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CHEMICALS IN CONSUMER PRODUCTS:

OCCUPATIONAL EXPOSURE ASSESSMENT, HEALTH IMPACTS,

AND PREDICTORS OF SEMI-VOLATILE ORGANIC CHEMICALS

by

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DEDICATION

Dedicated to my husband, Robert,

and my children, Isabel and Nathaniel.

Thank you for your love, support, and encouragement.

CHEMICALS IN CONSUMER PRODUCTS:

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ABSTRACT

The public comes into contact with numerous semi-volatile organic chemicals (SVOCs) on a daily basis, and there is a lack of knowledge about exposure and health effects associated with many SVOCs, particularly newer compounds. Our objective was to characterize occupational exposure to SVOCs in nail salon workers, analyze exposure to one class of SVOCs in pregnant women and their young children, and examine associations between prenatal exposure and birth outcomes.

From 10 female nail salon workers in the Boston area (2016–2017), we compared phthalates, phthalate alternatives, and organophosphate esters (OPEs) or their metabolites measured in pre- and post-shift urine samples and silicone wrist bands (SWBs). From 134 mother infant pairs from the Newborn Epigenetics STudy (NEST), a North Carolina birth cohort (2009–2011), we used multivariable and weighted quantile sum (WQS) regression models to estimate associations between individual and mixtures of prenatal serum per- and polyfluoroalkyl substances (PFAS) concentrations. In a subsample of 84 NEST offspring aged 3–6 years enrolled in the Toddlers Exposure to SVOCs in Indoor Environments (TESIE) study (2014–2016), we estimated associations of child serum

PFAS concentrations with environmental, behavioral, and demographic predictors.

Among nail salon workers, post-shift urine concentrations were generally higher than pre-shift for SVOC metabolites. Correlations between metabolites in urine and SWBs suggested occupation as a source of exposure. The PFAS mixture index was negatively associated with gestational age at birth among all and male offspring with less evidence of an association among females or for other birth outcomes. Diet, drinking water, maternal serum PFAS concentrations during pregnancy, and air concentrations inside the home were predictors of certain child serum PFAS concentrations.

Nail technicians are occupationally exposed to SVOCs, with evidence of SWBs as a useful exposure assessment tool for future studies. We observed negative associations between prenatal PFAS concentrations and gestational length; male offspring may be more susceptible than females. Eating habits, drinking water source, prenatal serum concentrations, and air concentrations inside the home were predictive of child serum PFAS concentrations. Our results suggest that exposure to SVOCs is multi-faceted and of potential public health concern.

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CHAPTER ONE: INTRODUCTION

Consumer products contain a myriad of chemicals that the public comes into contact with daily in their homes, cars, and workplaces. Semi-Volatile Organic Compounds (SVOCs), are used in many consumer products for a multitude of reasons. There is a lack of knowledge about exposure to and potential public health implications associated with many SVOCs, particularly newer compounds.

Semi-Volatile Organic Compounds (SVOCs)

SVOCs, such as phthalates, organophosphate esters (OPEs), and many per- and polyfluoroalkyl substances (PFAS) are organic chemicals that partition between the gas and condensed phases of matter, and are used in a broad range of consumer products such as stain repellents, pesticides, electronics, personal care products, furniture, and food packaging (Weschler & Nazaroff, 2008). In the indoor environment, SVOCs can exist in air as vapor, or they can adsorb to airborne particles, dust, and other surfaces including the human body (Little et al., 2012). Since SVOCs are usually not chemically bound to the products that contain them, they slowly release into the indoor environment, where they can persist for years (Weschler & Nazaroff, 2008). SVOC exposure occurs through inhalation, ingestion, and dermal absorption (Weschler & Nazaroff, 2008).

Several SVOCs, such as polybrominated diphenyl ethers (PBDEs), are established toxicants that have been banned from commercial use (Weschler & Nazaroff, 2008). Other SVOCs are not as well studied, and while some have shown evidence of negative

health impacts, such as reproductive and endocrine system effects, researchers know very little about the potential health impacts of many others (Weschler & Nazaroff, 2008). More than a thousand SVOCs are on the United States (US) EPA's high-production-volume (HPV) chemical list, meaning that the US produces or imports more than a million pounds of the chemical each year (US EPA, 2007; Weschler & Nazaroff, 2008). Due to the large quantities used in consumer products, studies have suggested that metabolites of some SVOCs, such as triphenyl phosphate (TPHP), some phthalates, and certain PFAS, are nearly ubiquitous in human blood and/or urine, highlighting the need for further study of these SVOCs to determine their potential for negative health impacts (Calafat et al., 2007; Meeker et al., 2013).

Phthalates

Phthalates are man-made SVOCs that are widely used as plasticizers to make thousands of consumer products including medical equipment, pharmaceuticals, food packaging, vinyl flooring, personal care products, and toys (FDA, 2020; Library of Congress. Congressional Research Service, 2008; U.S. Food and Drug Administration, 2013). In personal care products, they are commonly used to make items such as nail polish and hair spray more flexible and less likely to crack, and increases longevity, and as a fixative in perfumes (FDA, 2020). Because of their widespread use, exposure to many phthalates is ubiquitous or nearly so in the US population (Zota et al., 2014).

Several phthalates are thought to be harmful to human health, including di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), benzyl butyl phthalate (BBP),

diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and di-n-octyl phthalate (DnOP) (Library of Congress. Congressional Research Service, 2008). Dibutyl phthalate (DBP), which was historically used in nail polish (Young et al., 2018), for example, is associated with birth defects and negative developmental and reproductive system effects (ATSDR, 2001; Hauser & Calafat, 2005). Other potential adverse health outcomes associated with some phthalates include: preterm birth, early onset puberty, delayed psychomotor development in children, cardiovascular, and neurological effects (ATSDR, 2002, 2001; Harley et al., 2019). Because of health concerns, DBP and other phthalates have been replaced by other compounds, including OPEs such as TPHP, terephthalates such as di(2-ethylhexyl) terephthalate (DEHTP), or other phthalate alternatives such as 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) (Mendelsohn et al., 2016; Silva et al., 2017; Young et al., 2018). Less is known about the health impacts of many of these SVOCs, but they are thought to be less harmful to public health.

Organophosphate Esters

OPEs are a group of SVOCs that are commonly used as plasticizers and flame retardants (Belcher et al., 2014; Butt et al., 2014; Doherty et al., 2019; Meeker et al., 2013). TPHP, for example, is used in plastics, polymers, resins, and other consumer products including polyurethane foam furniture, polyvinyl chloride plastics, and electronics (Belcher et al., 2014; Butt et al., 2014; Hoffman et al., 2014; Meeker et al., 2013; Meeker & Stapleton, 2010; Mendelsohn et al., 2016; Patisaul et al., 2013; Van den Eede et al., 2013; van der Veen & de Boer, 2012). TPHP is also an ingredient in many

brands of nail polish as it increases flexibility and longevity, and helps the nail polish stick onto the fingernail (CosmeticsInfo, 2016; EWG, 2018; Mendelsohn et al., 2016). Use of TPHP is widespread (~10–50 million pounds produced annually); its use in consumer products may be increasing as a substitute for toxic compounds such as bisphenol A (BPA) (used in plastics) and pentabromodiphenyl ether (pentaBDE) (a mixture of PBDEs banned in the US, but previously used as a flame retardant in furniture) (Butt et al., 2014; Hoffman et al., 2014; Meeker & Stapleton, 2010; Mendelsohn et al., 2016; Pillai et al., 2014; van der Veen & de Boer, 2012).

Because of its broad use, TPHP is ubiquitous in the indoor environment, and people are chronically exposed to it largely through inhalation and ingestion of house dust (Butt et al., 2014; Hoffman et al., 2014; Meeker & Stapleton, 2010; Mendelsohn et al., 2016; Pillai et al., 2014; van der Veen & de Boer, 2012). Inclusion of SVOCs in personal care products can lead to somewhat different exposure pathways; a previous study determined that the primary route of exposure to TPHP from applied nail polish is through dermal absorption rather than inhalation (Mendelsohn et al., 2016). TPHP is metabolized into its diester metabolite, diphenyl phosphate (DPHP) and other phase II conjugate metabolites, which can be measured in urine (Butt et al., 2014; Hoffman et al., 2014; Meeker et al., 2013; Mendelsohn et al., 2016; Van den Eede et al., 2013). Studies suggest that metabolites of TPHP are ubiquitous in human urine, underscoring the need for future studies to characterize the health risks associated with this SVOC (Butt et al., 2014; Meeker et al., 2013; Pillai et al., 2014; Van den Eede et al., 2013). The health impacts of TPHP exposure in humans are not well understood, however, from

epidemiological, *in vitro, and in vivo* studies there is evidence that it is associated with early onset puberty, impaired metabolic, reproductive, and endocrine system functions, increased cytotoxicity and anxiety, and decreased bone health (Meeker et al., 2013; Belcher et al., 2014; Patisaul et al., 2013; Pillai et al., 2014; Kojima et al., 2013; Preston et al., 2017).

Per- and Polyfluoroalkyl Substances (PFAS)

PFAS are a group of chemicals that have water and stain-resistant properties; many are resistant to degradation by UV radiation, weather, or other chemicals, and as such are used in numerous consumer products (Ahrens et al., 2013; ATSDR, 2018; Fraser et al., 2012, 2013; Houde et al., 2006). Common products that contain PFAS include surfactants, lubricants, semiconductors, paints, adhesives, carpet and upholstery, clothing, paper and textile coatings, food packaging, nonstick cookware, stain and water repellants, cleaning products, pharmaceuticals, pesticides, personal care products, and fire-fighting foam (Ahrens et al., 2013; ATSDR, 2018; Calafat et al., 2007; Fraser et al., 2012, 2013; Houde et al., 2006). Likely routes of exposure are through inhalation, ingestion of contaminated food (directly from food or from food packaging), drinking water, breastmilk, dust, and through skin absorption (ATSDR, 2018; Calafat et al., 2007; Callan et al., 2016; Fraser et al., 2012, 2013; Shoeib et al., 2011).

PFAS are ubiquitous in indoor environments, and can be transported around the globe on ocean currents and in the atmosphere (Ahrens et al., 2013; ATSDR, 2018; Fraser et al., 2013; Houde et al., 2006; Shoeib et al., 2008, 2011). Because of the

chemical properties listed above, PFAS and/or their partial degradation products are of particular public health concern due to their persistence and bioaccumulation in the environment, water, wildlife, and humans (ATSDR, 2018; Fraser et al., 2012; Houde et al., 2006; Shoeib et al., 2008). In human serum, the half-life of perfluorooctanoic acid (PFOA), for example, is approximately 3–4 years, demonstrating the persistence of these chemicals in the human body (ATSDR, 2018; Houde et al., 2006).

Studies have shown that several PFAS, including perfluorooctane sulfonic acid (PFOS), PFOA, and perfluorononanoic acid (PFNA), are ubiquitous or nearly ubiquitous in human serum and blood (ATSDR, 2018; Calafat et al., 2007; Callan et al., 2016; Fraser et al., 2012, 2013; Joensen et al., 2009; Kato et al., 2011; Maisonet et al., 2012; Nelson et al., 2010). In biomonitoring studies, the most common PFAS typically found in human blood/serum is PFOS followed by PFOA with adult males averaging higher concentrations than adult females; North Americans (citizens of the US and Canada) generally have the highest body burdens of PFAS in the world (Calafat et al., 2007; Fraser et al., 2012; Houde et al., 2006; Kato et al., 2011; Nelson et al., 2010). The hypothesis that volatile precursors to perfluorinated carboxylic acids (PFCAs) (e.g., PFOA) and perfluorinated sulfonates (e.g., PFOS) contribute to body burdens of PFOA and PFOS complicates PFAS exposure assessment (Fraser et al., 2012). For example, fluorotelomer alcohols (FTOH) can metabolize to form PFOA and other PFCAs, and fluorinated sulfonamides (including sulfonamidoethanols (FOSEs)) can metabolize to form PFOS (Fraser et al., 2012). Concentrations of PFOS, however, may be changing over time as production of PFOS and its precursor chemicals ceased in the US in 2002,

and biomonitoring studies have shown a decreasing concentration in serum collected since then (Calafat et al., 2007; Fraser et al., 2012; Kato et al., 2011).

Epidemiological studies have suggested that increased exposure to PFAS may be associated with increased blood cholesterol levels and uric acid levels, altered thyroid hormone levels, liver damage, and decreased infant head circumference and semen quality (ATSDR, 2018; Callan et al., 2016; Dallaire et al., 2009; Joensen et al., 2009; Nelson et al., 2010). PFAS can cross the placental barrier potentially affecting the developing fetus (Callan et al., 2016; Joensen et al., 2009). Some studies have demonstrated an association between elevated PFAS exposure and decreased birth weight (Callan et al., 2016; Maisonet et al., 2012).

Nail Salon Workers

The nail salon industry is one of the fastest growing industries in the US, and the number of nail technicians has more than tripled over the past decade and a half (Goldin et al., 2014; Thu Quach et al., 2008). In 2018, there were 395,658 nail technicians with licenses and 54,386 nail salons in the United States (Nails Magazine, 2018). Women make up 96% of those employed in nail salons, many of whom are of reproductive age (Roelofs et al., 2008). Nail salon employees encounter a variety of chemicals and particulates in the products that they use such as toluene, formaldehyde, and DBP that are known to be harmful to human health (Goldin et al., 2014; Roelofs et al., 2008). In addition to other harmful chemicals, many brands of nail polish contain SVOCs such as TPHP, which the label may or may not list as an ingredient (Mendelsohn et al., 2016;

Patel & Steffier, 2000). Recent findings suggest that people that paint their nails daily to monthly may have higher levels of DPHP in their urine, suggesting that nail polish is a significant source of temporarily elevated exposure to TPHP (Mendelsohn et al., 2016). Although the route of exposure to SVOCs from the products they use is poorly understood, nail salon workers are likely to be chronically exposed to higher levels of these chemicals than the general public. There is growing concern about the health impacts of working in a nail salon as this is a vulnerable population made up of a large proportion of immigrants.

Early Life Exposures

The prenatal period and early childhood are periods of development during which individuals may be more susceptible to the negative health impacts associated with exposures to SVOCs, some of which may lead to significant short- and long-term health consequences (Barker, 2007; Hales et al., 1991). For example, some epidemiological studies have suggested that increased prenatal exposure to certain PFAS may be associated with adverse birth outcomes (Apelberg et al., 2007; Chen et al., 2012; Johnson et al., 2014; Lam et al., 2014; Sagiv et al., 2017; Starling et al., 2017; Woods et al., 2017b). Sources of exposure to SVOCs and the health consequences associated with exposure in children are generally less understood than for adults; it is therefore important to better characterize predictors of children's serum PFAS concentrations.

Research Objectives

Since there are few previous studies characterizing biomarkers of exposure to SVOCs among nail salon workers (Hines et al., 2009; Kwapniewski et al., 2008; Tran & Kannan, 2015), pregnant women (Kingsley et al., 2018; Sagiv et al., 2015), and children (Harris et al., 2017; Kingsley et al., 2018; Winkens et al., 2017) additional research is necessary to better understand exposure to SVOCs among these populations. Additionally, there have not been previous studies that have used various biomonitoring tools to examine multiple exposure pathways to these SVOCs, including biological samples (i.e., urine and/or serum), hand wipes, dust, air, and silicone wristbands (SWBs), to gain a better understanding of SVOC exposures among these populations.

Some epidemiological studies have suggested that increased prenatal exposure to certain PFAS may be associated with adverse birth outcomes such as decreased gestational age at birth and decreased birth weight (Apelberg et al., 2007; Chen et al., 2012; Johnson et al., 2014; Lam et al., 2014; Starling et al., 2017; Winkens et al., 2017; Woods et al., 2017a). However, other studies suggest that inverse associations reported previously with birth weight, particularly those that assessed exposure in late pregnancy serum or in cord blood, may be biased because of uncontrolled confounding by plasma volume expansion (PVE) and glomerular filtration rate (GFR), which may be associated with PFAS concentrations measured in the serum and also birth outcomes (Bach et al., 2015; Steenland et al., 2018; Verner et al., 2015). Cumulative exposure to low concentrations of a multitude of chemicals may be associated with negative health effects, even when there is a lack of evidence for health effects associated with the

concentration of each individual substance (Carrico et al., 2015; Schecter et al., 2013). Pregnant women are likely exposed to mixtures of PFAS that are often highly correlated, raising the possibility of confounding, interactions, or cumulative effects between co-exposures (Braun et al., 2016). However, few previous studies of birth outcomes have examined more than one PFAS at a time (Kalloo et al., 2020; Woods et al., 2017b). Thus, further research is necessary to estimate the joint effects of multiple PFAS to better understand the overall potential health impacts of PFAS exposure on neonates, which often occur as mixtures.

