]) AND ("motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR "motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields])) OR "neuro*"[All Fields]) AND "behav*"[All Fields]	516,979
4	#1 AND #2 NOT (bisphenol[Title])) NOT (phthalate[Title])	((((((((((("polycycle"[All Fields] OR "polycycles"[All Fields] OR "polycyclic"[All Fields] OR "polycyclics"[All Fields] OR "polycyclization"[All Fields] OR "polycyclizations"[All Fields]) AND ("aromatic"[All Fields] OR "aromatically"[All Fields] OR "aromaticities"[All Fields] OR "aromaticity"[All Fields] OR "aromatics"[All Fields] OR "aromatization"[All Fields] OR "aromatizations"[All Fields] OR "aromatize"[All Fields] OR "aromatized"[All Fields] OR "aromatizes"[All Fields] OR "aromatizing"[All Fields]) AND "hydrocarbon*"[All Fields] AND "PAH"[All Fields]) OR "polyaromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polynuclear aromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polycyclic organic matter"[All Fields]) AND "POM"[All Fields]) OR "naphthalene"[All Fields] OR "fluorene"[All Fields] OR "phenanthrene"[All Fields] OR "anthracene"[All Fields] OR "pyrene"[All Fields] OR "benz*"[All Fields] OR "chrysene"[All Fields] OR "perylene"[All Fields]) AND ("infant"[All Fields] OR "fetal"[All Fields] OR "prenatal"[All Fields] OR "perinatal"[All Fields] OR "child"[All Fields] OR "children"[All Fields]) AND ("neurodevelopment outcome"[All Fields] OR "neurodevelopment*"[All Fields] OR (("neuro*"[All Fields] AND "cognitive"[All Fields]) OR "motor"[All Fields] OR "behavior*"[All Fields]))) NOT "bisphenol"[Title]) NOT "phthalate"[Title]	1,874

Table C.1. Continued.

Search #	Query	Search Details	Results
5	#1 AND #3	(((((((((("polycycle"[All Fields] OR "polycycles"[All Fields] OR "polycyclic"[All Fields] OR "polycyclics"[All Fields] OR "polycyclization"[All Fields] OR "polycyclizations"[All Fields]) AND ("aromatic"[All Fields] OR "aromatically"[All Fields] OR "aromaticities"[All Fields] OR "aromaticity"[All Fields] OR "aromatics"[All Fields] OR "aromatization"[All Fields] OR "aromatizations"[All Fields] OR "aromatize"[All Fields] OR "aromatized"[All Fields] OR "aromatizes"[All Fields] OR "aromatizing"[All Fields]) AND "hydrocarbon*"[All Fields] AND "PAH"[All Fields]) OR "polyaromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polynuclear aromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polycyclic organic matter"[All Fields]) AND "POM"[All Fields]) OR "naphthalene"[All Fields] OR "fluorene"[All Fields] OR "phenanthrene"[All Fields] OR "anthracene"[All Fields] OR "pyrene"[All Fields] OR "benz*"[All Fields] OR "chrysene"[All Fields] OR "perylene"[All Fields]) AND ("neurodevelopment outcome"[All Fields] OR "neurodevelopment*"[All Fields] OR (("neuro*"[All Fields] AND "cognitive"[All Fields]) OR "motor"[All Fields] OR "behavior*"[All Fields]))	36,030
6	#4 AND #5 NOT (bisphenol[Title])) NOT (phthalate[Title]) AND (“human”))	(((((((((("polycycle"[All Fields] OR "polycycles"[All Fields] OR "polycyclic"[All Fields] OR "polycyclics"[All Fields] OR "polycyclization"[All Fields] OR "polycyclizations"[All Fields]) AND ("aromatic"[All Fields] OR "aromatically"[All Fields] OR "aromaticities"[All Fields] OR "aromaticity"[All Fields] OR "aromatics"[All Fields] OR "aromatization"[All Fields] OR "aromatizations"[All Fields] OR "aromatize"[All Fields] OR "aromatized"[All Fields] OR "aromatizes"[All Fields] OR "aromatizing"[All Fields]) AND "hydrocarbon*"[All Fields] AND "PAH"[All Fields]) OR "polyaromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polynuclear aromatic hydrocarbon"[All Fields]) AND "PAH"[All Fields]) OR "polycyclic organic matter"[All Fields]) AND "POM"[All Fields]) OR "naphthalene"[All Fields] OR "fluorene"[All Fields] OR "phenanthrene"[All Fields] OR "anthracene"[All Fields] OR "pyrene"[All Fields] OR "benz*"[All Fields] OR "chrysene"[All Fields] OR "perylene"[All Fields]) AND ("infant"[All Fields] OR "fetal"[All Fields] OR "prenatal"[All Fields] OR "perinatal"[All Fields] OR "child"[All Fields]) AND ("neurodevelopment outcome"[All Fields] OR "neurodevelopment*"[All Fields] OR (("neuro*"[All Fields] AND "cognitive"[All Fields]) OR (("motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR "motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields]) AND "skill*"[All Fields]) OR "behavior*"[All Fields])) NOT "bisphenol"[Title]) NOT "phthalate"[Title]) AND "human"[All Fields])	412

Table C.2. Study search strategy: eligibility criteria for prenatal PAH exposure and neurodevelopment outcomes.

Study Element	**Eligibility Criteria**
Type of Studies	Observational (Epidemiologic)
Study Participants	▪ Birth cohort or longitudinal studies: o Pregnant women and their infants living in the study location during the study time-period. ▪ Birth cohort, longitudinal, or high-quality case-control or cross-sectional studies: o Children ages 0-16 living in the study location during the study time-period o Consented to participate in study after informed of study protocol o Agreed to allow study investigators to sample biomarkers (maternal blood or urine, umbilical cord blood, fetal blood or urine, placental tissue) and analyze for presence and concentration of PAHs in biomarker o Agreed to release relevant maternal-infant anthropometric data and child neurodevelopment test data for study
Measure of Exposure	▪ PAH in biomarker collected during pregnancy, or within 24-hours of the end of pregnancy in birth cohort and longitudinal studies ▪ PAH in biomarker collected before or within the time-period that the neurodevelopment assessment takes place ▪ Airborne PAH detected in personal or stationary air monitoring
Outcome	▪ Neurodevelopment Effect: (examples: psychomotor, cognitive and/or socio-behavioral development) assessed using a validated assessment instrument by a trained professional. Examples include: o Bayley Scales of Infant Development (BSID) I, II or III o Wechsler Preschool & Primary Scale of Intelligence (WPPSI) I, II, III or R o Child Behavior Checklist (CBCL) o Conner's ADHD-DSM-IV Scale (CADS)
Measure of Association	▪ Risk Ratio with Standard Deviation or Confidence Interval ▪ Odds Ratio with Standard Deviation or Confidence Interval ▪ Correlation with Standard Deviation or Confidence Interval ▪ Mean Difference with Standard Deviation or Confidence Interval ▪ Regression coefficient, β with Standard Deviation or Confidence Interval
Measure of Dispersion	▪ Standard deviation ▪ Standard error ▪ Confidence interval based on a reported alpha or *p*-value
Response Variable	▪ Continuous, Categorical or Binary
Time-Period	▪ Any
Geographic Location	▪ Any
Analytical Method	▪ Information reported in study regarding: ▪ Sample collection, storage, and preparation ▪ Instrument model and manufacturer ▪ Quality assurance/quality control procedures ▪ Limit of detection (LOD)

Table C.3. Primary study inclusion and exclusion criteria – neurodevelopment outcomes.

Inclusion Criteria	**Exclusion Criteria**
Study Criteria • Study participants are pregnant recently post-partum women and their infants, or children. • Study design: cohort, case-control, cross-sectional that measured PAH exposure during pregnancy, at end of pregnancy, or postnatally, and at least 6 months before neurodevelopment assessment. • Exposure Matrix: data collected from: o appropriate biomarkers (blood, urine, placental tissue, genetic markers), o personal air sampling, o modeled exposure (i.e., air, emissions, occupation, diet). • Neurodevelopment outcomes • Measure of association reported. • Measure of dispersion reported. • Measures of association and dispersion reported can be combined with data from other studies in a meta-analysis to produce a mean effect. Study in English language Published peer-reviewed literature sources: • Journal articles • Text resources • E-books • Print books • Reviews-for citations only "Gray" Literature Sources: • Conference proceedings • Government documents • Technical reports • Theses and dissertations – for citations only	Study Criteria • Studies that did not measure prenatal PAH exposure. • Nested studies on a population already covered under another study. • Birth outcomes: o Fetal death o Neural tube defects o Birth defects Literature Sources • Reference entries • Newspaper articles • Patents • E-Audio and e-Video • Microform • Maps • Journals • Blogs • CD or DVD-ROM

Table C.4. Neurodevelopment assessments, subscales, assessment instruments, and age at assessment reported in included primary studies.

Study, Year	Neurodev. Domains	Neurodev. Assessment	Instrument	Subscale	Age (yrs.)	Comparison	Continuous / Dichotomous Outcome
Alemany, et al., 2018; Mortamais, et al., 2017; Perera, et al., 2012b	Cognitive	Attention	Attentional Network Test (ANT)	Inattentiveness	7-10	Difference in mean score in high v. low exposure groups.	Continuous
		Working Memory	2-Back Test, Words; Numbers	Storage	7-10		
			2-Back Test, Words; Numbers	Processing	7-10		
			2-Back Test, Words; Numbers	Executive function	7-10		
	Behavior	ADHD Symptoms	ADHD-DSM-IV	Inattentiveness	7-10		
				Hyperactivity/Impulsivity	7-10		
		Behavior Problems	Strengths and Difficulties Questionnaire (SDQ)	Emotional Problems	7-10		
				Peer problems	7-10		
				Conduct problems	7-10		
				Hyperactivity	7-10		
Blazcova, 2020	Cognitive	Non-Verbal Intelligence	Raven Colored Progressive Matrices (RCPM)	Reasoning by analogy	5	Above v. below median score in high v. low exposure groups.	Dichotomous
				Adaptive thinking – ability to form perceptual relations	5		
				Problem-solving	5		
	Psychomotor	Visual-Motor Functioning	Bender Visual Motor Gestalt Test	Motor function	5		
	Cognitive			Visual perception	5		

Table C.4. Continued.

Study, Year	Neurodev. Domains	Neurodev. Assessment	Instrument	Subscale	Age (yrs.)	Comparison	Continuous / Dichotomous Outcome
Cao, et al., 2020; Lin et al., 2021; Perera, et al., 2008	Psychomotor	Motor behavior	Gesell Developmental Schedules (GDS)	Gross motor skills	2	Change in score per 1 unit change in ln-PAH.	Continuous
				Fine motor skills	2		
	Cognitive	Language behavior		Vocabulary, word comprehension, conversation, word production	2		
	Psychomotor	Adaptive behavior		Eye-hand coordination, imitation, object recovery, comprehension, discriminative performance, perception, completion, number conception	2		
	Behavior	Personal and social behavior		Reactions to persons, personal habits, initiative, and independence, play responses, acquired information	2		
Edwards, et al., 2010	Cognitive	Non-Verbal Intelligence	RCPM	Reasoning by analogy	5	Change in score in children with high v. low PAH exposure groups.	Continuous
			RCPM	Adaptive thinking – ability to form perceptual relations	5		
			RCPM	Problem-solving	5		
Jedrychowski, et al., 2015; Peterson, et al., 2015	Cognitive	Intelligence	Weschler Intelligence Scale for Children-Revised (WISC-R)	Full scale IQ	7	Mean difference in scores between children with detectable v. non-detectable PAH-DNA adducts.	Continuous
			WISC-R	Verbal IQ	7		
			WISC-R	Performance IQ	7		

Table C.4. Continued.

Study, Year	Neurodev. Domains	Neurodev. Assessment	Instrument	Subscale	Age (yrs.)	Comparison	Continuous / Dichotomous Outcome
Jorcano, et al., 2019; Margolis, et al., 2016; Pagliaccio, et al., 2020; Perera, et al., 2011; 2012b; Peterson, et al., 2015	Behavior	Anxiety/ Depression	Child Behavior Check List (CBCL)	Anxiety/Depressed Syndrome Scale	7-11	Above v. below 93rd percentile in high v. low exposure groups.	Dichotomous
				Withdrawn/Depressed Syndrome Scale			
		Aggressive Symptoms		Rule-breaking Syndrome Scale			
				Aggression Scale			
		Depressive/Anxiety Symptoms	SDQ	Emotional Problems Scale			
		Aggressive Symptoms		Conduct Problems Scale			
Kalkbrenner, et al., 2010; von Ehrenstein, et al., 2014	Cognitive	Autism Spectrum Disorder	DSM-IV-TR	Autism Spectrum Symptoms	5, 8	Cases v. controls in high v. low exposure groups.	Dichotomous
Margolis, et al., 2016;	Cognitive	Attention Problems	Deficient Emotional Self-Regulation (DESR) of the CBCL	Attention Problems Scale	3-5, 7, 9, 11	Mean difference in scores between children detectable v non-detectable adducts	Continuous
	Behavior	Social Impairment	Social Responsiveness Scale	Social Awareness	11		
				Social Cognition			
				Social Communication			
				Social Motivation			
				Autistic Mannerisms			
Margolis, et al., 2021	Behavior	Inhibitory Control	A Developmental Neuropsychological Assessment (NEPSY-II)	Inhibition Subtest	8-14	Mean difference in scores between children with high v. low PAH exposure.	Continuous
	Cognitive	Reading Skills	Woodcock-Johnson Tests of Achievement-III (WJ-III)	Basic Reading Index	13-15	Mean difference in scores between children with high v. low PAH exposure.	Continuous

Table C.4. Continued.

Study, Year	Neurodev. Domains	Neurodev. Assessment	Instrument	Subscale	Age (yrs.)	Comparison	Continuous / Dichotomous Outcome
Nie, et al., 2019	Psychomotor	Motor Response	Neonatal Behavioral Neurological Assessment (NBNA)	Passive Tone Active Tone Primary Reflexes	3 days	Mean difference in scores between children with high v. low PAH exposure.	Continuous
	Behavior	Stimulus Response		Behavioral Response			
Pagliaccio, et al., 2020; Perera, et al., 2011; 2012b	Cognitive	Attention Problems	Deficient Emotional Self-Regulation (DESR) of the CBCL	Attention Problems Scale	11	Above v. below median score in high v. low PAH exposure groups.	Dichotomous
Perera, et al., 2006; 2007; 2015	Cognitive	Mental Development	Bayley Scales of Infant Development-Revised (BSID-II)	Visual Performance Scale Language Scale Attention Scale	2	Score < 85 (impaired) v. > 85 (normal) in children with high v. low PAH exposure	Dichotomous
	Psychomotor	Psychomotor Development		Gross Motor Skills Fine Motor Skills			
Perera, et al., 2009; Perera, et al., 2012a	Cognitive	Intelligence	Wechsler Preschool and primary Scale of Intelligence-Revised (WPPSI-R)	Full Scale IQ Visual IQ Performance IQ	5	Mean difference in scores between children with high v. low PAH exposure	Continuous
Perera, et al., 2014	Behavior	ADHD Symptoms	Conners Parent Rating Scale- Revised (CPRS-R)	Impulsivity Hyperactivity Inattentiveness	9	Score < 65 (impaired) v. > 65 (normal) in children with high v. low PAH exposure	Dichotomous
Talbott, et al., 2015	Cognitive	Autism Spectrum Disorder	Social Communication Questionnaire (SCQ)	Social Relating Score Communication Score Range of Interests Score	5-9	Score > 15 (ASD) v. < 15 (normal) in children with high v. low PAH exposure	Dichotomous
Wallace, et al., 2022	Behavior	Behavior Problems	Brief Infant-Toddler Social and Emotional Assessment (BITSEA)	Problem Score Competence Score	2	Scores =/> 75th percentile for age (adverse) v. < 75th (normal) in children with high v. low PAH exposure	Dichotomous

Table C.5. Characteristics of included primary studies – neurodevelopment outcomes.

Study, year	Study Design	Data collection time period	Location	Study population	Sample size	Exposure Matrix	Exposure Period
Alemany, et al., 2018	Prosp. Cohort	2012-2014	Barcelona and Sant Cugat des Valles, Spain	Pregnant women and their infants/children	1,564	ambient air model	3rd trimester
Blazkova, et al., 2020	Prosp. Cohort	2013-2019	Ceska Budejovice and Karvina, Czech Republic	Pregnant women and their infants/children	169	ambient air model; maternal urine	3rd trimester
Cao, et al., 2020	Prosp. Cohort	2009-2012	Tongliang, China	Chinese pregnant women; their infants/children	158	maternal urine	3rd trimester
Edwards, et al., 2010	Prosp. Cohort	2001-2006	New York, US	African American and Dominican pregnant women; their infants/children	158	personal air sampling	2nd & 3rd trimester
Jedrychowski, et al., 2015	Prosp. Cohort	2000-2008	Krakow, Poland	Caucasian pregnant women and their infants/children	170	cord blood; personal air sampling	EOP; child age 3 years
Jorcano, et al., 2019	Prosp. Cohort	2004-2015	Netherlands, Spain	Pregnant women and their infants/children	NL: 3,120; ES: 484	ambient air modeling	child age 5 years
Kalkbrenner, et al., 2010	Case-Control	1992-2004	North Carolina; West Virginia	Pregnant women and their infants/children	NC: 1335; WV: 1939	ambient air model	entire pregnancy
Lin, et al., 2021	Prosp. Cohort	2014-2016	Qingdao, China	Chinese pregnant women; their infants/children	306	maternal urine; cord blood	EOP
Margolis, et al., 2016	Prosp. Cohort	1998-2016	New York, US	African American and Dominican pregnant women; their infants/children	462	maternal blood	EOP
Margolis, et al., 2021	Prosp. Cohort	1998-2020	New York, US	African American and Dominican pregnant women; their infants/children	462	personal air sampling	3rd trimester
Mortamais, et al., 2017	Prosp. Cohort	2012-2013	Barcelona, Spain	Pregnant women and their infants/children	238	indoor and ambient air model	child age 6-8 years
Nie, et al., 2019	Prosp. Cohort	2009-2010	Taiyuan, China	Chinese pregnant women; their infants/children	247	maternal urine	3rd trimester

Table C.5. Continued.