This research aims to address gaps in prior literature and broaden understanding of predictors of exposure and the birth outcomes associated with exposure to SVOCs among nail salon workers, pregnant women, and their offspring. To achieve these objectives, we conducted research among Greater Boston Area nail salon workers, and among a cohort of pregnant women enrolled in the Newborn Epigenetics STudy (NEST) birth cohort and their offspring enrolled in the Toddlers Exposure to SVOCs in Indoor Environments (TESIE) study based in central North Carolina. In the study of nail salon workers in the Greater Boston Area, we collected pre- and post-shift urine samples and SWBs worn on lapels and wrists from 10 female nail technicians in 2016–2017. We characterized occupational exposures to SVOCs by examining their presence on SWBs and comparing pre- and post-shift biomarkers in urine. In the NEST and TESIE studies, maternal serum samples were collected between 5.6 and 29.6 weeks gestation (mean 12.6 weeks) between 2009 and 2011 and analyzed for PFAS to examine associations between PFAS and birth outcomes, including gestational age at birth and birth weight in 134

mother-infant pairs. Additionally, we examined predictors of maternal serum PFAS concentrations based on data from medical records and questionnaires administered during prenatal visits. Finally, at home visits with TESIE participants (2014–2016), we administered questionnaires and collected child serum and environmental samples, and used maternal serum samples from the NEST study to characterize predictors of serum PFAS concentrations in 84 child participants aged three to six years.

The primary aim of *Chapter 2* was to use biomarkers measured in urine and SWBs to characterize occupational exposure of nail salon workers to phthalates, phthalate alternatives, and OPEs. During site visits at salons, we collected pre- and post-shift urine samples, and asked participants to wear SWBs on their wrists and pinned to their lapels over the course of a work day, and analyzed these samples for SVOCs or their metabolites. Pre- and post-shift urine concentrations were compared to each other, and compared to urinary concentrations of SVOCs from women from the National Health and Nutrition Examination Survey to determine occupational exposures.

The primary aim of *Chapter 3* was to determine if prenatal exposure to PFAS is associated with birth outcomes among TESIE study offspring. We utilized prenatal serum samples collected from mothers enrolled in the NEST study to determine prenatal PFAS exposure. We examined the associations between individual and mixtures of PFAS with several birth outcomes, including gestational age at birth, birth weight, and birth weight for gestational age z-score. We adjusted for potential confounding variables, including mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw. A secondary aim of *Chapter*

3 was to identify predictors of maternal serum PFAS concentrations based on behavioral characteristics, physiology, and sociodemographic factors from medical records and questionnaires administered during prenatal visits.

The aim of *Chapter* 4 was to identify predictors of child serum PFAS concentrations at age three to six years in TESIE child participants. At home visits with participants, we collected data on child, maternal, and housing characteristics via questionnaire, and also collected dust, hand wipes, and child serum samples. Additionally, we obtained maternal serum samples from the NEST study. Serum and environmental samples were analyzed for PFAS, and were used along with questionnaire data to characterize environmental, demographic, and behavioral predictors of PFAS exposure in children. We adjusted for potential confounding variables, including child sex, breastfeeding, child body mass index, maternal parity at birth, and maternal education at the time the child was sampled. A subset of TESIE children were also asked to wear silicone wristbands for 7 days (n=26) and/or have a sorbent-impregnated passive air sampler placed in their home for 21 days (n=17) to further characterize predictors of PFAS serum concentrations.

Chapter 5 summarizes the findings from Chapters 2–4, and lists the limitations of our studies, the public health implications of our results, and discusses potential directions for future studies.

CHAPTER TWO: Exposure of nail salon workers to phthalates, di(2-ethylhexyl) terephthalate, and organophosphate esters: A pilot study

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Abstract

Relatively little is known about exposure of nail technicians to semi-volatile organic compounds (SVOCs) in nail salons. We collected pre- and post-shift urine samples and silicone wrist bands (SWBs) worn on lapels and wrists from 10 female nail technicians in the Boston area in 2016–17. We analyzed samples for phthalates, phthalate alternatives, and organophosphate esters (OPEs) or their metabolites. Post-shift urine concentrations were generally higher than pre-shift for SVOC metabolites; the greatest change was for a metabolite of the phthalate alternative di(2-ethylhexyl) terephthalate (DEHTP): mono(2-ethyl-5-carboxypentyl) terephthalate (MECPTP) more than tripled from 11.7 to 36.6 μg/g creatinine. DEHTP biomarkers were higher in our study participants' post-shift urine compared to 2015–2016 National Health and Nutrition Examination Survey females. Urinary MECPTP and another DEHTP metabolite were moderately correlated (r=0.37–0.60) with DEHTP on the SWBs, suggesting occupation as a source of exposure. Our results suggest that nail technicians are occupationally exposed to certain phthalates, phthalate alternatives, and OPEs, with metabolites of DEHTP showing the largest increase across a work day. The detection of several of these SVOCs on SWBs suggests that they can be used as a tool for examining potential occupational exposures to SVOCs among nail salon workers.

Introduction

Nail salon workers encounter a variety of exposures from the products they use at work, including semi-volatile organic compounds (SVOCs), which are added to personal care products, including nail polish, to increase flexibility and longevity, improve fragrance, and help nail polish adhere to fingernails (CosmeticsInfo, 2016; U.S. Food and Drug Administration, 2013). The SVOC most frequently used in nail polish in the past was dibutyl phthalate (DBP) (Young et al., 2018), which is associated with birth defects and negative developmental and reproductive system effects (ATSDR, 2001; Hauser & Calafat, 2005). Because of health concerns, DBP and other phthalates have been replaced by compounds claimed to be less harmful to human health: organophosphate esters (OPEs) such as triphenyl phosphate (TPHP), terephthalates such as di(2-ethylhexyl) terephthalate (DEHTP), or other phthalate alternatives such as 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) (Mendelsohn et al., 2016; Silva et al., 2017; Young et al., 2018). However, choosing safer products may be challenging as labels may not list all ingredients (Mendelsohn et al., 2016; Young et al., 2018).

SVOCs partition in the indoor environment between vapor, particles, and surfaces, including human skin (Little et al., 2012). Exposure occurs through inhalation, ingestion (e.g., via dust), and dermal absorption (Little et al., 2012). The latter can occur following contact with products containing SVOCs, indoor surfaces, or air-to-skin partitioning (Weschler & Nazaroff, 2008). Many SVOCs are metabolized into measurable urinary metabolites (CDC, 2019; Mendelsohn et al., 2016).

Nail salon workers are likely chronically more exposed to many SVOCs found in

nail products than the general public, however, few studies have been conducted on SVOC exposure of nail salon workers (Hines et al., 2009; Kwapniewski et al., 2008; Tran & Kannan, 2015). Hines et al. (2009) examined occupational exposure to certain phthalates, including dimethyl phthalate (DMP), DBP, di-isobutyl phthalate (DiBP), benzylbutyl phthalate (BzBP), and di(2-ethylhexyl) phthalate (DEHP), and reported that nail salon workers had significantly higher ($p<0.05$) post-work shift urinary metabolites of these chemicals than the U.S. adult population from the National Health and Nutrition Examination Survey (NHANES). Kwapniewski et al. (2008) examined pre- versus post-shift DBP exposure among manicurists and found significantly higher ($p<0.05$) urinary metabolites of DBP in post-shift urine samples compared to pre-shift samples with glove use mitigating this effect. Tran and Kannan (2015) analyzed air samples for DMP, DEP, DiBP, DBP, BzBP, and DEHP from various indoor environments, and found that hair and nail salons had the highest total median concentrations of phthalates, an order of magnitude greater than the other indoor environments tested.

We are not aware of any research on nail technician exposures to newer phthalate alternative compounds such as DEHTP and TPHP. We therefore conducted a pilot study using urinary biomarkers to characterize pre- versus post-shift exposure to a wide range of SVOCs among nail salon workers in the Greater Boston Area. Silicone wristbands (SWBs) can be used to estimate SVOC exposure, and may function partly as personal passive air samplers, and also sample particulates and surface films (Hammel et al., 2016); to our knowledge, SWBs have not been previously used with nail salon technicians. A secondary goal of this study was to determine whether SWBs can be used

as an exposure assessment tool to measure SVOCs encountered during a single work shift among nail salon workers.

Materials and Methods

This study was approved by IRBs at Harvard T.H. Chan School of Public Health and Boston University School of Public Health. All participants provided informed consent in their native language prior to enrollment. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subject research.

Study population

For this pilot study, we recruited and enrolled 10 nail salon technicians from seven nail salons in the Greater Boston, Massachusetts area as previously described (Ceballos et al., 2019). Eligible nail salon workers were non-smoking females greater than 18 years of age employed full time (≥35 hours per week) in nail salons primarily offering nail salon services. Participants were compensated for their time.

We assessed exposure of nail salon workers to SVOCs—focusing on exposure to phthalates, phthalate alternatives (e.g., DINCH, DEHTP), and organophosphate esters (OPEs)—over the course of one work shift between November 2016 and June 2017 (Table 2.1 shows analytes and abbreviations). Upon enrollment, we scheduled a sampling visit for a shift where the participant had worked the previous day. We employed a Vietnamese translator during sampling visits when necessary. Prior to our study visit, we

asked participants not to apply nail polish to themselves within 72 hours before sampling. We collected pre- and post-shift spot urine samples on site, and asked participants to wear a SWB on their wrist and pinned to their lapel. Due to one participant opting not to wear one of the SWBs, and misplacement of another, we collected nine each of SWBs pinned to lapels and worn on wrists. At the end of the work shift, we administered a questionnaire including both work-related and non-work-related questions on factors that potentially contribute to exposure.

Urine Sampling

Participants provided spot urine samples (~30mL) in sterile polypropylene containers using nitrile gloves to prevent contamination. Samples were stored on ice and transported to the Beth Israel Deaconess Medical Center (BIDMC) laboratory. Samples were stored at -20º C, thawed and aliquoted into 3mL polypropylene microvials and stored at -80º C until shipped for analysis.

Urine samples were analyzed at the Division of Laboratory Services at the National Center for Environmental Health, CDC (Atlanta, GA) for creatinine and metabolites of SVOCs as previously described (Jayatilaka et al., 2017; Silva et al., 2007, 2017). Briefly, urinary conjugates of target analytes were first hydrolyzed by enzymatic hydrolysis. We then extracted the deconjugated urinary metabolites using solid phase extraction, separated the target analytes from each other and other compounds present in urine using high-performance liquid chromatography, and quantified the target biomarkers using isotope-dilution tandem mass spectrometry. During analysis, we

included a duplicate urine aliquot from two separate participant samples for each SVOC compound for quality assurance/quality control. The relative percent difference between samples for SVOC compounds included in our analyses above the limit of detection (LOD) (Table 2.1) ranged from 0% – 13.1% for phthalates, 0.4% – 5.7% for phthalate alternatives, and 0.8 – 30.4% for OPEs.

Passive Air Sampling

SWBs were prepared for sampling as previously described (Hammel et al., 2016). Briefly, researchers purchased commercially available SWBs (www.24hourwristbands.com), solvent-cleaned and dried them in a fume hood, wrapped them in aluminum foil, and placed them in pre-cleaned amber glass jars until use. We collected four field blank SWBs during the course of the study, which were transported to randomly selected study nail salons, removed from the amber jars and aluminum foil, rewrapped immediately, and placed on ice. At the end of each participant's work shift, we collected and wrapped the SWBs in aluminum foil and placed them in amber jars in coolers on ice, and transported them to BIDMC laboratory for storage at -20º C until shipped for analysis. All SWBs were handled with nitrile gloves.

SWBs were analyzed at Duke University as previously described (Anderson et al., 2017; Hammel et al., 2016). Briefly, SWBs were weighed but not washed before analysis, spiked with internal standards dTDCPP and $^{13}C_{12}$ TPHP, extracted, concentrated and analyzed by gas chromatography mass spectrometry (GC/MS). Recoveries of dTDCPP and $^{13}C_{12}$ TPHP averaged 93.3% and 68.9%, respectively, for all samples. Since

the field blanks account for residual background levels that may be present on all SWBs, the LOD (Table 2.1) was calculated as three times the standard deviation of the levels measured in the field blanks. SVOC concentrations in SWBs were blank corrected using the average concentrations measured in the field blanks. Results were expressed as ng/g SWB.

Since participants had different work-shift lengths, and thus SWBs were worn for different durations, we also controlled for work shift length in our analyses (Table S2.2 and S3). However, we do not know whether the chemicals are in the linear or saturation phase of uptake on the SWBs during the nail technicians' work shifts, as to our knowledge a calibration study of the uptake of these chemicals in SWBs has not been published. Because of this, and the fact that these work shift-duration-adjusted data were almost perfectly correlated with the unadjusted data (Table S2.1), we focus on the unadjusted data in our results section.

Statistical Analysis

Where instrumental readings were unavailable, urine and SWB non-detected data points were imputed using NDExpo's regression on order statistics (ROS) application: a robust method to handle non-detects, described by Helsel[18]. We conducted statistical analyses for compounds detected in at least 50% of samples. We used the Shapiro-Wilk test to examine whether SVOC concentrations were normally distributed; as concentrations were approximately log-normally distributed, we log-transformed data, and report geometric means (GM), geometric standard deviations (GSD), medians, and

ranges. We used paired t-tests to compare: 1) SVOC levels on SWBs worn on the lapels versus wrists and 2) pre- and post-shift creatinine-corrected SVOC urinary metabolite concentrations. Post-shift urine concentrations of MECPTP, however, were not normally or log-normally distributed, and we used the nonparametric Wilcoxon Rank Sum test to compare the pre- and post-shift samples. We computed Spearman correlations between parent SVOCs in SWBs (a measure of external exposure during the shift) and their metabolites in urine, using the difference between post- and pre-shift creatinine-corrected concentration (an estimate of total exposure during the work shift). Statistical significance was set at $p<0.05$. We compared nail technician creatinine-corrected urinary SVOC metabolites to those found in the general U.S. female population aged 3 and older in the NHANES 2015–2016 presented in the National Report on Human Exposure to Environmental Chemicals updated tables, the first time such data were available for DEHTP; the exception was for OPE metabolites for which we used NHANES 2013–2014 data of U.S. females aged 6 and older (CDC, 2019; Silva et al., 2019). We performed all statistical analyses using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC).

Results

Participant characteristics are presented in Table 2.2. A detailed description of personal protective equipment utilized by participants was described previously (Ceballos et al., 2019).

SVOCs in Urine

Descriptive statistics of the SVOC metabolites detected in participant urine, along with the post-/pre- shift change in SVOC concentrations are listed in Table 2.3. While the majority of post-shift creatinine-corrected GM urinary SVOC metabolite concentrations were similar or higher than pre-shift urinary concentrations, none reached statistical significance. Despite this, the post-shift GM concentration was more than triple that of the pre-shift samples for MECPTP. There was a general trend for higher urinary metabolite concentrations in post-shift urine samples among many but not all participants (Figure S2.1, supplemental material).

Table 2.3 also presents a comparison of our results with females in NHANES. Most SVOC metabolites were similar or higher in the U.S. female population than in our study population's post-shift urine samples, however metabolites of DEHTP (MECPTP and MEHHTP) were higher in post-shift urine samples from our study participants than in NHANES females.

SVOCs in Air

A few of the participants' SWB concentration results were estimated above the highest point on the calibration curve for individual SVOCs, including one each with high levels of DBP, DEHP, and DEHTP, and one with high levels of both DiNP and DEHTP; these values were included in the overall analyses. Descriptive statistics of the SVOC concentrations detected in lapel and wrist SWBs, along with the differences in SVOC concentrations and correlations between lapel/wrist are listed in Table 2.4. With the exception of TCIPP and TDCIPP, SVOC levels in lapel SWBs were higher compared with those worn on participants' wrists; however, none of these differences reached statistical significance (Table 2.4, Figure S2.2). Correlations between concentrations of SVOCs detected in lapel and wrist SWBs varied; only the phthalate alternative DEHA reached statistical significance ($r=0.81$, $p<0.05$).

Air vs. Urine SVOCs

The correlations between differences between pre- and post-shift urinary SVOC metabolites and their parent compounds detected in SWBs are shown in Table 2.5. For DEHP, although not statistically significant, the difference in post- compared to pre-shift urinary concentrations was more correlated with SWBs worn on the lapel than on the wrist. The difference between pre- and post-shift shift urinary metabolites of DEHTP (MECPTP, MEHHTP) were moderately correlated with DEHTP on lapel SWBs and wrist SWBs.

Discussion

To our knowledge, our pilot study is the first to characterize nail salon worker exposure to phthalates, phthalate alternatives and organophosphate esters, using both biomonitoring and silicone wristbands (SWBs), a relatively novel tool. This study provides evidence of exposure to many of these compounds and demonstrates the usefulness of SWBs.