Study, year	Study Design	Data collection time period	Location	Study population	Sample size	Exposure Matrix	Exposure Period
Pagliaccio, et al., 2020	Prosp. Cohort	1998-2019	New York, US	African American and Dominican pregnant women; their infants/children	319	personal air sampling	3rd trimester
Perera, et al., 2006	Prosp. Cohort	1998-2003	New York, US	African American and Dominican pregnant women; their infants/children	181	personal air sampling	3rd trimester
Perera, et al., 2007	Prosp. Cohort	2001-2006	New York, US (World Trade Center cohort)	African American and Dominican pregnant women; their infants/children	98	cord blood	EOP
Perera, et al., 2008	Prosp. Cohort	2002-2004	Tongliang, China	Chinese pregnant women; their infants/children	217	cord blood	EOP
Perera, et al., 2009	Prosp. Cohort	1998-2008	New York, US	African American and Dominican pregnant women; their infants/children	249	personal air sampling	3rd trimester
Perera, et al., 2011	Prosp. Cohort	1998-2008	New York, US	African American and Dominican pregnant women; their infants/children	96	cord blood	EOP
Perera, et al., 2012a	Prosp. Cohort	1998-2010	Tongliang, China	Chinese pregnant women; their infants/children	100	cord blood	EOP
Perera, et al., 2012b	Prosp. Cohort	1998-2010	New York, US	African American and Dominican pregnant women; their infants/children	223	maternal blood	3rd trimester
Perera, et al., 2014	Prosp. Cohort	1998-2013	New York, US	African American and Dominican pregnant women; their infants/children	250	maternal blood; cord blood	EOP
Perera, et al., 2015	Prosp. Cohort	1998-2006	New York, US	African American and Dominican pregnant women; their infants/children	368	cord blood	EOP

Table C.5. Continued.

Study, year	Study Design	Data collection time period	Location	Study population	Sample size	Exposure Matrix	Exposure Period
Peterson, et al., 2015	Prosp. Cohort	1998-2015	New York, US	African American and Dominican pregnant women; their infants/children	255	personal air sampling; child urine	3rd trimester; child age 5 years
Talbott, et al., 2015	Case-control	2005-2013	Pennsylvania, US	Children with clinical diagnosis of ASD; and controls	5,187	ambient air model	entire pregnancy; child age 1 and 2 years
Von Ehrenstein, et al., 2014	Case-Control	1995-2013	California, US	Pregnant women and their infants/children	109,062	ambient air modeling	entire pregnancy
Wallace, et al., 2022	Prosp. Cohort	2006-2014	Tennessee, US	Pregnant women and their infants/children		maternal urine	2nd and 3rd trimester

Table C.6. Additional characteristics of included primary studies – neurodevelopment outcomes.

Study, year	PAHs Assessed [a]	Outcome Type	Neurodev. Domain(s)	Neurodev. Subdomain(s)	Instrument [a]	Age at Assessment
Alemany, et al., 2018	Total PAHs	Dichotomous	Cognitive; Behavior	Attention Problems; Behavior Problems; ADHD	ANT; 2-back word/number SDQ; ADHD-DSM-IV	7-11 years
Blazkova, et al., 2020	Total PAHs, NAP, BaP	Continuous	Cognitive	Intelligence; Motor Skills	RCPM; BG	5 years
Cao, et al., 2020	Total PAHs, NAP, FLU, PHE, PYR	Continuous	Cognitive; Psychomotor; Behavior	Language Skills; Motor Skills; Adaptive Behavior; Social Behavior	GDS	2 years
Edwards, et al., 2010	Total PAHs	Continuous	Cognitive	Intelligence	RCPM	5 years
Jedrychowski, et al., 2015	Total PAHs	Continuous	Cognitive	Intelligence	WISC-R	7 years
Jorcano, et al., 2019	Total PAHs	Dichotomous	Behavior	Anxiety/Depression; Behavior Problems	CBCL	9-10 years
Kalkbrenner, et al., 2010	Total PAHs	Dichotomous	Cognitive	Autism Spectrum Disorder	DSM-IV-TR	8 years
Lin, et al., 2021	Total PAHs, NAP, FLU, PHE, CHR, PYR	Continuous	Cognitive; Psychomotor; Behavior	Language Skills; Motor Skills; Adaptive Behavior; Social Behavior	GDS	1 year
Margolis, et al., 2016	Total PAHs	Dichotomous	Cognitive; Behavior	Attention Problems	CBCL	3-11 years
Margolis, et al., 2021	Total PAHs	Continuous	Cognitive; Behavior	Intelligence; Adaptive Behavior	WJ-II; NEPSY-II; CBCL	7-9 years
Mortamais, et al., 2017	Total PAHs	Dichotomous	Behavior	ADHD	ADHD-DSM-IV	7-9 years

Table C.6. Continued.

Study, year	PAHs Assessed [a]	Outcome Type	Neurodev. Domain(s)	Neurodev. Subdomain(s)	Instrument [a]	Age at Assessment
Nie, et al., 2019	Total PAHs, NAP, FLU, PHE, PYR	Continuous	Psychomotor; Behavior	Reflexes; Adaptive Behavior	NBNA	3 days
Pagliaccio, et al., 2020	Total PAHs	Dichotomous	Cognitive; Behavior	Attention Problems; Anxiety / Depression; Behavior Problems	CBCL	11 years
Perera, et al., 2006	Total PAHs	Continuous	Cognitive; Psychomotor	Intelligence; Motor Skills	BSID-II	1, 2, and 3 years
Perera, et al., 2006	Total PAHs	Dichotomous	All	Neurodevelopment Delay	BSID-II	1, 2, and 3 years
Perera, et al., 2007	Total PAHs	Continuous	Cognitive; Psychomotor	Intelligence; Motor Skills	BSID-II	2 years
Perera, et al., 2008	Total PAHs	Continuous	Cognitive; Psychomotor; Behavior	Language Skills; Motor Skills; Adaptive Behavior; Social Behavior	GDS	2 years
Perera, et al., 2008	Total PAHs	Dichotomous	All	Neurodevelopment Delay	GDS	2 years
Perera, et al., 2009	Total PAHs	Continuous	Cognitive	Intelligence	WPPSI-R	5 years
Perera, et al., 2011	Total PAHs	Dichotomous	Behavior	Anxiety/Depression	CBCL	4-6 and 6-8 years
Perera, et al., 2012a	Total PAHs	Continuous	Cognitive	Intelligence	WPPSI-R	5 years
Perera, et al., 2012b	Total PAHs	Dichotomous	Cognitive; Behavior	Attention Problems; Anxiety / Depression; ADHD	CBCL; DSM-IV	6-7 years

Table C.6. Continued.

Study, year	PAHs Assessed [a]	Outcome Type	Neurodev. Domain(s)	Neurodev. Subdomain(s)	Instrument [a]	Age at Assessment
Perera, et al., 2014	Total PAHs	Dichotomous	Behavior	ADHD	CBCL; CPRS-R; DSM-IV	9 years
Perera, et al., 2015	Total PAHs	Continuous	Cognitive	Intelligence	BSID-II	2 years
Peterson, et al., 2015	Total PAHs	Continuous	Cognitive	Intelligence	WISC-IV	7-9 years
Peterson, et al., 2015	Total PAHs	Dichotomous	Cognitive; Behavior	Attention Problems; Anxiety / Depression; ADHD	CBCL; DSM-IV	7-9 years
Talbot, et al., 2015	Total PAHs	Dichotomous	Cognitive	Autism Spectrum Disorder	Diagnosis; SDQ	5-8 years
Von Ehrenstein, et al., 2014	Total PAHs	Dichotomous	Cognitive	Autism Spectrum Disorder	DSM-IV-TR	3-6 years
Wallace, et al., 2022	NAP, FLU, PHE, PYR	Dichotomous	All; Behavior	Neurodevelopment Delay; Behavior Problems	BSID-III	3 years

[a] See Abbreviations and Acronym section for descriptions of PAHs, and assessment instrument abbreviations, respectively.

Table C.7. Statistical power by neurodevelopment outcome.

	Q-*df* [a]	Heterogeneity Level [b]	Effect size [c]	k_{sub}	n_{pooled}	Power
Continuous Outcomes, Summary Effect: Cohen's *d*						
Cognitive-all	774.30	high	0.045	44	2685	0.13
Cognitive-Intelligence	417.23	high	0.004	24	1,804	0.03
Cognitive-Language Skills	351.26	high	0.101	20	681	0.15
Psychomotor-all	1,171.64	high	0.371	65	1,372	0.15
Psychomotor-Motor Skills	1,097.25	high	0.672	38	1,125	1.00
Psychomotor-Reflexes	0.00	low	0.007	27	247	0.03
Behavior-all	736.19	high	0.147	51	1284	0.46
Behavior-Adaptive	155.42	high	0.127	30	1,128	0.33
Behavior-Social	580.43	high	0.171	21	681	0.35
Dichotomous Outcomes, Summary Effect: Odds Ratio						
ASD	1.44	low	0.158	4	117,205	1.00
Attention Problems	56.92	moderate	0.813	10	2,997	1.00
ADHD	0.00	low	0.011	20	2,454	0.05
Anxiety/Depression	50.13	moderate	0.362	19	4989	1.00
Behavior Problems	114.70	high	0.064	17	6842	0.46
Neurodevelopmental Delayed	11.70	low	0.070	28	1113	0.90

[a] Between-study variance.

[b] Heterogeneity level based on the effect size, average number of subjects per group, and ksub. See Equation 8a in Appendix E. Low: 0 - 25%. Moderate: >25% - 75%. High: > 75% [217].

[c] Effect size is calculated as the absolute value of 1 – summary effect.

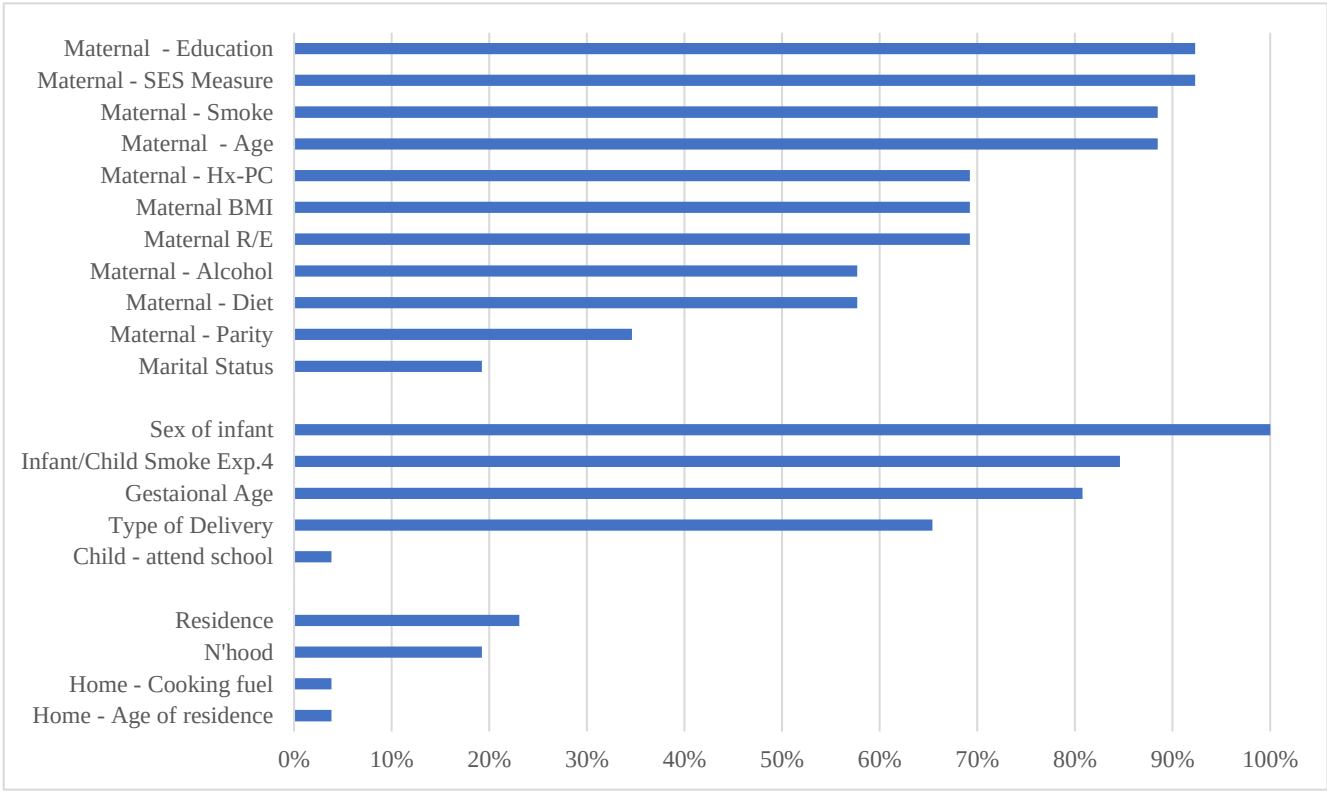

Figure C.1. Covariates[a] reported in primary birth outcome studies, as a percent of total (n = 26).

[a] Maternal Hx-PC: maternal history of pregnancy complications. Infant/Child Smoke Exp. 4: infant or child exposure to tobacco smoke before age 4 years. N'hood: neighborhood characteristics.

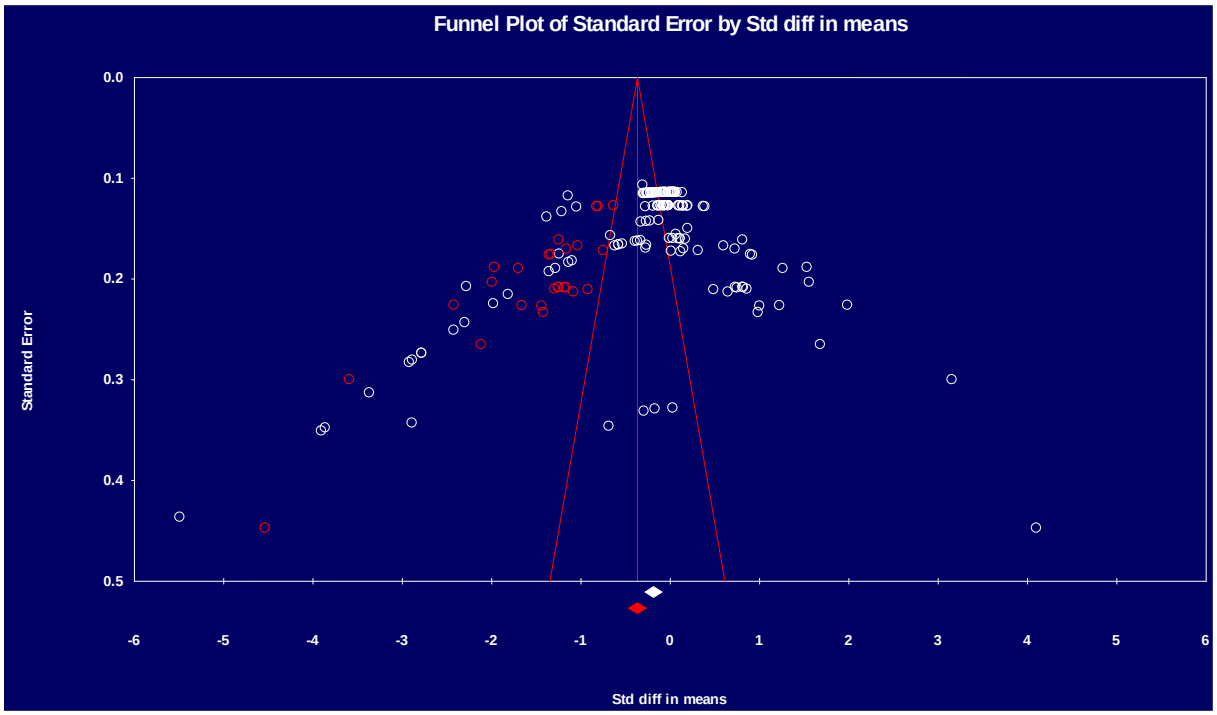

Figure C.2. Publication Bias Analysis Funnel Plot of Continuous Outcomes.[a]

[a] We used Duval and Tweedie's Trim and Fill method. The CMA software imputed estimates of 26 missing studies under a random effects model. For continuous outcomes, this resulted in a smaller predicted summary effect size (Cohen's d: -0.368; 95%CI: -0.467, -0.269), compared to our overall estimate (Cohen's d: -0.188; 95%CI: -0.282, -0.093). The likelihood that unpublished studies would change the direction of our findings for continuous outcomes is very low.