Our most striking finding was evidence suggesting nail salon workers are occupationally exposed to the phthalate alternative DEHTP, with post-shift urinary concentrations of a DEHTP metabolite (MECPTP) more than triple the concentrations of pre-shift concentrations. This change was moderately correlated with DEHTP levels on SWBs, suggesting an occupational exposure source rather than primarily other exposure sources such as diet that are unlikely to be picked up by SWBs. Increases of MECPTP during the day have previously been observed in general populations, however these increases were generally lower than what we observed for our pre- to post-shift change (e.g. 1.6 times from NHANES compared to 3.1 times in our study, respectively), and further research is necessary to better understand this trend (Silva et al., 2019).

Concentrations of DEHTP metabolites (MECPTP and MEHHTP) in nail technician post-shift urine samples were also higher than what was observed in NHANES. This difference may be underestimated, as there is a significant downward trend in GM concentrations of MECPTP and MEHHTP (along with some other SVOCs) in NHANES with increasing age, and the NHANES female population includes children 18 and younger (Silva et al., 2019), while our study population only enrolled adult

females over age 18. Although DEHTP is used as a replacement for the phthalate DEHP, literature on DEHTP exposure is relatively sparse, but suggests increasing exposure in the U.S. and Europe (Nagorka et al., 2011; Silva et al., 2017, 2019). Due to the lack of studies examining the health consequences associated with DEHTP exposure in humans to date, we do not fully understand whether increasing human exposure or long-term exposure to low levels of it will negatively impact human health. Metabolites of DEHTP are generally higher in females than in males (Silva et al., 2019), suggesting exposure via personal care products or a similar source linked to behavioral differences between males and females. Interestingly, DEHTP is not a traditional SVOC in nail polish and we do not know the source of the DEHTP in nail salons. Although DEHTP may be present in some nail polishes, we found no evidence for this in a recent nail product study (Young et al., 2018). DEHTP is likely present in other personal care products or materials used in nail salons, such as lotions, waxes, or skin scrubbing exfoliants.

Previous studies have found higher concentrations of certain phthalates (e.g., DEP and DBP) in nail salons compared to other indoor environments (Tran & Kannan, 2015), and higher concentrations of certain SVOC urinary metabolites from nail salon workers compared to the U.S. general population (e.g. MBP and MEHP) (Hines et al., 2009). While there was an upward trend for SVOC urinary metabolites from pre- to post-shift in our study, none reached statistical significance, perhaps due to small sample size. Exposure to many phthalates, phthalate alternatives, and OPEs is ubiquitous in the U.S. due to their common usage in personal care and other consumer products (CDC, 2019; Silva et al., 2007, 2019). Some SVOCs are also present in food or food packaging, a

potential explanation for the lack of correlation between urine and SWBs for some compounds as SWBs do not capture dietary exposure sources.

Post-shift urinary concentrations from our study participants were generally lower than concentrations from U.S. females from NHANES, with the exception of urinary metabolites of DEHTP, TCEP, and TPHP (CDC, 2019; Silva et al., 2019). As use of some of the more toxic phthalates such as DBP and DEHP have been reduced and replaced in the U.S. over time with alternatives such as DEHTP due to potential health concerns, concentrations of urinary metabolites such as MBP and MEHP have decreased, while metabolites from phthalate alternatives such as MECPTP and MEHHTP have increased (Koch et al., 2017; Silva et al., 2019; Zota et al., 2014). Factors that may partly explain the lower urinary metabolite concentrations from our participants include that NHANES includes females under 18, which our study excludes, and that the NHANES data were largely from an earlier time period (2013–2014 and 2015–2016) than our study (2016–2017).

Our pilot study demonstrated relatively high detection frequencies of a number of SVOCs on SWBs after having been worn by nail salon workers for only one shift (e.g., 6 to 11 hours). Little is known about the kinetics of uptake of SVOCs by SWBs and we are aware of only one previously published occupational exposure study (of polycyclic aromatic hydrocarbons) (O'Connell et al., 2014). The fact that SWBs not only function as passive air monitors, but can pick up material from contact with surfaces and skin was evident in SWBs utilized by our study participants, as many appeared dusty and/or had debris on the surface upon collection at the end of the work shift. Interestingly, TPHP

concentrations on lapel and wrist SWBs were not correlated, perhaps suggesting that different exposure sources of these compounds are encountered based on contact with skin and surfaces (more likely with wrist SWBs) versus those in the air (more likely with lapel SWBs). More research is needed to understand this difference and its implications for exposure routes. The results for DEHTP also add to the small body of literature validating the use of SWBs with biomonitoring results (Hammel et al., 2016, 2018; O'Connell et al., 2014).

The replacement of phthalates with alternatives, and the corresponding increased exposure to the latter, is of concern since often we do not fully understand the toxicity of the alternatives (Lakind & Birnbaum, 2010). For example, DEHTP is thought of as a safer alternative to DEHP, a known male reproductive toxicant, since it has not been shown to cause reproductive toxicity (Gray et al., 2000). However, exposure to DEHTP may be associated with other health concerns. A dietary study of DEHTP fed to F-344 rats over 104 weeks found reduced weight gain and exacerbated geriatric retinal degeneration with chronic, high dietary exposure (6,000 or 12,000 ppm) (Deyo, 2008). TPHP, another replacement chemical found in nail polish, has recently been identified as an endocrine disrupter that may be negatively associated with thyroid function and reproductive health (Carignan et al., 2017; Meeker & Stapleton, 2010; Preston et al., 2017). Future, larger biomonitoring studies of nail salon workers will help to verify and identify replacement chemicals of particular concern from changes in formulations to products used in nail salons.

Our study has a number of limitations, particularly the small sample size that

limited statistical power. We used the difference between post- and pre-shift metabolite concentrations in urine as a measure of exposure during the work day, but while this approach has several advantages (e.g., assessing exposure across inhalation, dermal and other routes), it also has disadvantages. The appearance of metabolites in urine has a time lag due to pharmacokinetics (e.g., absorption, metabolism rate). As we were not able to collect urine later in the day after the shift (or the following first morning void), we may have missed some exposure. The human half-lives of many of these compounds is not known, but believed to be on the order of hours to days. Thus, if we collected participants' urine for a longer time period (e.g. 24 or 48 hours after their work shift) we would likely obtain a better understanding of these occupational exposures. As we only sampled participants on days when they had worked the previous day, pre-shift urine samples may partly reflect previous occupational exposure for the relatively more persistent SVOCs. A potential explanation of why we generally saw higher concentrations on SWBs pinned to participants' lapels compared to the ones worn on their wrists is that those on the wrist may have been covered up by participants' sleeves, thus in future studies it would be beneficial to ensure that all SWBs are exposed to salon air for the duration of participants' work shifts. Additionally, asking participants to wear SWBs during working hours on multiple work days during a given work week may have captured more information on occupational SVOC exposures. We did not attempt to assess exposure at home, while commuting, or via diet.

Strengths of our study of nail salon workers include the use of biomonitoring, demonstration of the use of SWBs, collection of these samples in a sometimes difficult to

reach population, and analysis for a wide spectrum of SVOCs. An additional strength is the paired use of biomonitoring and SWB data, which suggested that the increase of urinary DEHTP metabolites was due to occupational exposure rather than other sources such as diet.

Higher concentrations of SVOC urinary metabolites detected in post-shift urine samples compared to pre-shift samples and the presence of parent compounds detected on SWBs worn during the work shift indicate that nail salon workers are occupationally exposed to SVOCs. The higher concentrations of DEHTP metabolites in our study population compared to the U.S. female population from the NHANES study, and the more than tripling of pre- to post-shift concentrations of MECPTP measured in urine suggests that nail salon workers are exposed to DEHTP during the work day. Finally, the detection of several phthalates, phthalate alternatives, and OPEs on SWBs worn during the work shift indicates that SWBs can be used as an exposure assessment tool for nail salon workers for future studies. Future, larger biomonitoring studies with more statistical power, and a longer sampling timeframe would help further clarify which SVOCs nail technicians are exposed to at work. Finally, it would be useful to compare the SVOCs detected on SWBs to active air samples collected during the work day to validate the effectiveness of SWBs as an occupational exposure assessment tool in nail salons.

Table 2.1. Parent Compounds and Metabolites[†] Examined in Silicone WristBands (SWBs) and Urine Among Nail Salon Workers (2016–2017) in the Greater Boston Area

Parent Compound in SWB			Urinary Metabolite		
Name	**Acronym**	**LOD[£]**	**Name**	**Acronym**	**LOD[¥]**
Phthalates					
Butylbenzyl phthalate	BBzP	6.7	Monobenzyl phthalate	MBzP	0.3
Di-n-butyl phthalate	DBP	1,120	Mono-hydroxybutyl phthalate	MHBP	0.4
			Mono-n-butyl phthalate	MBP	0.4
Di-iso-butyl phthalate	DiBP	17.6	Mono-isobutyl phthalate	MiBP	0.8
			Mono-hydroxy-isobutyl phthalate	MHiBP	0.4
Diethyl phthalate	DEP	31.5	Monoethyl phthalate	MEP	1.2
Dimethyl phthalate	DMP	1.8	Not measured		
Di(2-ethylhexyl) phthalate	DEHP	9.3	Mono-2-ethylhexyl phthalate	MEHP	0.8
			Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP	0.4
			Mono-2-ethyl-5-oxohexyl phthalate	MEOHP	0.2
			Mono-2-ethyl-5-carboxypentyl phthalate	MECPP	0.4
Di-isodecyl phthalate[#]	DiDP[#]	#	Mono carboxyisononyl phthalate	MCNP	0.2
Di-isononyl phthalate	DiNP	17.2	Mono-isononyl phthalate	MiNP	0.9
			Mono carboxyisooctyl phthalate	MCOP	0.3
			Monooxononyl phthalate	MONP	0.4
Di-n-octyl phthalate[#]	DOP[#]	#	Mono-3-carboxypropyl phthalate	MCPP	0.4
Phthalate Alternatives					
1,2-Cyclohexane dicarboxylic acid, diisononyl ester[#]	DINCH[#]	#	Cyclohexane-1 2-dicarboxylic acid monohydroxy isononyl ester	MHiNCH	0.4
			Cyclohexane-1 2-dicarboxylic acid monocarboxyisooctyl ester	MCOCH	0.5
Diethylhexyl adipate	DEHA	1.8	Not measured		
Trioctyltrimellitate	TOTM	0.04	Not measured		
Di(2-ethylhexyl) terephthalate	DEHTP	1.3	Mono-2-ethyl-5-carboxypentyl terephthalate	MECPTP	0.2
			Mono-2-ethyl-5-hydrohexyl terephthalate	MEHHTP	0.4

†There may be additional parent compounds and metabolites; # Not examined in SWB; [£]Units are ng/g; [¥]Units are µg/g

Table 2.1 (Continued). Parent Compounds and Metabolites† Examined in Silicone Wrist Bands (SWBs) and Urine Among Nail Salon Workers (2016–2017) in the Greater Boston Area

Parent Compound in SWB			Urinary Metabolite		
Name	**Acronym**	**LOD£**	**Name**	**Acronym**	**LOD¥**
Organophosphate Esters					
Tris(1-chloro-2-propyl) phosphate	TCIPP	6.7	Bis(1-chloro-2-propyl) phosphate	MBzP	0.3
Tris(2-chloroethyl) phosphate	TCEP	30.6	Bis-2-chloroethyl phosphate	MHBP	0.4
Tris(1,3-dichloro-2-propyl) phosphate	TDCIPP	1.2	Bis(1,3-dichloro-2-propyl) phosphate	MBP	0.4
Tri-n-butyl phosphate	TBuP	#	Dibutyl phosphate	MiBP	0.8
Triphenyl phosphate	TPHP	6.1	Diphenyl phosphate	MHiBP	0.4
Brominated Flame Retardant				MEP	1.2
2-ethylhexyl-2,3,4,5-tetrabromobenzoate#	EH-TBB#	#	2,3,4,5-tetrabromobenzoic acid		

†There may be additional parent compounds and metabolites; # Not examined in SWB; £Units are ng/g; ¥Units are µg/g

Table 2.2. Characteristics of 10 Nail Salon Participants, Greater Boston Area (2016–2017)

Participant Characteristics	N Participants (n=10)	Median	Range
Current Age		45	21 – 64[†]
Country of Origin (Primary Language Spoken)			
USA (English)	4		
Vietnam (Vietnamese)	6		
Occupational Title			
Nail Technician	8		
Nail Salon Owner	2		
Employment History			
Full-Time in Nail Salon		10	<1 – 23[†]
Part-Time in Nail Salon		6	<1 – 33[†]
Hours worked			
Per Week		40	20 – 50[£]
Day of Sampling		9	6 – 11[£]
Number of Procedures			
Regular Manicure	8		1 – 5[¥]
Acrylic Manicure	2		3 – 9[¥]
Gel Manicure	3		1 – 4[¥]
Refill	1		1[¥]
Pedicure	8		1 – 3[¥]

[†]Years
[£]Hours
[¥]Number of procedures

Table 2.3. Descriptive Statistics for Creatinine-Corrected SVOC metabolites examined in Pre- and Post-Shift Urine Samples from Nail Salon Workers in the Greater Boston Area (2016–2017)

	Pre-shift urine Concentrations (µg/g) (n=10)					Post-shift urine Concentrations (µg/g) (n=10)					[Post/Pre Shift]	NHANES[#]
Biomarker	% >LOD	GM	GSD	Median	Range	% >LOD	GM	GSD	Median	Range	Difference	GM
Phthalates												
MBzP	70	1.6	2.7	1.2	<0.3 – 14.0	70	1.9	2.7	1.9	<0.3 – 12.2	0.3	5.2
MHBP	50	0.79	2.0	0.7	<0.4 – 2.5	40	N/A	N/A	<0.4	<0.4 – 3.0	N/A	1.13
MBP	90	7.2	2.0	7.6	<0.4 – 24.0	90	8.7	2.5	9.1	<0.4 – 50.3	1.5	11.7
MiBP	90	4.5	1.7	4.4	<0.8 – 12.3	70	5.1	1.8	5.8	<0.8 – 11.4	0.6	9.75
MHiBP	80	2.1	1.3	1.9	<0.4 – 3.6	60	1.8	1.6	1.8	<0.4 – 4.8	-0.3	3.27
MEP	100	27.9	2.0	22.0	11.2 – 86.7	100	37.9	3.1	30.7	12.8 – 515	10.0	43.6
MEHP	50	1.2	2.8	1.2	<0.8 – 9.8	40	N/A	N/A	<0.8	<0.8 – 4.4	N/A	N/A
MEHHP	90	4.0	2.4	3.1	<0.4 – 15.9	90	5.1	2.4	7.4	<0.4 – 15.3	1.1	6.29
MEOHP	90	2.6	2.5	2.3	<0.2 – 11.1	90	3.3	2.7	3.8	<0.2 – 11.2	0.7	4.08
MECPP	100	7.4	2.3	6.2	3.0 – 39.1	100	8.7	2.0	9.4	3.7 – 28.9	1.3	9.98
MCNP	70	0.9	3.0	0.7	<0.2 – 6.2	70	1.2	2.6	0.9	<0.2 – 4.8	0.3	1.90
MiNP	10	N/A	N/A	<0.9	<0.9 – 4.8	10	N/A	N/A	<0.9	<0.9 – 4.9	N/A	N/A
MCOP	90	2.9	2.0	3.4	<0.3 – 7.4	90	4.2	2.2	4.4	<0.3 – 17.2	1.3	9.06
MONP	50	0.9	2.1	0.9	<0.4 – 2.7	60	1.4	2.7	1.1	<0.4 – 6.7	0.5	2.32
MCPP	30	N/A	N/A	<0.4	<0.4 – 2.2	30	N/A	N/A	<0.4	<0.4 – 2.4	N/A	1.24

GM = Geometric Mean; GSD = Geometric Standard Deviation; LOD = Limit of Detection; N/A Not calculated: proportion of results below limit of detection was too high to provide a valid result

[#]NHANES phthalate and phthalate alternative data collected in 2015–2016, organophosphate esters and brominated flame retardant data collected in 2013–2014

Table 2.3 (Continued). Descriptive Statistics for Creatinine-Corrected SVOC metabolites examined in Pre- and Post-Shift Urine Samples from Nail Salon Workers in the Greater Boston Area (2016–2017)