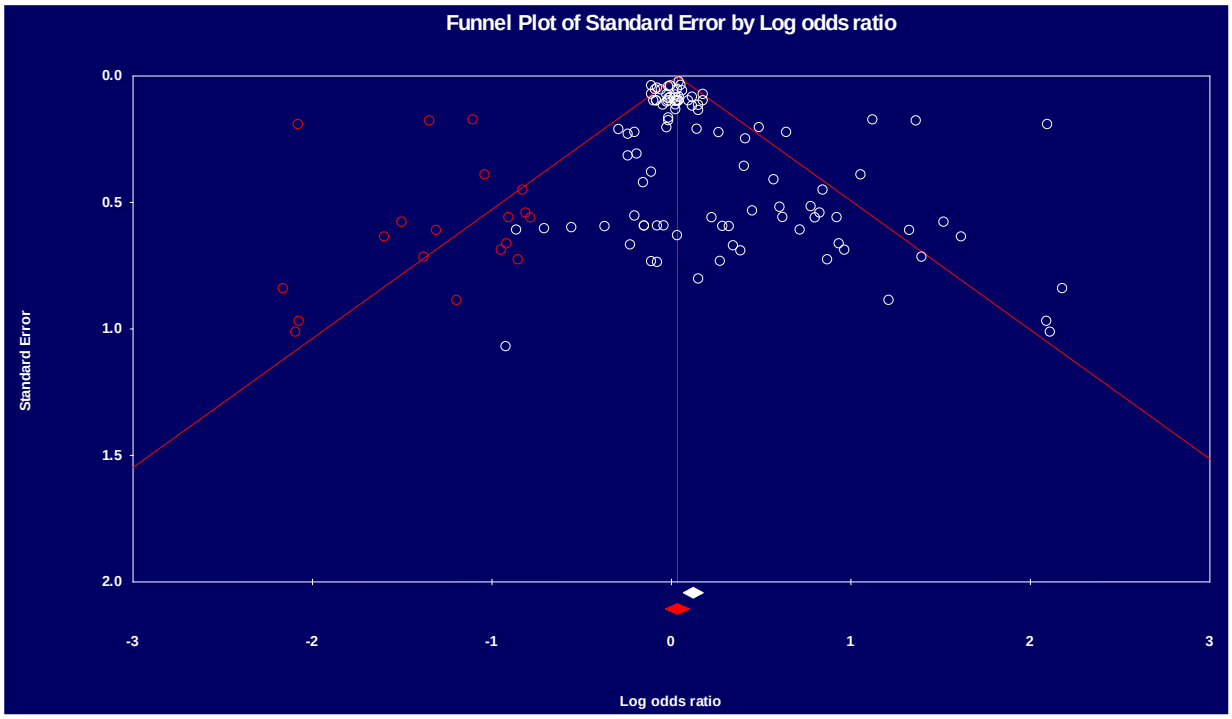

Figure C.3. Publication Bias Analysis Funnel Plot of Dichotomous Outcomes.[a]

[a] Using Duval and Tweedie's Trim and Fill method. The CMA software imputed estimates of 19 missing studies under a random effects model. The imputed estimate was smaller (OR: 1.034; 95%CI: 0.966, 1.107), compared to our overall estimate (OR: 1.129; 95%CI: 1.068, 1.194), and would change the significance of our findings from statistically significant to not significant. There is a small likelihood that the results from unpublished studies would change the direction of our findings for dichotomous outcomes.

Figure C.4. Locations of studies included in meta-analysis – Neurodevelopment Outcomes [412,413].

Appendix D. Instructions for Making Risk of Bias Determinations

The information below is based on the Risk of Bias determinations made for birth outcomes, unless noted text was specific to neurodevelopment outcomes, which are highlighted.

Answer LOW RISK, PROBABLY LOW RISK, PROBABLY HIGH RISK, HIGH RISK or NOT APPLICABLE and provide details/justification.

These questions have been modified from previous applications of the Navigation Guide, with edits intended so that answering "Yes" to each question aligns with a rating of "High risk of bias", "Probably Yes" → "Probably high risk of bias", "Probably No" → "Probably low risk of bias" and "No" → "Low risk of bias."

1. Study Design – is the study design appropriate to address the study question and allow for causal inference (especially Bradford Hill Criteria of specificity, temporality, biological plausibility)?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

EITHER
a) Study design includes exposure assessment with biomarkers at multiple time points during pregnancy/early-life, OR
b) Study design includes exposure assessment with biomarker(s) at a single time during pregnancy/early life, but in conjunction with personal air monitoring data during pregnancy.

Criteria for a judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):
a) Study design includes exposure assessment at a single time point during pregnancy/early-life, but utilizes a biomarker with a relatively long half-life (PAH-DNA adduct), OR
b) Study design includes exposure assessment at multiple time points during pregnancy/early-life using a biomarker with a short half-life (i.e., maternal urine).
c) Study design includes air monitoring at a single time point or short time period (< 1 week) during pregnancy/early-life but utilizes a biomarker in conjunction with personal air monitoring data during pregnancy; OR
d) Study design uses air monitoring collected at multiple time points during pregnancy/early-life to model exposure.

Criteria for a judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):
a) Study design includes exposure assessment of a biomarker with a short-half life (i.e., maternal urine) at a single time point during pregnancy/early-life, OR
b) Study design uses air monitoring collected for a short time period (< 1 week) during pregnancy/early-life to model exposure; OR
c) Study design uses emissions data at multiple time points during pregnancy to model exposure, OR
d) Study design models dietary intake of PAH during pregnancy/early-life, based on maternal responses to food frequency questionnaire.

e) Study design models occupational exposure to PAHs during pregnancy/early-life, based on maternal responses to questionnaires in conjunction with job hazard analysis (JHA) or job exposure matrix (JEM) by qualified industrial hygienist(s).

Criteria for a judgment of HIGH risk of bias (i.e., answer: "Yes"):

a) Study design uses air monitoring data collected at a single time point shortly before delivery, OR
b) Study design uses emission data at a single time point or shortly before delivery to model exposure.

2. Source Population - are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

EITHER:

a) The descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates were sufficiently detailed and adequate data on the distribution of relevant study sample and population characteristics were supplied to support the assertion that risk of selection effects was minimal.

OR

b) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects, adequate support was given indicating that potential selection effects were *not* differential across both exposure and outcome.

OR

c) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects and there was no support indicating that potential selection effects were *not* differential across both exposure and outcome, selection factors appeared to be well-understood, were measured in the data set, and appropriate adjustment post hoc techniques were used to control for selection bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about participant selection to permit a judgment of low risk of bias, but there is indirect evidence that suggests that inclusion/exclusion criteria, recruitment and enrollment procedures, and participation and follow-up rates were consistent across groups as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about participant selection to permit a judgment of high risk of bias, but there is indirect evidence that suggests that inclusion/exclusion criteria, recruitment and enrollment procedures, and participation and follow-up rates were inconsistent across groups, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

a) There were indications from descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates and data on the distribution of relevant study sample and population characteristics that risk of selection effects were substantial; and

b) There was no support to indicate that potential selection effects were *not* differential across both exposure and outcome; and

c) Adjustment post hoc techniques were not used to control for selection bias.

3. Exposure Assessment - were exposure assessment methods lacking accuracy, e.g., allowing misclassification?

Note: For this risk of bias domain, we will separately consider each exposure assessment metric within the same study since different exposures measures may have different risks of bias, i.e., biomarkers versus air modeling, etc. We will divide an individual study up into separate data sets according to the number of separate exposures analyzed in the study. For example, if the study categorizes exposures by "air monitoring" and "urinary biomarkers", we will treat/analyze each of these exposures groups as three separate data sets; if a study assigns an exposure on a chemical by chemical or pollutant by pollutant basis, each chemical will be assessed as a separate data set, etc. Therefore, our review's denominators will be "X included studies" and "X included data sets".

Risk of bias will be assessed for each data set. The risk of bias over the body of evidence will be rated by review authors' review of risk of bias across all datasets (not across all studies). Our rationale for breaking up studies into data sets is that:

1) there is empirical evidence that risk of bias varies depending on which exposure was measured (i.e., chemical component) and how it was measured (i.e., exposure metric).
2) there is a need to transparently distinguish among these potential biases within a given study; and
3) a scientifically preferable alternative method to address this aspect of heterogeneity in the data has not been identified.