	Pre-shift urine Concentrations (µg/g) (n=10)					Post-shift urine Concentrations (µg/g) (n=10)					[Post/Pre Shift]	NHANES[#]
Biomarker	% >LOD	GM	GSD	Median	Range	% >LOD	GM	GSD	Median	Range	Difference	GM
Phthalate Alternatives												
MHiNCH	20	N/A	N/A	<0.4	<0.4 – 2.3	20	N/A	N/A	<0.4	<0.4 – 2.0	N/A	N/A
MCOCH	20	N/A	N/A	<0.5	<0.5 – 2.7	20	N/A	N/A	<0.5	<0.5 – 2.7	N/A	N/A
MECPTP	100	11.7	3.3	17.4	1.0 – 50.1	100	36.6	4.3	26.9	11.5 – 1,286	24.9	22.5
MEHHTP	100	6.1	2.1	6.4	1.5 – 22.7	100	9.5	3.4	7.4	2.1 - 166	3.4	5.45
Organophosphate Esters												
BCIPP	90	0.5	2.3	0.6	<0.1 – 1.6	90	0.7	2.3	0.8	<0.1 – 2.4	0.2	N/A
BCEP	60	0.6	4.5	0.5	<0.1 – 4.3	70	0.6	2.5	0.5	<0.1 – 2.0	0.0	0.476
BDCIPP	80	0.8	2.2	0.8	<0.1 – 2.4	90	0.8	2.0	0.7	<0.1 – 2.4	0.0	0.993
DBuP	50	0.4	4.4	0.3	<0.1 – 7.6	20	N/A	N/A	<0.1	<0.1 – 9.1	N/A	0.227
DPHP	90	1.1	2.9	0.8	<0.1 – 6.5	90	1.3	2.1	1.3	<0.1 – 4.1	0.2	1.13
Brominated Flame Retardant												
TBBA	10	N/A	N/A	<0.05	<0.05 – 0.3	0	N/A	N/A	<0.05	<0.05	N/A	N/A

GM = Geometric Mean; GSD = Geometric Standard Deviation; LOD = Limit of Detection; N/A Not calculated: proportion of results below limit of detection was too high to provide a valid result

[#]NHANES phthalate and phthalate alternative data collected in 2015–2016, organophosphate esters and brominated flame retardant data collected in 2013–2014

Table 2.4. Descriptive Statistics for SVOCs Examined in Silicone Wristbands (SWBs) Worn During a Work Shift by Nail Salon Workers in the Greater Boston Area (2016–2017)

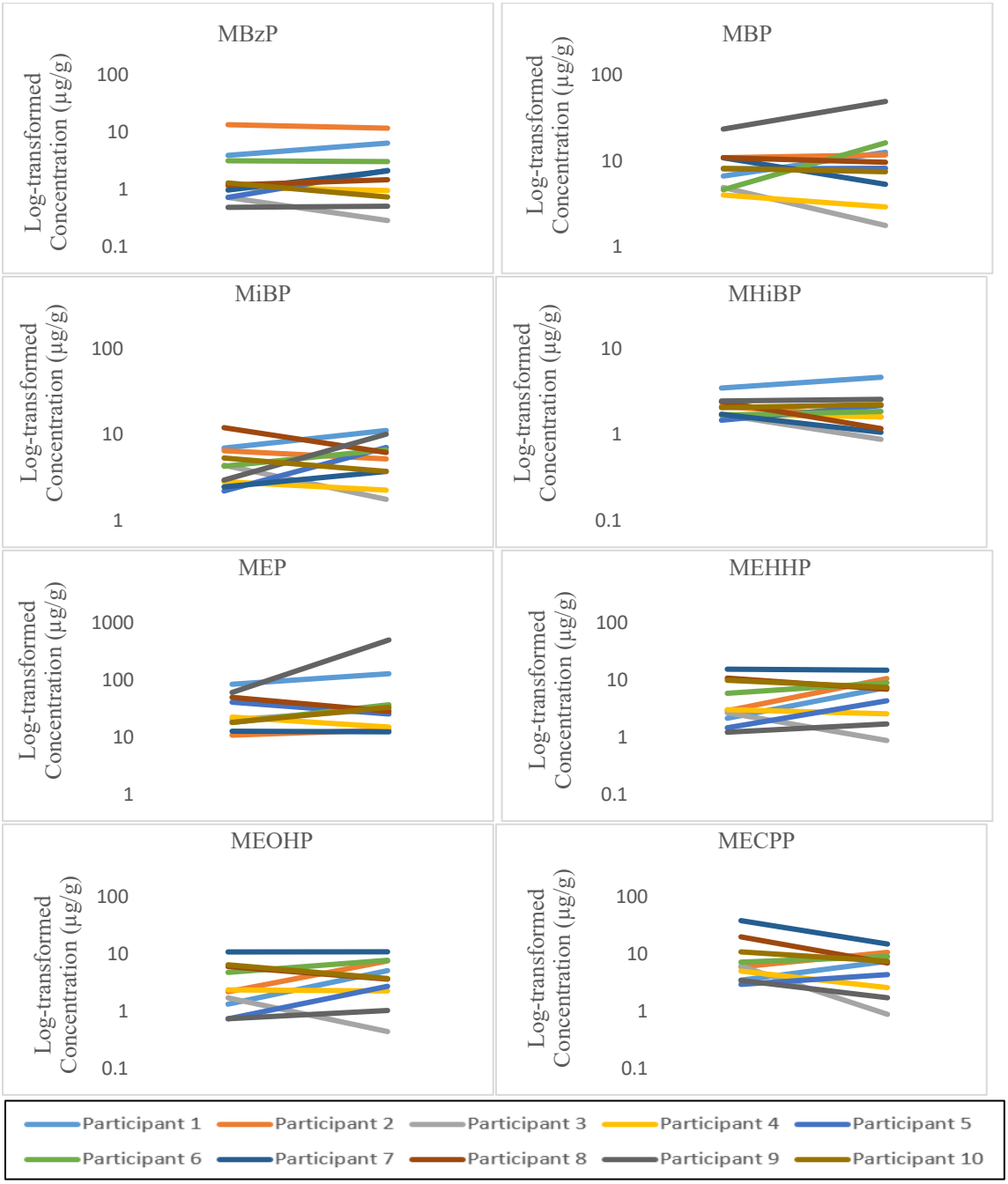
	Lapel SWB Concentrations (ng/g) (n=9)					Wrist SWB Concentrations (ng/g) (n=9)					[Lapel/Wrist]	Wrist/Lapel
Compound	% >LOD	GM	GSD	Median	Range	% >LOD	GM	GSD	Median	Range	Ratio	Correlation[#]
Phthalates												
BBzP	44.4	N/A	N/A	<6.7	<6.7 – 45.7	22.2	N/A	N/A	<6.7	<6.7 – 22.3	N/A	N/A
DBP	0.0	N/A	N/A	<1,120	All <1,120	11.1	N/A	N/A	<1,120	<1,120 – 1,697	N/A	N/A
DiBP	33.3	N/A	N/A	<17.6	<17.6 – 56.1	33.3	N/A	N/A	<17.6	<17.6 – 143	N/A	N/A
DEP	22.2	N/A	N/A	<31.5	<31.5 – 576	22.2	N/A	N/A	<31.5	<31.5 – 967	N/A	N/A
DMP	33.3	N/A	N/A	<1.8	<1.8 – 3.8	33.3	N/A	N/A	<1.8	<1.8 – 5.8	N/A	N/A
DEHP	100	195	4.3	251	27.0 – 3,572	55.6	29.6	22.5	42.4	<9.3 – 2,004	6.6	0.17
DiNP	88.9	182	4.1	200	<17.2 – 1,339	55.6	32.7	31.0	50.7	<17.2 – 4,719	5.6	-0.21
Phthalate Alternatives												
DEHA	77.8	4.5	18.9	5.0	<1.8 – 1,364	55.6	1.8	25.6	2.3	<1.8 – 260	2.5	**0.81***
TOTM	100	2.8	6.5	2.2	0.17 – 70.5	55.6	0.41	89.9	1.4	<0.04 – 493	6.8	0.67
DEHTP	100	105	4.3	81.9	11.1 – 1,636	77.8	21.8	29.1	20.8	<1.3 – 5,817	4.8	0.21
Organophosphate Esters												
TCIPP	77.8	29.2	3.5	40.9	<6.7 – 161	88.9	39.7	4.3	39.5	<6.7 – 199	0.73	0.48
TCEP	11.1	N/A	N/A	<30.6	<30.6 – 56.2	0.0	N/A	N/A	<30.6	All <30.6	N/A	N/A
TDCIPP	77.8	3.5	4.1	3.3	<1.2 – 27.4	88.9	8.8	3.8	15.7	<1.2 – 35.0	0.39	0.14
TPHP	88.9	153	4.3	257	<6.1 – 1,006	100	95.8	3.4	132	11.8 – 368	1.6	0.07

GM = Geometric Mean; GSD = Geometric Standard Deviation; LOD = Limit of Detection; [#]Spearman Correlation
N/A Not calculated: proportion of results below method detection limit was too high to provide a valid result
*Spearman correlation statistically significant ($p<0.05$)
Note: Not all compounds listed in Table 2.1 were measured in SWBs

Table 2.5. Correlations between SVOCs in Silicone Wristbands (SWBs) and Creatinine-Corrected Urinary Metabolites in Post-Shift minus Pre-shift Urine Samples from Nail Salon Workers in the Greater Boston Area (2016–2017)

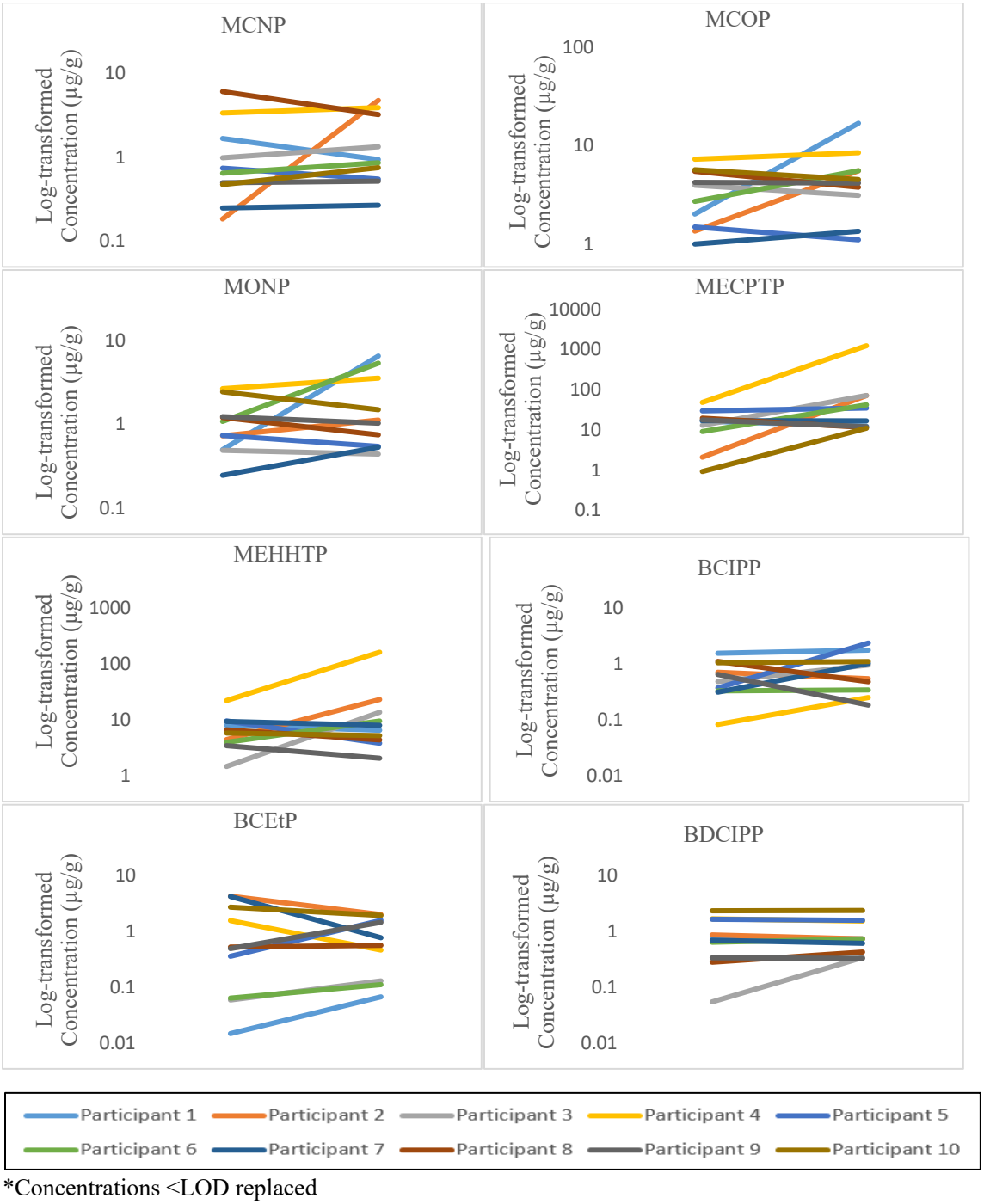
SWB Parent Compound	Urinary Metabolite	Spearman correlation coefficients for Difference of post-shift and pre-shift urine/ Lapel SWB	Wrist SWB
Phthalates			
DEHP	**MEHP**	0.18	0.15
	MEHHP	0.28	0.18
	MEOHP	0.17	0.07
	MECPP	0.63	0.22
DiNP	**MCOP**	0.27	0.45
	MONP	-0.08	0.30
Phthalate Alternatives			
DEHTP	**MECPTP**	0.60	0.37
	MEHHTP	0.38	0.57
Organophosphate Esters			
TCIPP	**BCIPP**	-0.40	-0.30
TDCIPP	**BDCIPP**	-0.10	0.20
TPHP	**DPHP**	0.13	0.28

Figure S2.1. Comparison of Creatinine-Corrected Pre- and Post-Shift Concentrations* of Phthalates, Phthalate Alternatives, and Organophosphate Esters (ng/g) Detected ≥50% in Individual Nail Salon Workers' Urine in the Greater Boston Area (2016–2017)



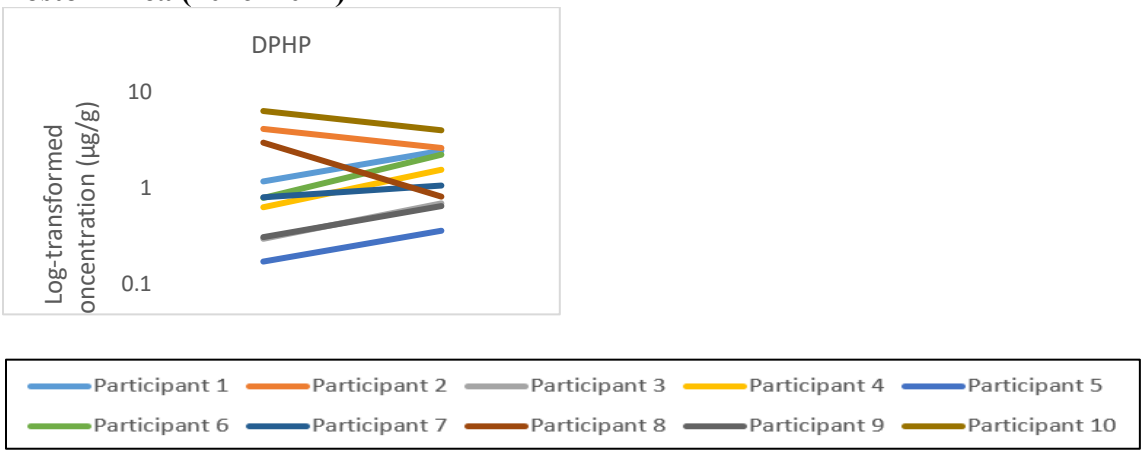
*Concentrations <LOD replaced

Figure S2.1 (Continued). Comparison of Creatinine-Corrected Pre- and Post-Shift Concentrations* of Phthalates, Phthalate Alternatives, and Organophosphate Esters (ng/g) Detected ≥50% in Individual Nail Salon Workers' Urine in the Greater Boston Area (2016–2017)



*Concentrations <LOD replaced

Figure S2.1 (Continued). Comparison of Creatinine-Corrected Pre- and Post-Shift Concentrations* of Phthalates, Phthalate Alternatives, and Organophosphate Esters (ng/g) Detected ≥50% in Individual Nail Salon Workers' Urine in the Greater Boston Area (2016–2017)



*Concentrations <LOD replaced

Figure S2.2. Concentrations of SVOCs Detected ≥50% on Silicone Wristbands Worn on the Lapel or Wrist During a Work Shift by Nail Salon Workers in the Greater Boston Area (2016–2017)

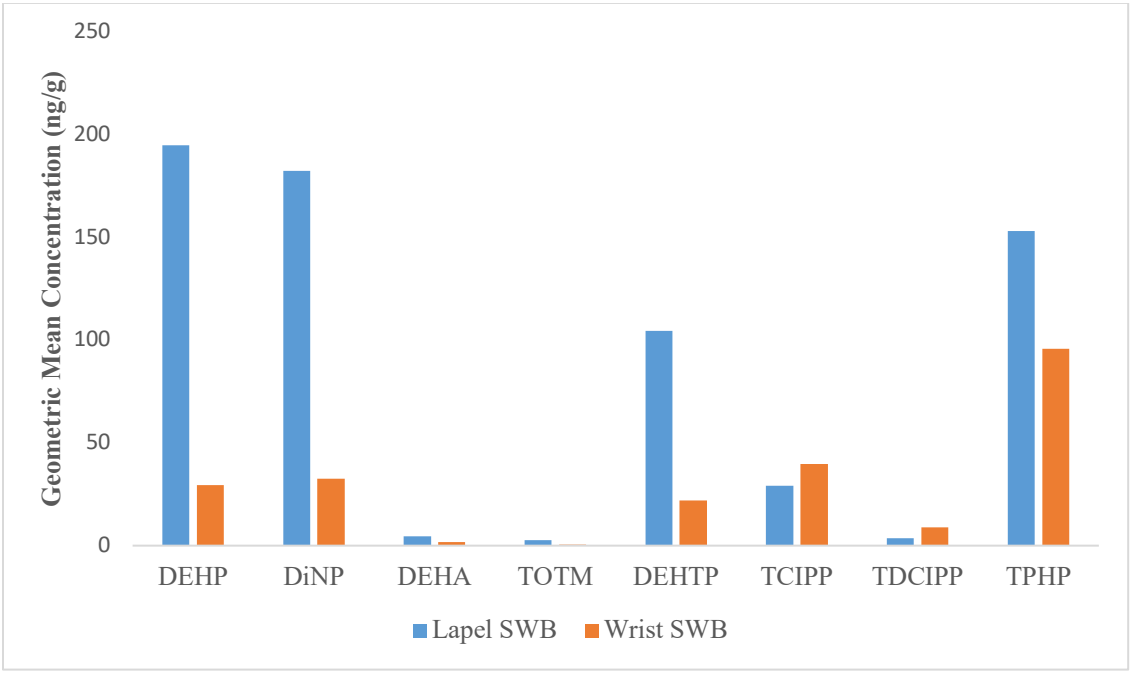


Table S2.1. Correlations between SVOCs in Silicone Wrist Bands (SWBs) measured in ng/g and SVOC concentrations measured in SWBs corrected for work shift length $(ng/g)^{-hr}$ from Nail Salon Workers in the Greater Boston Area (2016–2017)

	Spearman correlation coefficients	
SWB Parent Compound	**Lapel SWB**	**Wrist SWB**
Phthalates		
DEHP	1.0	1.0
DiNP	1.0	1.0
Phthalate Alternatives		
DEHA	1.0	1.0
TOTM	0.98	1.0
DEHTP	0.98	1.0
Organophosphate Esters		
TCIPP	1.0	1.0
TDCIPP	1.0	1.0
TPHP	0.98	1.0

Table S2.2. Descriptive Statistics for SVOCs Examined in Silicone Wrist Bands (SWBs) Worn During a Work Shift Adjusted for Work-Shift Duration by Nail Salon Workers in the Greater Boston Area (2016–2017)

	Lapel SWB Concentrations $(ng/g)^{-hr}$ (n=9)					Wrist SWB Concentrations $(ng/g)^{-hr}$ (n=9)					[Lapel/Wrist]	Wrist/ Lapel
Compound	**% >MDL**	**GM**	**GSD**	**Median**	**Range**	**% >MDL**	**GM**	**GSD**	**Median**	**Range**	**Difference**	**Corr[#]**
Phthalates												
BBzP	44.4	N/A	N/A	<MDL	<MDL – 5.1	22.2	N/A	N/A	<MDL	<MDL – 2.0	N/A	N/A
DBP	0.0	N/A	N/A	N/A	N/A	11.1	N/A	N/A	<MDL	<MDL – 179	N/A	N/A
DiBP	33.3	N/A	N/A	<MDL	<MDL – 6.2	33.3	N/A	N/A	<MDL	<MDL – 13.0	N/A	N/A
DEP	22.2	N/A	N/A	<MDL	<MDL – 52.4	22.2	N/A	N/A	<MDL	<MDL – 87.9	N/A	N/A
DMP	33.3	N/A	N/A	<MDL	<MDL – 0.43	33.3	N/A	N/A	<MDL	<MDL – 0.53	N/A	N/A
DEHP	100	21.9	4.0	25.1	4.5 – 397	55.6	3.5	19.2	4.5	<MDL – 182	6.3	0.17
DiNP	88.9	20.5	3.9	22.3	<MDL – 149	55.6	3.9	26.4	5.3	<MDL – 429	5.3	-0.21
Phthalate Alternatives												
DEHA	77.8	0.51	16.9	0.46	<MDL – 152	55.6	0.22	21.8	0.25	<MDL – 23.6	2.3	**0.81***
TOTM	100	0.31	5.9	0.29	0.03 – 7.8	55.6	0.05	76.4	0.15	<MDL – 44.8	6.2	0.64
DEHTP	100	11.8	3.9	9.0	1.9 – 182	77.8	2.6	25.7	33.7	<MDL – 529	4.5	0.21

GM = Geometric Mean; GSD = Geometric Standard Deviation; MDL = Method Detection Limit; [#]Spearman Correlation
N/A Not calculated: proportion of results below method detection limit was too high to provide a valid result
*Spearman correlation statistically significant ($p<0.05$)
Note: Not all compounds listed in Table 2.1 were measured in SWBs

Table S2.2 (Continued). Descriptive Statistics for SVOCs Examined in Silicone Wrist Bands (SWBs) Worn During a Work Shift Adjusted for Work-Shift Duration by Nail Salon Workers in the Greater Boston Area (2016–2017)

	Lapel SWB Concentrations $(ng/g)^{-hr}$ (n=9)					Wrist SWB Concentrations $(ng/g)^{-hr}$ (n=9)					[Lapel/Wrist]	Wrist/ Lapel
Compound	**% >MDL**	**GM**	**GSD**	**Median**	**Range**	**% >MDL**	**GM**	**GSD**	**Median**	**Range**	**Difference**	**Corr[#]**
Organophosphate Esters												
TCIPP	77.8	3.3	3.9	4.5	<MDL – 19.5	88.9	4.7	4.5	4.4	<MDL – 33.2	0.70	0.48
TCEP	11.1	N/A	N/A	<MDL	<MDL – 6.2	0.0	N/A	N/A	<MDL	N/A	N/A	N/A
TDCIPP	77.8	0.39	4.8	0.44	<MDL – 4.6	88.9	1.1	3.7	1.8	<MDL – 3.7	0.35	0.43
TPHP	88.9	17.2	4.7	33.8	<MDL – 134	100	11.4	3.5	12.0	1.3 – 49.0	1.5	0.10

GM = Geometric Mean; GSD = Geometric Standard Deviation; MDL = Method Detection Limit; [#]Spearman Correlation
N/A Not calculated: proportion of results below method detection limit was too high to provide a valid result
*Spearman correlation statistically significant ($p<0.05$)
Note: Not all compounds listed in Table 2.1 were measured in SWBs

Table S2.3. Correlations between SVOCs in Silicone Wristbands (SWBs) and Creatinine-Corrected Urinary Metabolites in Post-Shift minus Pre-shift Urine Samples Adjusted for Work-Shift Duration from Nail Salon Workers in the Greater Boston Area (2016–2017)

SWB Parent Compound	Urinary Metabolite	Spearman correlation coefficients for Difference of post-shift and pre-shift urine/ Lapel SWB	Wrist SWB
Phthalates			
DEHP	**MEHP**	0.18	0.15
	MEHHP	0.28	0.18
	MEOHP	0.17	0.07
	MECPP	0.63	0.22
DiNP	**MCOP**	0.27	0.45
	MONP	-0.08	0.30
Phthalate Alternatives			
DEHTP	**MECPTP**	0.52	0.33
	MEHHTP	0.33	0.55
Organophosphate Esters			
TCIPP	**BCIPP**	-0.17	-0.30
TDCIPP	**BDCIPP**	-0.10	0.40
TPHP	**DPHP**	0.03	0.28

CHAPTER THREE: Per- and Polyfluoroalkyl Substances serum concentrations in pregnant women from North Carolina: Predictors and associations with birth outcomes

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Abstract

Introduction

Per- and polyfluoroalkyl substances (PFAS) are commonly used as water and stain repellents in consumer products and can contaminate drinking water sources. Research suggests that prenatal PFAS exposure may impact fetal growth and development, but findings remain mixed and little is known about joint effects of PFAS mixtures. The goal of this study was to examine associations between maternal serum concentrations of PFAS during pregnancy and birth outcomes.

Methods

Study participants included 134 mother-child pairs from the North Carolina-based TESIE Study (2009–2011). Sera collected between 5.6 and 29.6 weeks gestation (mean 12.6 weeks) were analyzed for ten PFAS by on-line solid-phase extraction coupled with high-performance liquid chromatography-tandem mass spectrometry. We used multivariable regression models to estimate total and sex-specific associations of individual PFAS with gestational age at birth, birth weight, and birth weight for gestational age z-score. We used weighted quantile sum regression to derive a PFAS mixture index and estimated the association of this index with birth outcomes.

Results

In WQS regression models, the PFAS mixture index was negatively associated with gestational age at birth among all (β = -3.2 [-6.1, -0.31] days) offspring. The linear

isomer of perfluorooctanoic acid (n-PFOA) contributed most to this association (weight = 0.32). The PFAS mixture index was also negatively associated with gestational age at birth among male offspring (β = -6.2 [-11.1, -1.3] days). Similarly, n-PFOA (weight = 0.42) contributed most to this association. A weaker and less precise negative association was observed between the PFAS mixture index and gestational age at birth among female offspring (β = -0.82 [-4.3, 2.6] days). We observed less evidence of associations between the PFAS mixture index and birth weight for all (β = -78.7 [-219, 61.3] grams) and male (β = -191 [-393, 10.6] grams) offspring; there was some evidence of confounding by plasma volume expansion and/or glomerular filtration rate. Furthermore, gestational age at birth likely contributed to this association. Associations with birth weight for gestational age z-score were weaker and less consistent.

Conclusion

We observed negative associations between some prenatal PFAS concentrations and birth outcomes, particularly gestational length. Our data suggest that male offspring may be more susceptible than females. Our results also highlight the importance of examining associations between mixtures of multiple PFAS and birth outcomes rather than individual PFAS. Finally, we found evidence that the mechanism of the association observed between PFAS concentrations and birth weight may be through reduced gestational length rather than growth restriction.

Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made fluorinated chemicals that have water and stain-resistant properties and have been in production since the 1950s. PFAS are resistant to environmental degradation (ATSDR, 2018; Calafat et al., 2007; CDC, 2019). PFAS have commonly been used in fire-fighting foams, food packaging and consumer products such as carpet, upholstery, and clothing (ATSDR, 2018). As such, PFAS are ubiquitous in indoor environments and are commonly detected in human serum and blood (ATSDR, 2018; Calafat et al., 2007; Fraser et al., 2013; Houde et al., 2006; Manzano-Salgado et al., 2017; Sagiv et al., 2015; Shoeib et al., 2011; Starling et al., 2017). Routes of exposure include inhalation of contaminated air and dust; ingestion of food (directly from food or from food packaging), drinking water, breastmilk, and dust; and direct contact with items containing PFAS (such as personal care products). PFAS are able to cross the placental barrier, leading to exposure to the developing fetus (ATSDR, 2018; Verner et al., 2016).

According to the Developmental Origins of Health and Disease hypothesis, early life exposures to harmful chemicals, potentially during critical windows of development, may lead to significant short- and long-term health consequences (Barker, 2007; Hales et al., 1991). Some epidemiological studies have suggested that increased prenatal exposure to certain PFAS may be associated with adverse birth outcomes such as decreased gestational age at birth and decreased birth weight (Apelberg et al., 2007; Chen et al., 2012; Johnson et al., 2014; Lam et al., 2014; Sagiv et al., 2017; Starling et al., 2017; Woods et al., 2017b). However, other studies, including a meta-analysis, suggest that

inverse associations reported previously with birth weight, particularly those that assessed exposure in late pregnancy serum or in cord blood, may be exaggerated because of uncontrolled confounding by plasma volume expansion (PVE) and glomerular filtration rate (GFR) (Bach et al., 2015; Steenland et al., 2018; Verner et al., 2015). Low GFR later in pregnancy could confound the association between PFAS and birth outcomes because GFR is associated with both decreased birth weight and gestational age at birth, as well as with increased PFAS maternal serum concentrations (Park et al., 2018; Steenland et al., 2018).

Few previous studies of birth outcomes have examined more than one PFAS at a time (Kalloo et al., 2020; Woods et al., 2017b). However, in reality, people are likely exposed to mixtures of PFAS that are often highly correlated, raising the possibility of confounding, interactions, or cumulative effects between co-exposures (Braun et al., 2016). Cumulative exposure to low concentrations of a multitude of chemicals may be associated with negative health effects, even when there is a lack of evidence for health effects associated with the concentration of each individual substance (Carrico et al., 2015; Schecter et al., 2013). Thus, although most studies have examined impacts of individual PFAS only, estimating the joint effects of multiple PFAS is necessary to understand the overall potential health impacts of PFAS exposure, which often occur as mixtures of PFAS.

The primary objective of this study was to estimate associations of mixtures of maternal serum PFAS concentrations during pregnancy with three outcome measures: gestational age at birth, birth weight, and birth weight for gestational age z-score, a

measure of fetal growth. We estimated associations for individual PFAS, and also used weighted quantile sum (WQS) regression to estimate cumulative associations for multiple PFAS with a weighted PFAS mixture index (Carrico et al., 2015). Given previous literature demonstrating that serum PFAS concentrations vary by behavioral characteristics, physiology, and sociodemographic factors (Calafat et al., 2007; Sagiv et al., 2015, 2017), a secondary objective was to examine these factors as predictors of maternal serum PFAS concentrations.

Methods

Study Population

This study is in collaboration with the Newborn Epigenetics STudy (NEST) at Duke University that examined the associations between prenatal diet, nutrition, and epigenetic modifications with health outcomes including obesity in childhood or later in life (Hoyo et al., 2011). As previously described, eligible women were at least 18 years of age, pregnant, and received prenatal care at the Duke University Division of Maternal and Fetal Medicine (DMFM) (Hoyo et al., 2011). The NEST study enrolled approximately 2,585 pregnant women that were 4–24 weeks pregnant (2005–2011). Race/ethnicity for this cohort was approximately 27% non-Hispanic White, 40% non-Hispanic Black, and 29% Hispanic. NEST study researchers administered questionnaires, collected participant serum samples during pregnancy, and obtained labor and birth outcome data from medical records (Hoyo et al., 2011).

The Toddlers Exposure to Semi-Volatile Organic Chemicals (SVOCs) in Indoor Environments (TESIE) study is a sub-sample of NEST, with participation restricted to children aged 3–6 years at recruitment. As previously described, TESIE aimed to evaluate pre- and postnatal exposures to SVOCs and examine associations with health outcomes in about 200 NEST offspring (Hoffman et al., 2018). Briefly, TESIE researchers re-contacted families that participated in the NEST study between 2014 and 2016 through mailed letters, emails, and follow-up phone calls, and invited them to participate. A total of 203 children from 190 homes enrolled in the TESIE study. We excluded participants that were missing exposure information (n=36; due to insufficient serum volume remaining or maternal non-consent to the PFAS analysis), missing data on both birth weight and gestational age at birth (n=6), multiple births (n=20), or whose mothers were classified as 'other' race (n=3) due to the small number in this category. After exclusions, 134 infants were included in our analyses. Mothers provided informed consent for their child's participation in TESIE and for use of their data and archived serum from the original NEST study. The Duke University Institutional Review Board approved human subject protocols. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Birth Outcomes and Potential Confounding Variables

Gestational age at birth, birth weight, and data on potential confounders, including

information on demographics, education, parity, body mass index (BMI), prenatal smoking, and gestational age at blood draw were abstracted from medical records and questionnaires. Birth weight for gestational age z-score reflects fetal growth, and allows us to evaluate if an infant deviates from the sex- and gestational age-specific population mean birth weight (i.e. to control for sex and gestational age) in our models (Curtis et al., 2016; Oken et al., 2003). We used the online calculator from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Project to calculate sex-specific birth weight for gestational age z-scores from our gestational age at birth, birth weight, and infant sex data (*INTERGROWTH-21st*, 2017). As previously described, the INTERGROWTH-21st Project is a multi-center, multi-ethnic, international, population-based project that aims to provide researchers with international newborn standards to compare infants born to geographically diverse mothers who are generally healthy, well-nourished, and receive adequate prenatal care (i.e., infants who are at low risk of fetal growth impairment) (Villar et al., 2014). The INTERGROWTH 21st Project birth weight for gestational age z-scores were based on sex-specific mean birth weight for completed weeks and days of gestation and were converted to a standardized z-score (Villar et al., 2014).