The following list of considerations represents a collection of factors that may potentially influence the internal validity of the exposure assessment in a systematic manner (not those that may randomly affect overall study results). ***These should be interpreted only as suggested considerations, and should not be viewed as scoring or a checklist.***

List of Considerations:

Exposure assessment metric:
1) *Modeling*
2) *Monitoring*
3) *Biomarkers*

For each, overall considerations include:
1) *What is the quality of the metric being used?*
2) *Has the metric been validated for the scenario for which it is being used?*
3) *Is the exposure measured in the study a surrogate for air pollution (i.e., distance to freeway)?*
4) *What was the temporal coverage (i.e., whole pregnancy, or a shorter duration)?*
5) *Did the analysis account for prediction uncertainty?*
6) *How was missing data accounted for, and any data imputations incorporated?*
7) *Were sensitivity analyses performed?*

For exposure assessment models:
1) *Were the input data in the study suspected to systematically under- or over-estimate exposure?*
2) *What type of model was used (geostatistical interpolation, land-use regression, dispersion models, personal air sampling models, hybrid models, etc.)?*
3) *Were meteorological variables incorporated in the air models and justified by authors in their selection?*
4) *Were data on land use, topography, traffic, monitoring data, emission rates, etc. incorporated and justified by authors in their selection?*
5) *What was the spatial variation (e.g., distance from source) and geographic/spatial accuracy (county, census tract, individual residence)?*
6) *What was the temporal specificity and variation (accuracy to level of pregnancy trimester, etc.?)*
7) *What was the address completeness (e.g., only home address at one point in time, or more complete address history throughout pregnancy and other locations such as work)?*
8) *What was the space-time coverage of the model?*
9) *Were time-activity patterns accounted for?*
10) *Was mixing height considered as a covariate?*

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

The reviewers judge that there is low risk of exposure misclassification, i.e.:
- There is high confidence in the accuracy of the exposure assessment methods, such as methods that have been tested for validity and reliability in measuring the targeted exposure; OR
- Less established or less direct exposure measurements are validated against well-established or direct methods; OR:

A) Biomarkers: a direct measure of two or more constituents of exposure during pregnancy was used, and there is sufficient evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment; or

B) Monitoring: direct and personal monitoring devices that were used that have been validated for the chemical and scenario for which it was used and there is sufficient evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment; or

C) Modeling: the model accounted for the time-activity pattern specific to each research participant, (e.g. includes more than exposure at the residential address) and included modeling methods that have been validated or shown to have a high degree of accuracy (e.g. spatial point location), and/or methods that are themselves validated with good agreement compared to person-based data collection; and there is sufficient evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.

AND if applicable (e.g., for laboratory measurements), appropriate QA/QC for methods are described and are satisfactory, with at least three of the following items reported, or at least two of the following items reported plus evidence of satisfactory performance in a high-quality inter-laboratory comparison:

- Limit of detection or quantification.
- standards recovery.
- measure of repeatability.
- investigation and prevention of blanks contamination.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

There is insufficient information about the exposure assessment methods to permit a judgment of low risk of bias, but there is indirect evidence that suggests that methods were robust, as described by the criteria for a judgment of low risk of bias. Studies only reporting that the QA/QC items above were satisfactory but not reporting all the actual numbers may receive a judgment of “probably low risk of bias.” Additionally:

A) Biomarkers: a measure that included at least 1 constituent of exposure during pregnancy that exposure is considered relevant and has been validated as a direct measure of exposure was used, or there is some evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.

B) Monitoring: methodologies which directly assess exposure were used, such as personal exposure instruments, but had not been validated for that purpose, or if such instruments were worn for less than 4 hours per day, or there is some evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.

C) Modeling (air monitoring or emissions): the model used methods that do not meet the criteria of including time-activity patterns AND spatial accuracy, and so may not have the level of

validation compared to person-based air measurement, but include measurements that have evidence of quality, such as good-quality data inputs, validated with biomarkers, or area-based air measurement, or other establishments of the accuracy of the data inputs and models, or there is some evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.

D) Modeling (dietary or occupational exposure): the model used methods that do not meet the criteria of including time-activity patterns, and so may not have the level of validation compared to person-based measurement (personal air monitoring), but include measurements that have evidence of quality, such as good-quality data inputs, validated with biomarkers, or other methods to establish the accuracy of the data inputs and models, or there is some evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about the exposure assessment methods to permit a judgment of high risk of bias, but there is indirect evidence that suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias. Additionally:

A) Biomarkers: this includes indirect measures of exposure but not specific to this exposure, such as oxidative stress, during the time period that exposure is considered relevant, or there is some evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

B) Monitoring: measurement of exposures that may not have been validated were used, or there is some evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

C) Modeling: models were used that have not been compared to person-based or area-based air measurements and have suspicion of problems estimating true exposure because, for example, they do not have spatial accuracy (e.g. county-level measures), do not pertain to the correct time frame, are based on limited data, or differ in methodology between cases and controls in a study, or there is some evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

The reviewers judge that there is high risk of exposure misclassification and any one of the following:

- There is low confidence in the accuracy of the exposure assessment methods; or
- Less established or less direct exposure measurements are not validated and are suspected to introduce bias that impacts the outcome assessment (example: participants are asked to report exposure status retrospectively, subject to recall bias); or
- Uncertain how exposure information was obtained; or:

A) Biomarkers: There is sufficient evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

B) Monitoring: Information from databases or otherwise was gathered that indirectly assessed exposure without considering variables noted in the List of Considerations above, such as spatial variability, land use regression, etc., or there is sufficient evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

C) Modeling: the model used has been demonstrated not to pertain to area-based or person-based measures or has otherwise been previously demonstrated to be unable to describe air levels of exposure for assigning exposure in a research situation, or there is sufficient evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

4. Outcome Assessment - were outcome assessment methods lacking accuracy?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

- Outcome classification based on a direct observational assessment by a qualified clinician using instruments and methods established by a health care facility.
- Outcome classification (cognitive, motor, behavioral and/or /emotional outcomes) based on a direct observational assessment by a qualified clinician/specialist using validated assessment instruments and methods; AND
- Outcome assessment instrument has been validated for use based on language and culture of the participant.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

- Outcome classification based on maternal report of data of last menstrual cycle.
- There is insufficient information about the outcome assessment methods to permit a judgment of low risk of bias, but there is indirect evidence that suggests that assessment methods were robust, as described by the criteria for a judgment of low risk of bias. Studies only reporting the outcome assessment instrument used, but not if the instrument has been validated for the particular outcome may receive a judgment of "probably low risk of bias."

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

- Outcome classification obtained from records of questionable quality (home birth records).
Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

- Outcome classification based on direct observational assessment, and with no other outcomes assessed.

5. Confounding and Analysis - was potential confounding inadequately incorporated?

1. *Tobacco smoke exposure*
   Tobacco smoke contains PAHs.

2. *Diet*
   Certain foods contain PAHs and certain cooking methods produce PAHs in foods.

3. *Residence (Urban versus Rural).*
   Rationale: Urban residences are associated with higher air pollution and more traffic. Other ways to consider region that are more germane to the area(s) studied could potentially reduce the ROB.

4. *Socioeconomic status.*
   This is measured differently from study to study, such as by education, income, race. Note that variables like marital status and insurance can even reflect aspects of social class. Sometimes social class is accounted for by individual-level measurements, and other times by group-level measurements (such as census variables). Where people live (neighborhood) is strongly influenced by SES. It's possible that a measured link between air pollutants and birth outcomes could be influenced artificially (confounded) by unknown aspects of SES.

5. *Maternal BMI.*
   Higher BMI is associated with higher PAH exposure.

6. *Time of year*
   Air pollutant concentrations vary by season. Concentrations of certain PAHs are higher in the heating months because of the use of fossil fuels or wood heating. Air pollutants will only vary by season if there is temporal refinement in the air pollutant measure, such as monthly or trimester-long values. A study with annual averages or air pollutant levels, or static levels such as distance to a road, will NOT show a correlation structure between season and air pollutants, and so season will not confound in this type of study.

7. *Occupation*
   Some occupations have higher risk of PAH exposure (chef, road construction, etc.).

Criteria for a judgment of LOW risk of bias (i.e., answer: “No”):

- The study appropriately assessed and accounted for (i.e., matched, stratified, or statistically controlled for) all important potential confounders, or reported that potential confounders were evaluated and omitted because inclusion did not substantially affect the results. The determination of specific confounders may be informed by, but not limited to, the studies included in the overall review.