Quantification of PFAS in Serum

NEST researchers collected maternal serum samples during pregnancy (mean gestational age: 12.6 weeks; range 5.6 to 29.6 weeks). Sera were stored at -80 ºC at Duke

University until shipped to the Division of Laboratory Sciences at the CDC for analysis. Serum was analyzed for PFAS using on-line solid-phase extraction coupled with high-performance liquid chromatography-isotope dilution-tandem mass spectrometry (Kato et al., 2011). Maternal sera were analyzed for the following PFAS: linear and branched perfluorooctane sulfonic acid (PFOS) (n-PFOS and Sm-PFOS, respectively), linear and branched perfluorooctanoic acid (PFOA) (n-PFOA and Sb-PFOA, respectively), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS), perfluorodecanoic acid (PFDA), perfluorooctane sulfonamide (FOSA), 2-(N-methyl-perfluorooctane sulfonamide) acetic acid (MeFOSAA), and 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid (EtFOSAA). We added the concentrations of the linear and branched isomers of both PFOS and PFOA to obtain total PFOS and total PFOA, respectively, to compare to the PFOS and PFOA data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of U.S. general population (CDC, 2019), which did not examine the linear and branched isomers separately during the same time frame.

Statistical analyses

Instrument values of maternal serum PFAS concentrations were not available from the laboratory when concentrations were below the limit of detection (LOD) of 0.1 ng/mL (range 0 to 134 samples <LOD). We therefore assigned a value of the LOD divided by the square root of two to samples below the LOD. PFAS that were detected in >65% of participants were included in our analyses. We examined univariate

distributions of all outcomes, exposures, and covariates to assess normality. We compared the geometric mean maternal serum PFAS concentrations from participants of our study to serum PFAS concentrations measured between 2009 and 2010, the closest available years to when our study serum samples were collected, in female NHANES participants aged 19 to 44 years. We examined correlations between maternal serum PFAS concentrations using Spearman correlations.

We used robust regression models with the MM estimation method to estimate associations of individual PFAS concentrations with birth outcomes in separate models. This method can withstand a high proportion of outliers and maintain its robustness, and has higher statistical efficiency than some other methods for dealing with outliers (SAS, 2008). Given the presence of outliers in our data, we chose to use robust regression to reduce the impact of those outliers on effect estimates. Birth weight and birth weight for gestational age z-score were approximately normally distributed; however, gestational age at birth was left skewed, and neither normally nor log-normally distributed. Both the outcomes and serum PFAS concentration variables were modeled as untransformed, continuous variables. We calculated the interquartile range (IQR) as Q3–Q1, where Q3 is the value of the 75th percentile and Q1 is the value of the 25th percentile of the concentration for each PFAS. Associations are reported as the change in birth outcome per IQR increase in PFAS.

We examined the association of the cumulative effect of multiple PFAS with birth outcomes using WQS regression, a method to evaluate associations of chemical mixtures with health outcomes, which can be used for studies with small to moderate sample sizes

and highly correlated exposures (Carrico et al., 2015; Czarnota et al., 2015; Gennings et al., 2013). For continuous outcome variables (y), WQS regression assumes that the outcome is a linear function of a weighted index of the exposure variables modeled as quantiles (e.g., q_i=0,1,2,3) with all mixture components acting in the same direction and no interaction between exposures:

$$y = \beta_0 + \beta_1 \left(\sum_{i=1}^{p} w_i q_i \right) + z'\gamma + \varepsilon ,$$

where the term in parentheses is the index, w_i is the weight for exposure i (assumed non-negative with all weights summing to one), z is a vector of confounders and ε is an error term. WQS generates a beta coefficient (β_1) for the index, which represents the change in birth outcome for a one-unit increase in the derived index representing quartiled PFAS, where each PFAS is weighted based on its overall contribution to the association with the outcome.

We set the number of bootstrap samples used in parameter estimation to 100. In the WQS models, one must place a constraint on whether the weights are derived from models where the β values are positive or negative. We selected the direction of the constraint as negative for all models, since, based on *a priori* knowledge, we hypothesized that serum PFAS concentrations would be negatively associated with the birth outcomes.

To identify potential confounders, we used *a priori* knowledge to create a Directed Acyclic Graph (DAG) of the relationship between maternal serum PFAS concentrations and birth outcomes. Our multivariable and WQS models were adjusted for

maternal age at delivery, maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), maternal education, parity, maternal smoking during pregnancy, maternal BMI at last menstrual period (LMP) (based on self-reported weight and height), and gestational age at blood draw. We also conducted stratified analyses by infant sex because infant sex is a potential effect measure modifier of the relationship between prenatal PFAS exposure and birth weight and gestational age at birth (Lauritzen et al., 2017; Manzano-Salgado et al., 2017).

As a secondary objective, we examined the association of maternal serum PFAS concentrations with sociodemographic and behavioral factors using multivariable linear regression. These factors included maternal age at delivery, maternal race/ethnicity, maternal education, parity, maternal smoking during pregnancy, maternal BMI at LMP, and gestational age of the fetus at blood draw. All predictor variables were included simultaneously in adjusted models. Maternal serum PFAS concentrations were log-normally distributed; therefore, we log-transformed those concentrations prior to analysis to examine predictors of PFAS concentrations. We report these associations as percent change in PFAS per unit change in predictor (% change = $(e^{\beta}-1)*100$).

Some participants had missing data on maternal education (n=3, ~2%), smoking during pregnancy (n=2, ~1.5%), and BMI at LMP (n=1, ~0.75%). We used multiple imputation with 10 imputations using the robust regression method in the proc mi procedure in SAS(SAS, 2015), and then combined results using proc mianalyze based on Rubin's rule (Rubin, 2004). In the WQS models, we did not use multiple imputation, as to our knowledge at the time of analysis that method had not been developed yet for

WQS regression. Instead, we replaced the missing mothers' education and prenatal smoking variables with the most frequent categories (college graduate and non-smoker, respectively), and BMI at LMP with the median BMI at LMP (26.5 kg/m^2). To ensure that substitution and multiple imputation did not introduce bias in the WQS and robust regression models, we compared results from the analyses with complete cases with those that included the replaced values.

We conducted several additional sensitivity analyses for the associations between PFAS and birth outcomes. 1) In our models examining the association between prenatal serum PFAS concentrations and birth outcomes, we restricted participants to those whose maternal serum was drawn in the 1st trimester to reduce potential confounding by GFR (Table S3.2). 2) We adjusted for gestational age at birth in models of serum PFAS concentrations and birth weight (Table S3.3). 3) We included all PFAS in a single mutually-adjusted model (Table S3.4). 4) We fit WQS regression models with the direction of association constrained to positive (versus negative in the main analyses) (Table S3.5).

We used the gWQS package version 2.0.1 in RStudio (version 3.4.2 (2017-09-28)); The R Foundation for Statistical Computing) to analyze the WQS regression models (Renzetti et al., 2016). We performed all other statistical analyses using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC).

Results

We included 134 mother-child pairs in our final analyses. Compared to participants, excluded mothers (n=69) had many similar characteristics including: age (median 29 versus 30 years, respectively), education (61% versus 64% had some college or a college degree), smoking during pregnancy (83% versus 85% reported not smoking), and BMI at LMP (median 26.5 versus 26.3 kg/m^2). However, there were some differences. Mothers of excluded infants were more likely to self-identify as Hispanic compared to those who were included (30% versus 15%, respectively) and were slightly more likely to be married or living with a partner (76% versus 69%, respectively). Excluded babies, on average, had shorter gestational ages at birth (median 38.1 versus 39.5 weeks, respectively) and lower birth weights (2,965 g versus 3,354 g, respectively), likely due to the inclusion of non-singleton births in that group, and were less likely to be the first child born to their mothers (28% versus 35%, respectively).

Participant characteristics

Participant characteristics are presented in Table 3.1. Mothers in our study ranged from 19 to 44 years (median 29 years). Approximately 45% of mothers self-identified as non-Hispanic white, 40% as non-Hispanic black, and 15% as Hispanic. Most mothers in our study had at least some college education (61%), at least one previous child (64%), were overweight or obese at LMP (58%), and did not smoke during pregnancy (83%). The majority of maternal serum samples were collected during the 1st trimester (67%). A

little over half of the offspring in our study were male (56%), most infants were born at full term (≥37 completed weeks gestation, 92%), and most had normal birth weights (≥2,500 grams, 89%).

PFAS detection and correlations

We detected n-PFOS, n-PFOA, Sm-PFOS, PFHxS, and PFNA in 100%, and PFDA in 88.8% of maternal serum samples (Table 3.2). We detected Sb-PFOA MeFOSAA, and EtFOSAA and FOSA in fewer than 40% of maternal serum samples; therefore, we did not include these PFAS in further statistical analyses. Linear PFOS and PFOA had the highest geometric mean concentrations (4.3 and 1.8 ng/mL, respectively). Compared to U.S. females aged 19 to 44 from NHANES, maternal serum PFAS concentrations in our study were fairly similar (Table 3.2).

In general, maternal serum PFAS concentrations were moderately to highly correlated (r=0.37–0.75) (Table 3.3). The exception was for PFDA and PFHxS, which were only weakly correlated (r=0.08). Linear and branched PFOS had the highest correlation coefficient (r=0.75).

Gestational age at birth

In adjusted models of individual PFAS, we observed a negative association between maternal serum n-PFOA and gestational age at birth among all offspring (β for

IQR increase=-2.2 [95% CI: -4.2, -0.25] days), with n-PFOS and Sm-PFOS also exhibiting negative, albeit weaker, associations (β = -0.30 [-1.7, 1.1] days and β = -0.44 [-2.1, 1.2] days, respectively) (Figure 3.1a, Table S3.1). In sex-stratified models, n-PFOA was negatively associated with gestational age at birth among male offspring (β = -3.6 [-6.6, -0.70] days), with PFNA and Sm-PFOS exhibiting weaker negative associations (β = -2.2 [-5.1, 0.78] days and β = -0.59 [-2.6, 1.4] days, respectively). Among females, we observed weak inverse associations between PFAS and gestational age at birth (range -0.78 to -2.8 days per IQR increase), with the exception of PFNA and PFHxS, but estimates were imprecise. The largest decreases in gestational age at birth among female offspring were for n-PFOA, Sm-PFOS, and n-PFOS: each IQR increase was associated with a 2.8 day decrease in gestational age at birth for n-PFOA and Sm-PFOS (95% CIs: -5.9, 0.19 days and -6.3, 0.67 days, respectively), and a 2.5 day decrease for n-PFOS (95% CI: -5.8, 0.76).

From WQS models, for each quartile increase in the derived PFAS mixture index, we observed a decrease of 3.2 (95% CI: -6.1, -0.31) days of gestation in all offspring (Figure 3.1a, Table S3.1). Linear PFOA, whose association with gestational age at birth was the largest in magnitude from among all individual PFAS, was also the strongest contributor to the WQS index (mean weight=32%). In sex-stratified models, the mixture index was associated with a reduction of 6.2 (95% CI: -11.1, -1.3) days of gestation among male offspring, with linear PFOA contributing the most to this association (mean weight=42%) (Table 3.4). Among female offspring, the association of the mixture index was closer to the null (β = -0.82 [-4.3, 2.6] days).

Birth weight

In adjusted models among all offspring, there were weak negative associations between most PFAS, except PFHxS and PFNA, and birth weight (range of βs: -3.8 to -79.2 grams per IQR increase), though the associations lacked precision (Figure 3.1b and Table S3.1). The largest decrease in birth weight for all offspring was observed for n-PFOA: birth weight decreased by 79.2 (95% CI: -196, 37.9) grams for each IQR increase.

PFNA was negatively associated with birth weight among male offspring in sex-stratified models: each IQR increase was associated with a 185-gram decrease in birth weight (95% CI = -341, -29.9 grams). All other individual PFAS were weakly negatively associated with birth weight among male offspring (range of βs: -12.5 to -134 grams per IQR increase), though these associations lacked precision. Among females, results were not as precise for most PFAS.

From WQS models, for each quartile increase in the derived PFAS mixture index, we observed a decrease of 78.7 grams (95% CI = -219, -61.3 grams) in all offspring (Figure 3.1b, Table S3.1). n-PFOA, whose association with birth weight had the largest magnitude from among all individual PFAS, was also the strongest contributor to the WQS index (mean weight=54%). In sex-stratified models, the mixture index was associated with a reduction of 191 grams (95% CI = -393, 10.6 grams) at birth among male offspring, with n-PFOA contributing the most to this association (mean weight=43%) (Table 3.4). There was no association among females.

Birth weight for gestational age z-score

Overall, results for associations between maternal serum PFAS and birth weight for gestational age z-score were less precise and closer to the null than the other two birth outcomes of interest. In adjusted models of birth weight for gestational age z-score that included all offspring, the largest effect estimate was for n-PFOS (β = -0.11 [-0.29, 0.07] points), which was also the case in sex-stratified models among male offspring only (β = -0.13 [-0.33, 0.06] points) (Figure 3.1c, Table S3.1). Among female offspring, n-PFOS also had the largest effect estimate, though the association was positive (β = 0.11 [-0.34, 0.56] points).

The results of adjusted WQS regression models for the association between the PFAS mixture index and birth weight for gestational age z-score appeared close to null for all offspring (β = -0.03 [-0.29, 0.23] points). In sex-stratified models, the mixture index was associated with a reduction of 0.11 (95% CI = -0.44, 0.23) points of birth weight for gestational age z-score among male offspring, with linear Sm-PFOS contributing the most to this association (mean weight=27%) (Table 3.4).

Predictors of maternal serum PFAS concentrations

Associations between maternal serum PFAS with potential predictors, reported as percent change in PFAS, are shown in Table 3.5. The strongest predictor of maternal serum PFAS concentrations in our analyses was maternal parity; mothers with previous children had lower serum PFAS concentrations than nulliparous mothers for all PFAS

(range: 21–74% lower for parous compared to nulliparous mothers). We also saw a general negative trend in maternal serum PFAS concentration with increasing week of gestational age at blood draw (range: 0.27–0.36% decrease in ng/mL per week) for all PFAS. With the exception of n-PFOS, black mothers generally had lower concentrations of serum PFAS than white mothers (range: 2–9% lower for black compared to white mothers), though these estimates were imprecise. Hispanic mothers generally had lower concentrations of some PFAS (n-PFOS, n-PFOA, Sm-PFOS, and PFHxS, range: 4-37%) than white mothers, but not PFNA or PFDA (range: 27.5–48.8%), though some of these estimates also lacked precision. With the exception of PFNA, mothers with a college degree generally had higher concentrations of serum PFAS compared to mothers with a high school diploma or GED (range: 6–24% higher), though this trend of mothers with higher education having higher concentrations of PFAS than those with lower education did not hold when we compared mothers with a college degree to those with some college or less than a high school degree.

Sensitivity Analyses

When we compared results from the analyses with complete cases with those that included the replaced missing covariate data in WQS models, we obtained very similar results (results not shown). In analyses restricted to maternal serum drawn in the 1st trimester, we found inverse associations between maternal serum PFAS concentrations and gestational age at birth that were generally similar or of greater magnitude compared

to our original analyses, for both individual PFAS models and WQS models (Table S3.2). Associations between maternal serum PFAS concentrations and the other two birth outcomes from analyses restricted to 1st trimester maternal serum samples were closer to the null or more positive than estimates from primary analyses, indicating potential confounding by PVE and/or GFR in the models that included participants with maternal serum collected later in pregnancy. In models of birth weight in which we additionally controlled for gestational age at birth as a covariate in the model, results were generally similar in direction, but of lower magnitude compared to the original analyses, suggesting that some of the association between serum PFAS concentrations and birth weight can be attributed to gestational age at birth (Table S3.3). When we included all PFAS in a single mutually adjusted model (Table S3.4), we found evidence of confounding by co-exposure in the individual PFAS models (the change in effect estimates for all PFAS changed by >10%). However, many of the individual PFAS were moderately to highly correlated, which suggests possible multicollinearity in the models that included all PFAS, which is why we examined these models only as sensitivity analyses. This multicollinearity underlines the importance of implementing an approach such as WQS regression that can accommodate correlated data and limits confounding by co-exposure by including all PFAS in the model. An assumption in WQS regression is that the mixture components act in the same direction. As mentioned above, this assumption is likely violated for some of our analyses among females, because associations between some of the individual PFAS and birth outcomes were in opposite directions. Table S3.5 displays the comparison of WQS associations between maternal serum PFAS and birth outcomes

when the WQS components were set as positive versus negative. The index effects were null when constrained in the positive direction.

Discussion

In sex-stratified models, we observed a negative association between the PFAS mixture index and gestational age at birth among male offspring, while the association was not as strong among females. The results for the other birth outcomes were not as clear. While it appears that there is a weak negative association between PFAS and birth weight among male offspring, we found evidence of confounding by physiology in that association, and that the mechanism of the association between prenatal serum PFAS concentrations and birth weight may in part be through shortened gestational length.

PFAS and Birth Outcomes

To our knowledge, our study is one of only a handful published that examined the cumulative effect of a mixture of prenatal PFAS on birth outcomes. Two of these studies examined birth outcomes in the Health Outcomes and Measures of Environment (HOME) Study, a prospective birth cohort study based out of Cincinnati, Ohio that recruited participants between 2003 and 2006 (Kalloo et al., 2020; Woods et al., 2017b). Woods et al. (2017) used Bayesian hierarchical linear models to examine the association between a mixture of different chemicals and birth weight in 272 mother-child pairs and

found that the average association between PFAS class and birth weight was -10.6 grams (95% credible interval=-51.5, 34.0). However, blood was collected during the 2nd trimester and authors did not control for PVE, GFR, or gestational age at blood draw; thus, there is potential for uncontrolled confounding by physiology. Kalloo et al. (2020) used k-means clustering to cluster mothers with similar chemical exposure patterns into three groups as well as principal component analysis (PCA) to identify six principal components (PCs) that explained >50% of the variance in biomarker concentrations in 380 mother-child pairs. In their adjusted analyses, they did not find an association between any of the clusters or PCs and gestational age at birth or birth weight for gestational age z-score (Kalloo et al., 2020). One explanation on why the findings from Kalloo et al. may have differed from our results of a negative association between some PFAS and gestational age at birth was that they included metals and other chemicals in addition to PFAS in the clusters and PCs they examined, and did not focus solely on PFAS. Thus, those cluster or PC profiles may not overall have been associated with gestational age at birth, while individual chemicals, such as PFAS, inside those clusters or PCs may have been.

Our findings of a negative association between individual prenatal PFAS and gestational age at birth are consistent with prior studies. In a Danish cohort of 3,535 mother-infant pairs, a doubling of PFOS, PFOA, PFNA, and perfluoroheptane sulfonatic acid (PFHpS) measured in 1st trimester maternal plasma was negatively associated with gestational age at birth (PFOS: β = -1.1 [-1.4, -0.4] days; PFOA: β = -0.4 [-1.0, 0.3] days; PFNA: β = -1.0 [-1.7, -0.3] days; and PFHpS: β = -1.2 [-1.9, -0.5] days) (Meng et al.,

2018). These estimates were smaller in magnitude but had greater precision (likely because of a much larger sample size) compared to our study (doubling of maternal serum PFOS, PFOA, and PFNA and gestational age at birth in all offspring from our study: β = -3.3 (-8.3, 1.7); -6.5 (-12.1, -0.87); and -7.1(-13.0, -1.3) days, respectively) (results not shown). Similarly, among an urban/suburban birth cohort in the northeastern United States (Project Viva) (n=1,645), PFOS and PFNA were negatively associated with gestational age at birth (per IQR increase, PFOS: β = -0.10 [-0.19, 0.00] weeks; PFNA: β = -0.07 [-0.17, 0.02] weeks) (Sagiv et al., 2017). These associations were also smaller in magnitude, but more precise than our findings (likely due to larger sample size) (PFOS: β = -0.21 [-0.50, 0.07] weeks; PFNA β = -0.37 [-0.65, -0.10] weeks).

Despite some previous study findings that suggested prenatal exposure to certain PFAS was negatively associated with birth weight, a recent meta-analysis (Steenland et al., 2018) determined that when blood was drawn close to conception or early in pregnancy, there was little evidence of an association between prenatal PFOA exposure (they did not examine exposure to other PFAS) and birth weight (β = -1.0 [-2.4, 0.4] grams). Steenland et al. (2018) suggested that since PVE and GFR increase throughout and peak towards the end of pregnancy, collecting serum samples later in pregnancy can lead to a decrease in maternal serum PFAS concentrations. Low PVE and GFR are associated with decreased birth weight and increased PFAS in serum (Steenland et al., 2018). Thus, studies that collected blood samples later in pregnancy and observed associations between PFOA and birth weight may be confounded by PVE or GFR. In our study, approximately a third of study participants had maternal serum collected after the

1st trimester, which could lead to potential confounding by PVE or GFR, as evidenced by the attenuated associations in analyses restricted to 1st trimester serum collection. Although two-thirds of our maternal serum samples were collected in the 1st trimester, and we control for gestational age at blood draw in our models, our results for the associations between birth weight and PFAS could have residual confounding by physiology, because we did not directly measure PVE or GFR.

Results for the association between maternal serum PFAS concentrations and birth weight for gestational age z-score were mostly null. This is mirrored in the Maternal Infant Research on Environmental Chemicals (MIREC) Study of 1,705 mother-infant pairs that found a weak inverse association in Bayesian hierarchical modeling between birth weight for gestational age z-score and prenatal PFOA with the null value included in the credible interval ($\log_{10}$ β = -0.10, 95% credible interval [-0.34, 0.13]) (Ashley-Martin et al., 2017). Similarly, among Project VIVA participants (n=1,645), researchers found only a weak inverse association between birth weight for gestational age z-score and an IQR increase in PFOS (β = -0.04 [-0.08, 0.01] points) and PFNA (β = -0.06 [-0.11, -0.01] points) (Sagiv et al., 2017). Because our overall results suggest that prenatal serum PFAS concentrations are negatively associated with gestational age at birth, with less evidence of an association between PFAS and birth weight, it is plausible that the weak PFAS-birth weight association is being driven in part by the association with gestational length.

Sex-specific effects

We observed that the estimated effect of the PFAS mixture index on gestational age at birth among male offspring was of greater magnitude and higher precision than the estimate for females, and that males were more susceptible to adverse effects of the PFAS mixture index than female offspring for all birth outcomes. n-PFOA appeared to be the strongest contributor to the PFAS mixture index effect between exposure and birth outcomes among male offspring. Few studies that we are aware of found sex differences similar to our findings, and each only for a specific PFAS and not for the other individual PFAS they examined. One study with similar mean concentrations of PFAS to ours, reported a sex difference for PFOS, with males having an odds ratio (OR) of 1.9 (95% CI = 0.98, 3.68) of being low birth weight for every doubling of PFOS in 1st trimester maternal plasma, while females had an OR of 0.73 (p-value for sex interaction = 0.01) (Manzano-Salgado et al., 2017). Another study with similar PFOA, but higher PFOS concentrations than measured in our study found a significant difference in the association between birth weight among male offspring (β = -526 [-828, -222] grams) for each ln-unit increase in PFOA compared to female offspring (β = -156 [-541, 228] grams) (p-value for sex interaction = 0.046) (Lauritzen et al., 2017). A third study with higher concentrations of PFOS and similar concentrations of PFNA to those measured in our study found a slight difference in the association between maternal serum PFOS and PFNA concentrations and gestational age at birth between males and females (β = -0.19 versus 0.01 weeks for PFOS and β = -0.19 versus 0.03 for PFNA for males compared to females, respectively) (Sagiv et al., 2017). Most other previous studies examining sex-

specific effects of prenatal PFAS exposure on birth weight did not find sex differences (Sagiv et al., 2017; Shoaff et al., 2018; Starling et al., 2017).

Potential mechanisms for associations between PFAS and birth outcomes

Although the exact mechanisms are unknown, several studies have examined potential mechanisms for the association between PFAS and birth outcomes. A recent study observed an inverse association between some prenatal PFAS exposures and maternal fasting glucose concentrations in mid-pregnancy; the authors suggested that reduced availability of maternal glucose could negatively impact the developing fetus (Starling et al., 2017). Another study reported associations between PFOS exposure and decreased maternal triglycerides and polyunsaturated fatty acids (PUFAs), which are important sources of energy for the developing fetus. A decrease in triglycerides and PUFAs could impair growth and development, thus negatively impacting birth outcomes (Kishi et al., 2015). Maternal PFOS exposure was inversely associated with glucocorticoids in another study, which are necessary for fetal development including lung and heart maturation during pregnancy, and could potentially lead to an inverse association between PFAS and birth outcomes (Goudarzi et al., 2017). PFAS exposure was found to be associated with altered thyroid hormone levels in some previous studies, which could impact thyroid function, which is necessary for development, and lead to potential negative impacts on birth outcomes (de Cock et al., 2014; Y. Wang et al., 2014). Finally, an *in vitro* study determined that certain PFAS disrupted estrogen and androgen receptors, with a mixture of PFAS having more than an additive effect on antagonization

of the androgen receptor (Kjeldsen & Bonefeld-Jørgensen, 2013). Previous studies have demonstrated that androgen is associated with birth weight (F. de Zegher et al., 1998; Francis de Zegher et al., 1999). Although a mechanism has yet to be determined for the sex-specific association that we observed between prenatal serum PFAS concentrations and birth outcomes, a possible explanation is that prenatal PFAS exposure may alter androgen and estrogen levels in the developing fetus. An alteration of these sex hormones could lead to different effects in male versus female offspring.

Predictors of maternal serum PFAS concentrations

Similar to previous studies (ATSDR, 2018; Calafat et al., 2007; Manzano-Salgado et al., 2017; Sagiv et al., 2015, 2017; Siebenaler et al., 2017; Starling et al., 2017), many PFAS were detected in study participants, and PFOS and PFOA had the highest concentrations. As also observed in previous studies (Boronow et al., 2019; CDC, 2019), there was some variability in maternal serum PFAS concentrations between racial/ethnic groups, with non-Hispanic whites trending towards higher PFAS concentrations than non-Hispanic black and Hispanic mothers. With the exception of those who had a high school diploma or GED, mothers with a college degree or higher tended to have higher serum concentrations of certain PFAS compared to those with less education. This is mostly consistent with previous studies that have noted a clear trend of increasing concentrations of certain PFAS with increased education (Calafat et al., 2007; Sagiv et al., 2015). Consistent with previous studies, parous mothers in our study had lower

concentrations of serum PFAS, on average, than nulliparous mothers, likely due to placental transfer during pregnancy and/or excretion of PFAS through breastmilk (Kishi et al., 2015; Sagiv et al., 2015). Finally, similar to previous findings (Mamsen et al., 2019; Sagiv et al., 2017), we observed that PFAS concentrations generally decreased with increasing week of pregnancy during which maternal serum samples were collected, which may be due to PVE and increased GFR.

Strengths and limitations

A major strength of this study is that we estimated the effect of a PFAS mixture on birth outcomes, which reduces the potential for mutual confounding by other PFAS and allows us to determine which PFAS contribute most to the PFAS mixture index effect on birth outcomes. Another strength of this study is the ethnic/racial diversity of the participant population, which allows us to generalize our results to a broader population. We were able to quantify maternal serum concentrations of both linear and branched isomers of PFOS and PFOA, which to our knowledge has not been examined in previous studies of PFAS and birth outcomes. We collected most of the maternal serum samples analyzed for prenatal PFAS in the 1st trimester (67.2%), which reduces the impact of confounding by physiology. Finally, we have information on several different prenatal factors, allowing us to control for many potential confounders.

A major limitation of this study is the relatively small sample size, which limited the precision of our estimates and precluded the use of more flexible statistical methods

for mixtures (e.g., Bayesian kernel machine regression). WQS may not be the most appropriate method of examining the cumulative effect of exposure to PFAS on birth outcomes for all of our analyses, given that we found that the assumption that the components all act in the same direction was violated for some of the models, particularly among females. Although we largely collected serum early in pregnancy, and controlled for gestational age at blood draw in our models, a potential limitation of our study is that PVE and changes in GFR during pregnancy may confound the association between prenatal PFAS and birth weight (Bach et al., 2015; Steenland et al., 2018; Verner et al., 2015). We did not measure albumin or creatinine (potential markers for PVE and GFR, respectively) as other studies (e.g., Project VIVA) have done (Sagiv et al., 2017), and thus could not control for those measures. We did not have data on some potentially important confounders of the association between PFAS and birth outcomes, including interpregnancy interval, income, and diet, which could potentially affect PFAS exposure, birth weight, and gestational age at birth (Sagiv et al., 2015). We did control for race/ethnicity, parity, maternal age, and maternal education, which may serve as proxies for some of these variables, thereby reducing concerns about unmeasured confounding.

Conclusion

We found evidence of an inverse association between the PFAS mixture index and gestational age at birth, particularly among male offspring. The association was driven by n-PFOA. Associations between maternal serum PFAS and the other birth

outcomes were not as precise and potentially confounded by physiology. Our finding of a sex-specific effect of PFAS on birth outcomes should be confirmed in larger studies that also evaluate interactive effects and control for PVE and GFR.

Table 3.1. Characteristics of mothers and infants participating in the TESIE birth outcomes study, central North Carolina, 2009–2011 (N=134)

Participant characteristic	N (%)	Mean (SD)	Range
Maternal age at delivery (years)		**29.6 (5.6)**	**19 – 44**
<27 years	44 (32.8)		
27–32 years	47 (35.1)		
33+ years	43 (32.1)		
Maternal race/ethnicity			
White, Non-Hispanic	60 (44.8)		
Black, Non-Hispanic	54 (40.3)		
Hispanic	20 (14.9)		
Marital Status			
Never Married	33 (24.6)		
Married	71 (53.0)		
Living with Partner	21 (15.7)		
Divorced/Separated	3 (2.2)		
Other	3 (2.2)		
Missing	3 (2.2)		
Maternal education			
Some College or College Graduate	82 (61.2)		
High School Graduate/GED	21 (15.7)		
<High School	28 (20.9)		
Missing	3 (2.2)		
Parity (previous births)		**1 (1.2)**	**0 – 5**
0	47 (35.1)		
1+	86 (64.2)		
Missing	1 (0.7)		
Maternal BMI at LMP (kg/m^2)		**27.3 (7.0)**	**16.2 – 58.5**
Underweight or normal (<25)	56 (41.8)		
Overweight or obese (≥25)	77 (57.5)		
Missing	1 (0.7)		
Maternal prenatal smoking			
Yes	21 (15.7)		
No	111 (82.8)		
Missing	2 (1.5)		
Offspring Sex			
Male	75 (56.0)		
Female	59 (44.0)		
Gestational age at blood draw (weeks)		**12.6 (4.8)**	**5.6 – 29.6**
1st trimester	90 (67.2)		
2nd trimester	41 (30.6)		
3rd trimester	3 (2.3)		
Gestational age at birth (weeks)		**39.2 (2.0)**	**29.9 – 41.7**
<37 weeks	11 (8.2)		
37+ weeks	123 (91.8)		
Birth Weight for Gestational Age Z-Score (points)		**0.30 (1.1)**	**-1.9 – 4.0**
<0	53 (39.6)		
>0	77 (57.5)		
Missing	4 (3.0)		

Birth Weight (grams)		**3,337 (616)**	**1,490 – 5,422**
<2,500 grams	11 (8.2)		
≥2,500 grams	119 (88.8)		
Missing	4 (3.0)		

GED = General Equivalency Diploma, BMI = body mass index = kg/m^2, LMP = last menstrual period

Table 3.2. Maternal serum concentrations of PFAS (ng/mL) among TESIE birth outcomes study participants (2009–2011) and among U.S. Females (2009–2010)

		TESIE Study Participants		NHANES*
PFAS	**N (%) >LOD†**	**IQR**	**GM (95% CI)**	**GM (95% CI)**
PFOS	134 (100)	3.2	5.8 (5.3, 6.3)	5.7 (5.6, 5.8)
n-PFOS	134 (100)	2.8	4.3 (4.0, 4.7)	N/A
PFOA	134 (100)	1.3	1.9 (1.7, 2.0)	2.2 (2.1, 2.3)
n-PFOA	134 (100)	1.2	1.8 (1.6, 1.9)	N/A
Sm-PFOS	134 (100)	1.0	1.4 (1.2, 1.5)	N/A
PFHxS	134 (100)	0.70	0.95 (0.86, 1.0)	0.86 (0.77, 0.96)
PFNA	134 (100)	0.40	0.77 (0.72, 0.83)	1.0 (0.91, 1.1)
PFDA	119 (88.8)	0.10	0.22 (0.20, 0.25)	0.24 (0.15, 0.34)
Sb-PFOA	52 (38.8)	N/A	N/A	N/A
MeFOSAA	27 (20.1)	N/A	N/A	0.16 (0.07, 0.25)
EtFOSAA	1 (0.7)	N/A	N/A	<LOD
FOSA	0 (0.0)	N/A	<LOD	<LOD