- AND the important potential confounders were measured consistently across study groups using valid and reliable methods, or the influence of covariate measurement error was determined, through sensitivity analysis, to be minimal.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

- The study appropriately accounted for most but not all the important potential confounders, AND this is not expected to introduce substantial bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

- The study evaluated some but not all the important potential confounders, AND this is expected to introduce substantial bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):
The study did not account for or evaluate multiple important potential confounders

- Important potential confounders were inappropriately measured and/or inappropriately analyzed across study groups.

6. Incomplete Outcome - were incomplete outcome data inadequately addressed?

Criteria for a judgment of LOW risk of bias (i.e., answer: “No”):

Participants were followed long enough to obtain outcome measurements
OR any one of the following:

- No missing outcome data; or
- Reasons for missing outcome data unlikely to be related to true outcome (censoring unlikely to introduce bias); or
- Attrition or missing outcome data balanced in numbers across exposure groups, with similar reasons for missing data across groups; or
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a relevant impact on the intervention effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a relevant impact on the observed effect size; or
- Missing data have been imputed using appropriate methods

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

- There is insufficient information about incomplete outcome data to permit a judgment of low risk of bias, but there is indirect evidence that suggests incomplete outcome data was adequately addressed, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

- There is insufficient information about incomplete outcome data to permit a judgment of high risk of bias, but there is indirect evidence that suggests incomplete outcome data was not adequately addressed, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

Participants were not followed long enough to obtain outcome measurements
OR any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across exposure groups; or
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce biologically relevant bias in intervention effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce biologically relevant bias in observed effect size; or
- Potentially inappropriate application of imputation.

7. Does the study report appear to have selective outcome reporting?

Criteria for a judgment of LOW risk of bias (i.e., answer: “No”):

- All the study’s pre-specified (primary and secondary) outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest have been reported in the pre-specified way.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

- There is insufficient information about selective outcome reporting to permit a judgment of low risk of bias, but there is indirect evidence that suggests the study was free of selective reporting, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

- There is insufficient information about selective outcome reporting to permit a judgment of high risk of bias, but there is indirect evidence that suggests the study was not free of selective reporting, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

Any one of the following:

- Not all the study’s pre-specified primary outcomes (as outlined in the protocol, methods, abstract, and/or introduction) have been reported; or
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data that were not pre-specified; or
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect); or
- One or more outcomes of interest are reported incompletely.

8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

Criteria for a judgment of LOW risk of bias (i.e., answer: “No”):

- The study did not receive support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples include the following:
    - Funding source is limited to government, non-profit organizations, or academic grants funded by government, foundations and/or non-profit organizations.
    - Chemicals or other treatment used in study were purchased from a supplier.
    - Company affiliated staff are not mentioned in the acknowledgements section.
    - Authors were not employees of a company with a financial interest in the outcome of the study.
    - Company with a financial interest in the outcome of the study was not involved in the design, conduct, analysis, or reporting of the study and authors had complete access to the data.
    - Study authors make a claim denying conflicts of interest.
    - Study authors are unaffiliated with companies with financial interest, and there is no reason to believe a conflict of interest exists.
    - All study authors are affiliated with a government agency (are prohibited from involvement in projects for which there is a conflict of interest or an appearance of conflict of interest).

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

- There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence that suggests the study was free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

- There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence that suggests the study was not free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

- The study received support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples of support include:
- Research funds.
- Chemicals, equipment, or testing provided at no cost.
- Writing services.
- Author/staff from study was employee or otherwise affiliated with company with financial interest.
- Company limited author access to the data.
- Company was involved in the design, conduct, analysis, or reporting of the study.
- Study authors claim a conflict of interest

9. Did the study appear to have other problems that could put it at a risk of bias?

Criteria for a judgment of LOW risk of bias (i.e., answer: “No”):

- The study appears to be free of other sources of bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

- There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence that suggests the study was free of other threats to validity.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

- There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence that suggests the study was not free of other threats to validity, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

- There is at least one important risk of bias. For example, the study:
  - Had a potential source of bias related to the specific study design used; or
  - Stopped early due to some data-dependent process (including a formal-stopping rule); or
  - The conduct of the study is affected by interim results (e.g., recruiting additional participants from a subgroup showing greater or lesser effect); or
  - Has been claimed to have been fraudulent; or
  - Had some other problem.

Appendix E. Equations Used to Generate Meta-Analysis Statistics.

Note - Unless otherwise noted, the term "log" used in the equations below refers to the natural log.

1. Equation used to transform effect size reported in primary studies from raw (arithmetic) scale to log scale [287].

   Eq. 1a. For variable X with a log-normal distribution,

   $$Z = \ln(X) \sim \mathrm{N}(\mu, \sigma_z^2)$$

   The standard result that the mean of X is:

   $$E[X] = \exp \mu + \frac{\sigma_z^2}{2}$$

   And the variance of X is:

   $$var(X) = (\exp(\sigma_z^2) - 1) * \exp(2\mu + \frac{\sigma_z^2}{2})$$

   Eq. 1b. Transformation of raw scale (X) to log scale (Z) [287].

   Step 1. Calculate the variance of X, for the *ith* observation:

   $$s_{x,i}^2 = \frac{1}{n} * var_X$$

   Step 2. Calculate the approximate mean on the log-scale:

   $$\bar{z}_i = \ln(\bar{x}_i) - \frac{1}{2} * \ln\left(\frac{s_{x,i}^2}{\bar{x}_i^2} + 1\right), (i = 1, 2)$$

   Step 3. Calculate the difference in means (d_z) on the log scale:

   $$d_z = \bar{z}_2 - \bar{z}_1$$

   Step 4. Calculate the approximate standard deviation on the log scale:

   $$s_{z,i} = \sqrt{\ln\left(\frac{s_{x,i}^2}{\bar{x}_i^2} + 1\right)}, (i = 1, 2)$$

   Step 5. Calculate the approximate variance on the log scale:

   $$var_{\bar{z}_i} = \frac{s_{z,i}^2}{n_i}$$

   Step 6. Calculate the approximate standard error on the log scale:

   $$SEd_z = \sqrt{var_{\bar{z}_2} + var_{\bar{z}_1}}$$

2. Equations used to convert effect sizes in primary studies with dichotomous outcomes to a common effect size (odds ratio) for meta-analysis.

   Eq. 2a. Convert raw mean difference (Mean 1 – Mean 2) to standardized mean difference (Cohen's *d*) [289]:

   Step 1. Calculate pooled SD of mean difference.

$$Mean\ difference\ SD_{pooled} = \sqrt{\left(\frac{(n1 - 1 * SD_1^2) + (n2 - 1 * SD_2^2)}{n1 + n2 - 2}\right)}$$

   Step 2. Calculate standardized difference in means (*d*) from raw mean difference.

$$d = \left(\frac{Mean1 - Mean2}{SD_{pooled}}\right)$$

   Step 3. Calculate standard error of *d*.

$$SE_d = \frac{\sqrt{\frac{1}{n1} + \frac{1}{n2} + d^2}}{2 * (n1 + n2)}$$

   Eq. 2b. Calculate Odds Ratio from standardized mean difference (Cohen's *d*) [289]:

   Step 1. Calculate log odds ratio (log_{OR}) from Cohen's *d*.

$$log_{OR} = \left(\frac{\pi * d}{\sqrt{3}}\right)$$

   Step 2. Calculate standard error of *d*.

$$SE_{log_{OR}} = \sqrt{\frac{\pi^2 * d^2}{3}}$$

   Step 3. Convert log_{OR} and $SE(_{logOR})$ to natural scale odd ratio (*OR*).

$$OR = e^{log_{OR}}, \text{ and } SE_{OR} = e^{SE_{log_{OR}}}$$

3. Equations used to convert effect sizes in primary studies with continuous outcomes to a common effect size (Cohen's *d*) for meta-analysis.

   Eq. 3a. Calculate Cohen's *d* from Pearson's product-moment correlation coefficient (*r*) [289]:

   Step 1. Calculate standardize mean difference (*d*) from *r*.

$$d = \left(\frac{2 * r}{\sqrt{1 - r^2}}\right)$$

Step 2. Calculate standard error of *d*.

$$SE_d = \sqrt{\left(\frac{4 * SE_r^2}{(1 - r^2)^3}\right)}$$

Eq. 3b. Calculate the Pearson's *r* from z-scores of data points [414].

$$r = \frac{\sum(z_x * z_y)}{n}$$

Eq. 3c. Calculate Pearson's *r* from of Spearman's rank correlation (*rho*) [415]:

$$r = 2 \sin\left(\frac{\pi}{6} * rho\right)$$

Eq. 3d. Estimate Pearson's *r* from regression coefficients to [416]:

Step 1. Estimate Pearson's r from beta coefficient:

$$r = \beta + .05\,\lambda$$

where β is the beta coefficient reported in the study and λ is an indicator variable that equals one when β is non-negative, and 0 when β is negative.

Step 2. Calculate Fisher's z' from of Pearson's *r* [417]:

$$Z = \left(0.5 * \ln\left[\frac{1 + r}{1 - r}\right]\right)$$

Fisher's z' approximates a normal distribution and is the data format entered into the CMA software, where the value is converted to Cohen's *d*.

Eq. 3e. Calculate Cohen's *d* from Chi^2 statistic [289]:

Step 1. Calculate Pearson's *r* from Chi^2 statistic.

$$r = \left(\frac{Chi^2}{n}\right)$$

Step 2. Calculate Cohen's *d* from Pearson's *r*. See Eq. 2c, step 1.

Step 3. Calculate standard error of *r* using Fisher's *z'* transformation.

$$SE_r = \left((1 * r^2) * \frac{1}{\sqrt{(n - 3)}}\right)$$

Step 4. Calculate standard error of *d* from standard error of *r*. See Eq. 2c, step 2.

4. Equations used to convert reported measure of precision in primary studies to a common measure of precision (95% CI) for meta-analysis.

   Eq. 4a. Calculate the confidence interval from a *p*-value for a difference [418].

   Step 1. Calculate the test statistic for a normal distribution test, z, from a *p*-value:

$$z = -0.862 + \sqrt{(0.743 - 2.404 * \log(p - value)}$$

   Step 2. Calculate the standard error:

$$SE = \frac{point\ estimate}{z}\ \ (ignore\ minus\ signs)$$

   Step 3. Calculate the 95% CI:

$$95\%\ CI = point\ estimate\ \pm 1.96 * SE$$

   Eq. 4b. Calculate the confidence interval from a *p*-value for a ratio after log-transformation[418]:

   Step 1. Calculate the test statistic for a normal distribution test, z, from a *p*-value (step 1 in Eq. X).

   Step 2. Log transform the point estimate (PE).

$$log_{PE} = \log(PE)$$

   Step 3. Calculate the standard error of the log-transformed point estimate:

$$SE = \frac{log_{PE}}{z}$$

   Step 4. Calculate the 95% CI on the log scale:

$$log_{95\%CI} = log_{PE}\ \pm 1.96 * SE$$

   Step 5. Convert 95% CI to natural scale:

$$95\%\ CI = e^{\pm\ log_{95\%CI}}$$

5. Equations used to calculate the weighted summarized mean of the distribution of effects, *M*, (i.e., the summary mean) for meta-analysis.

   Eq. 5a. Calculate the summary mean, *M*, under the random effects model [289].

   Step 1. Calculate the weight of each primary study, W_i, as the inverse of the study's variance, Var_i:

$$W_i = \frac{1}{Var_i}$$

   Step 2. Calculate the weighted summary mean, *M*, computed as the weighted mean of primary study effect sizes divided by the sum of the weights of primary studies:

$$M = \frac{\sum_{i=1}^{k} W_i * Y_i}{\sum_{i=1}^{k} W_i}$$

Step 3. Calculate the variance of the summary mean, Var_M:

$$Var_M = \frac{1}{\sum_{i=1}^{k} W_i}$$

Where *k* equals the number of primary studies included in the meta-analysis.

6. Equations used to calculate the distributions of within-study and between-study variation, and to test the hypothesis that the mean effect size equals zero).

Eq. 6a. Calculate Q_{obs}, a standardized measure of the weighted sum of squared (WSS) deviations of each study, Y_i, from the summary mean, *M*. *Q* is a standardized statistic sensitive to the ratio of observed variation to the within-study error and follows a Chi-squared distribution. *Q* is calculated by summing the WSS of each primary study from the summary effect:

$$Q_{obs} = \sum_{i=1}^{k} W_i * (Y_i - M)^2$$

Eq. 6b. Estimate *Q* for the underlying population true effects (i.e., the total true dispersion), Q_{true}:

$$Q_{TRUE} = Q_{obs} - Q_{error}$$

Where Q_{error} is the expected variation due to sampling error and is simply the degrees of freedom (*df*) of *k-1*. The value of (*Q* – *df*) reflects the excess between-study variation, i.e., the dispersion in the true effects on a standardized scale.

Eq. 6c. Calculate Tau-squared, T^2, the absolute estimate of the between-studies variation in the true effects. We used the Dersimonian and Laird method for sub-study analyses [419]:

$$T^2 = \frac{Q - df}{C}$$

Where *C* converts the value from a sum to an average and back to its original metric:

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

When $Q < df$, T^2 equals zero. When $Q > df$, it represents the excess between-study variation beyond what is expected from random error.

Eq. 6d. Calculate the total estimated variance, Var_y^* (* denotes a random effects model), as the sum of within-study variance, V_y, and between-study variance, T^2:

$$Var_Y^* = \sum \left(Var_{Y_i} + T^2\right)$$

Eq. 6e. Calculate the weight of each study for random effects model:

$$W_i^* = \frac{1}{Var_{y_i} + T^2}$$

Eq. 6f. Calculate I^2, a descriptive statistic (analogous to a signal-to-noise ratio) that estimates the amount of total variation explained by the variation of true effects, and calculated as the ratio of between-study variation (T^2) to the total variation (Var_Y^*):

$$I^2 = \frac{Var_{true}}{Var_{total}} = \frac{T^2}{T^2 + Var_Y^*} * 100\%$$

Eq. 6g. Calculate the prediction interval (PI), which estimates the distribution of true effects about the summary mean, *M (df = k - 2)*:

$$PI_{lower} = M - t_{df}^{\alpha} * \sqrt{(T^2 + Var_M)}, \qquad PI_{upper} = M + t_{df}^{\alpha} * \sqrt{(T^2 + Var_M)}$$

Eq. 6h. Calculate R^2, the proportion of T^2 explained by the covariates in the meta-regression model.

$$R^2 = \frac{T^2(in\ intercept\ in\ only\ model) - T^2(covariate\ model)}{T^2(in\ intercept\ in\ only\ model)}$$

Eq. 6i. Calculate Tau-squared, T^2, the absolute estimate of the between-studies variation in the true effects. We used the restricted maximum likelihood (REML) method for meta-regression analyses [219]:

$$\tau^2_{REML} = \max\left(0, \frac{\sum w_i^2 \left((y_i - \mu)(\tau^2_{ML})\right)^2}{\sum w_i^2}\right)$$

where $w_i = 1/v_i + \tau^2_{REML}$ is calculated by a process of iteration with an initial estimate of $\tau^2_{REML} \geq 0$. Each iteration step requires non-negativity [218].

7. Equations used to test the null hypothesis that the summary mean, *M*, is equal to zero (i.e., H_o: the effect size across primary studies is the same) [289].

Eq. 7a. Calculate the standard error of the summary mean, SE_M:

$$SE_M = \sqrt{\left(\frac{Var_M}{k * n}\right) + \frac{T^2}{k}}$$

Eq. 7b. Calculate the 95%CI of the summary mean, *M*:

$$95\%CI\ lower\ limit = M - 1.96 * SE_M, \quad 95\%CI\ upper\ limit = +1.96 * SE_M$$

Eq. 7c. Calculate the *z*-score of the summary mean, *M*:

$$Z_M = \frac{M}{SE_M}$$

Eq. 7d. Calculate the significance of the hypothesis test, based on the Chi^2 distribution of *Q*, $\alpha = 0.05$:

$$p = Q, df$$

8. Equations to calculate statistical power of meta-analysis results [215].

Eq. 8a. Use Eq. 7c to calculate Z_M under specific alternatives to calculate statistical power of a random effects meta-analysis result.

Step 1. Calculate lambda (λ) to represent an alternative true value for Z_M

$$\lambda = \frac{\delta}{\sqrt{Var_\delta}}$$

where δ is the alternative true effect size and Var_δ is its variance, calculated as:

$$Var_\delta = \frac{\sum(s^2 + T^2)}{k}.$$

Step 2. Calculate critical value for two-tailed α.

$$C_\alpha = \phi\left(1 - \frac{\alpha}{2}\right)$$

where ϕ is part of standard normal cumulative distribution calculation.

Step 3. Calculate statistical power.

$$Power = 1 - \phi(C_\alpha - \lambda) + \phi(C_\alpha - \lambda)$$

DEDICATION

I dedicate this body of work to my Mom, my Auntie Annie, and my Aunt Augustine. Three women who shaped my world view, who taught me to dream big, to seek justice, to not quit just because it is difficult, and to speak for those who cannot speak for themselves. I witnessed their sacrifice, their resilience, their joy, and sorrows. I am the product of the love these strong-willed, loving, and noble women had for me. Any achievement by my hand is because it was held in theirs.

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