Note: PFAS = per- and polyfluoroalkyl substances; PFOS = linear and branched PFOS combined; n-PFOS = linear PFOS; Sm-PFOS = branched PFOS; PFOA = linear and branched PFOA combined; n-PFOA = linear PFOA;
Sb-PFOA = branched PFOA; N/A = Not available; LOD = limit of detection; IQR = Interquartile Range
GM = geometric mean; 95% CI = 95% confidence interval
*Serum PFAS concentrations from U.S. NHANES females aged 19 to 44 years, 2009–2010. NHANES= National Health and Nutrition Examination Survey (CDC, 2019)
†LOD = 0.1 ng/mL

Table 3.3. Spearman correlations between TESIE birth outcomes study maternal serum PFAS concentrations, central North Carolina, 2009–2011 (N=134)

	n-PFOS	**n-PFOA**	**Sm-PFOS**	**PFHxS**	**PFNA**	**PFDA**
n-PFOS	1.0	0.57	0.75	0.53	0.59	0.48
n-PFOA		1.0	0.63	0.61	0.68	0.40
Sm-PFOS			1.0	0.64	0.48	0.37
PFHxS				1.0	0.37	0.08
PFNA					1.0	0.66
PFDA						1.0

Table 3.4. Estimated average weights from adjusted Weighted Quantile Sum regression and rank of importance for contributions of each PFAS to overall association of PFAS on birth outcomes[a] among TESIE study participants, central North Carolina, 2009–2011

		Gestational Age at Birth	
	All Offspring (n=134)	**Male Offspring (n=75)**	**Female Offspring (n=59)**
	β=-3.2 (-6.1, -0.31)	***β=-6.2 (-11.1, -1.3)***	***β=-0.82 (-4.3, 2.6)***
PFAS	**Weight (Rank)**	**Weight (Rank)**	**Weight (Rank)**
n-PFOS	0.09 (5)	0.06 (5)	0.04 (6)
n-PFOA	0.32 (1)	0.42 (1)	0.16 (3)
Sm-PFOS	0.14 (4)	0.27 (2)	0.13 (4)
PFHxS	0.19 (2)	0.13 (3)	0.36 (1)
PFNA	0.17 (3)	0.06 (4)	0.25 (2)
PFDA	0.08 (6)	0.05 (6)	0.05 (5)

		Birth Weight	
	All Offspring (n=130)	**Male Offspring (n=74)**	
	β=-78.7 (-219, 61.3)	***β=-191 (-393, 10.6)***	
PFAS	**Weight (Rank)**	**PFAS**	**Weight (Rank)**
n-PFOS	0.04 (6)	0.02 (6)	0.04 (6)
n-PFOA	0.54 (1)	0.43 (1)	0.54 (1)
Sm-PFOS	0.06 (4)	0.11 (3)	0.06 (4)
PFHxS	0.05 (5)	0.08 (5)	0.05 (5)
PFNA	0.21 (2)	0.28 (2)	0.21 (2)
PFDA	0.11 (3)	0.09 (4)	0.11 (3)

		Birth weight for Gestational Age Z-Score	
	All Offspring (n=130)	**Male Offspring (n=74)**	**All Offspring (n=130)**
	β=-0.03 (-0.29, 0.23)	***β=-0.11 (-0.44, 0.23)***	***β=-0.03 (-0.29, 0.23)***
PFAS	**Weight (Rank)**	**PFAS**	**Weight (Rank)**
n-PFOS	0.11 (4)	0.18 (4)	0.11 (4)
n-PFOA	0.15 (3)	0.22 (3)	0.15 (3)
Sm-PFOS	0.24 (2)	0.27 (1)	0.24 (2)
PFHxS	0.30 (1)	0.26 (2)	0.30 (1)
PFNA	0.08 (6)	0.007 (6)	0.08 (6)
PFDA	0.11 (5)	0.07 (5)	0.11 (5)

[a]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw

Table 3.5. Associations between maternal serum PFAS concentrations (ng/mL) and predictors[a], in mutually adjusted models, among TESIE study participants, central North Carolina, 2009–2011 (N=134)

Characteristic	Percent Change (95% Confidence Interval) n-PFOS	n-PFOA	Sm-PFOS	PFHxS	PFNA	PFDA
Maternal age at delivery (years)	1.4 (-0.64, 3.5)	0.25 (-1.6, 2.1)	1.9 (-0.29, 4.2)	0.13 (-2.1, 2.4)	1.3 (-0.40, 3.0)	2.9 (0.39, 5.5)
Black vs. White	14.1 (-9.3, 43.6)	-8.8 (-26.0, 12.3)	-5.6 (-26.3, 20.8)	-4.7 (-25.8, 22.6)	-2.1 (-19.0, 18.4)	-5.1 (-28.3, 25.6)
Hispanic vs. White	-9.2 (-33.6, 24.2)	-3.5 (-27.4, 28.4)	-36.3 (-54.5, -10.7)	-18.9 (-42.4, 14.1)	27.5 (-1.5, 65.1)	48.8 (1.8, 117)
Some College vs. College	0.85 (-24.2, 34.2)	0.15 (-22.7, 29.8)	-7.8 (-32.2, 25.3)	-10.9 (-34.8, 21.7)	15.4 (-8.9, 46.1)	7.6 (-24.0, 52.2)
HS/GED vs. College	-6.1 (-30.9, 27.7)	-10.4 (-32.2, 18.6)	-13.8 (-38.1, 20.1)	-24.3 (-45.9, 5.9)	0.02 (-22.4, 28.9)	-16.8 (-42.8, 20.8)
<HS vs. College	7.0 (-19.8, 42.9)	0.03 (-23.2, 30.2)	-7.7 (-32.5, 26.1)	-4.0 (-30.0, 31.8)	4.5 (-17.7, 32.7)	2.2 (-28.0, 45.1)
Nulliparous vs. Parous	45.4 (19.4, 77.1)	64.4 (37.2, 97.1)	74.0 (40.6, 115)	55.6 (25.2, 93.4)	24.6 (5.8, 46.7)	20.6 (-5.3, 53.5)
Maternal BMI[b] (kg/m^2) at LMP	0.61 (-0.72, 2.0)	1.1 (-0.14, 2.3)	1.6 (0.12, 3.1)	0.94 (-0.54, 2.5)	0.36 (-0.74, 1.5)	0.81 (-0.82, 2.5)
Yes vs. No Prenatal smoking	-7.1 (-27.9, 19.7)	28.2 (1.7, 61.6)	-6.1 (-28.5, 23.4)	8.9 (-17.5, 43.6)	14.4 (-7.3, 41.1)	-23.1 (-43.6, 4.8)
Gestational age at blood draw (weeks)	-0.35 (-0.60, -0.09)	-0.46 (-0.69, -0.22)	-0.29 (-0.57, -0.01)	-0.30 (-0.58, -0.01)	-0.27 (-0.48, -0.06)	-0.31 (-0.63, 0.001)

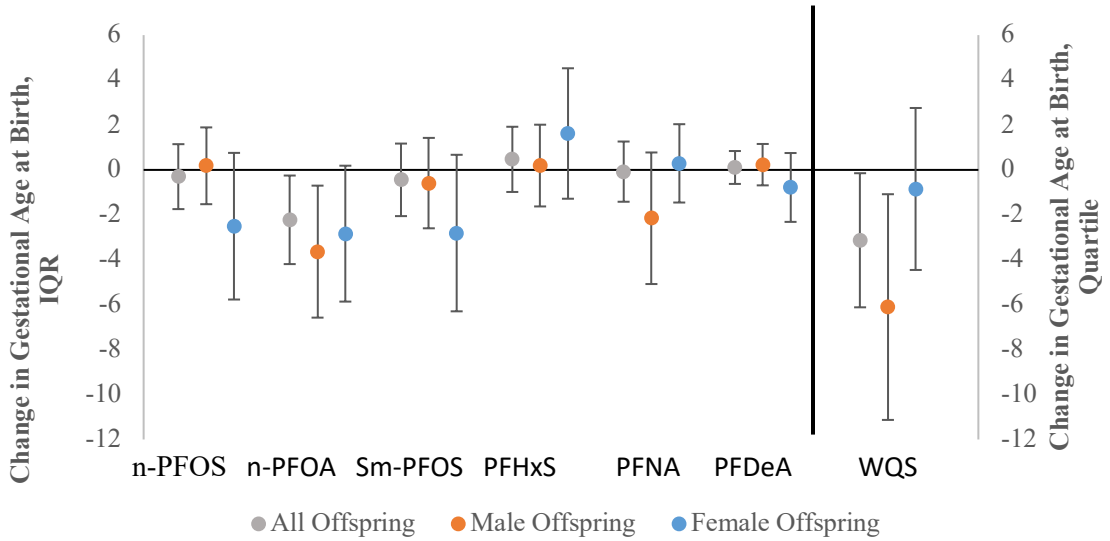
PFAS = per- and polyfluoroalkyl substances; HS = high school; GED = General Equivalency Diploma

[a]All models mutually adjusted for mother's age at delivery, race/ethnicity, education, smoking status during pregnancy, BMI at last menstrual period, parity, and gestational age of fetus at blood draw.

[b]BMI = body mass index = weight (kg)/height (m^2); LMP = last menstrual period

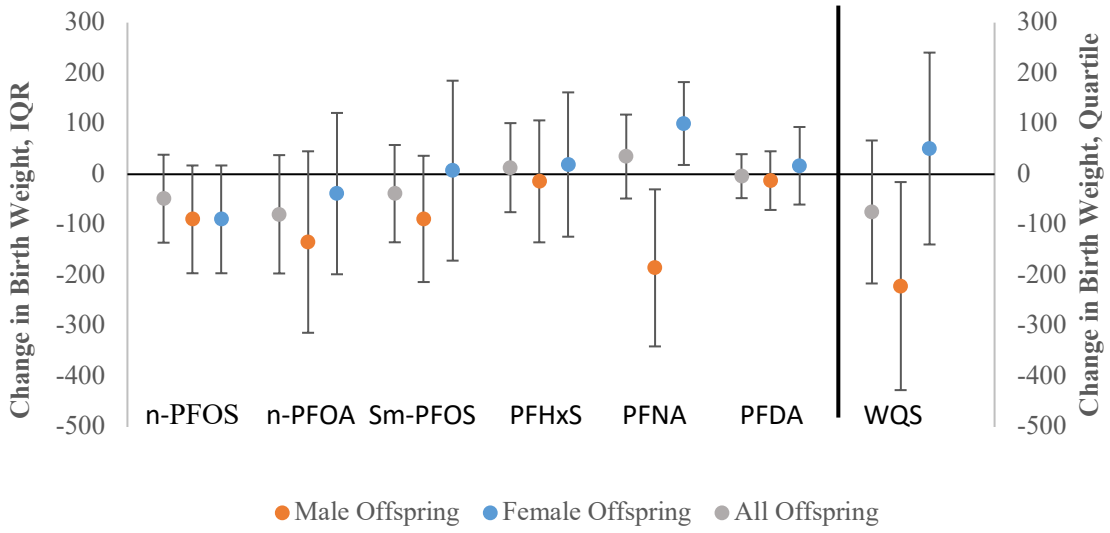
Figure 3.1. Adjusted[a] associations of A. gestational age at birth (days) and B. birth weight (grams) per IQR increase in maternal serum PFAS for individual PFAS compounds and per quartile increase in WQS index, among all offspring[1], male offspring[2], and female offspring[3] participants of the TESIE birth outcomes study, Central North Carolina, 2009–2011

A.



[a]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw, and gestational age at birth
[1]n = 134; [2]n = 75; [3]n = 59

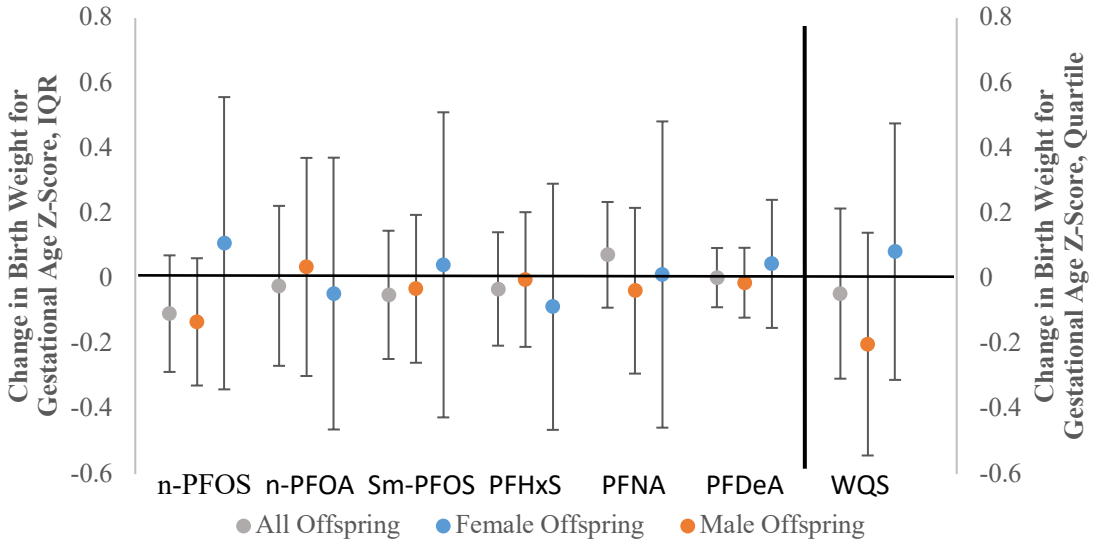
B.



[a]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw, and gestational age at birth
[1]n = 130; [2]n = 74; [3]n = 56

Figure 3.1. (Continued) Adjusted[a] associations of change in C. birth weight for gestational age z-score (points) with change in maternal serum PFAS IQR for individual PFAS compounds and per quartile for WQS for all offspring[1], male offspring[2], and female offspring[3] participants of the TESIE birth outcomes study, Central North Carolina, 2009–2011

C.



[a]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw, and gestational age at birth
[1]n = 130; [2]n = 74; [3]n = 56

Table S3.1. Associations between maternal serum PFAS (per IQR[a] increase for individual PFAS, or per quartile increase in WQS PFAS mixture index) and gestational age at birth (days), birth weight (grams), and birth weight for gestational age z-score (points) for participants of the TESIE birth outcomes study, central North Carolina, 2009–2011

	Gestational Age at Birth					
	All Offspring (n=134)		Male Offspring (n=75)		Female Offspring (n=59)	
PFAS	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)
n-PFOS	-0.36 (-1.7, 0.95)	-0.30 (-1.7, 1.1)	0.28 (-1.1, 1.7)	0.18 (-1.5, 1.9)	-2.7 (-5.4, 0.06)	-2.5 (-5.8, 0.76)
n-PFOA	-0.49 (-2.2, 1.2)	-2.2 (-4.2, -0.25)	0.55 (-1.5, 2.6)	-3.6 (-6.6, -0.70)	-2.0 (-4.8, 0.75)	-2.8 (-5.9, 0.19)
Sm-PFOS	-0.14 (-1.4, 1.1)	-0.44 (-2.1, 1.2)	0.35 (-1.0, 1.7)	-0.59 (-2.6, 1.4)	-1.7 (-4.5, 1.1)	-2.8 (-6.3, 0.67)
PFHxS	0.59 (-0.66, 1.9)	0.47 (-0.98, 1.9)	0.51 (-0.88, 1.9)	0.19 (-1.6, 2.0)	0.85 (-1.7, 3.4)	1.6 (-1.3, 4.5)
PFNA	0.41 (-0.80, 1.6)	-0.08 (-1.4, 1.3)	0.19 (-2.1, 2.5)	-2.2 (-5.1, 0.78)	0.48 (-1.1, 2.0)	0.29 (-1.5, 2.0)
PFDA	0.11 (-0.51, 0.72)	0.11 (-0.62, 0.84)	0.18 (-0.45, 0.81)	0.23 (-0.69, 1.2)	-0.23 (-1.7, 1.3)	-0.78 (-2.3, 0.75)
WQS	-2.1 (-4.7, 0.53)	-3.2 (-6.1, -0.31)	-3.2 (-7.4, 1.0)	-6.2 (-11.1, -1.3)	-0.69 (-3.6, 2.2)	-0.82 (-4.3, 2.6)
	Birth Weight					
	All Offspring (n=130)		Male Offspring (n=74)		Female Offspring (n=56)	
PFAS	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)
n-PFOS	-52.4 (-136, 31.6)	-48.4 (-135, 38.7)	-68.1 (-168, 32.2)	-89.2 (-196, 17.4)	16.0 (-164, 196)	-89.2 (-196, 17.4)
n-PFOA	-87.0 (-192, 17.8)	-79.2 (-196, 37.9)	-61.8 (-209, 85.4)	-134 (-314, 45.5)	-106 (-264, 51.2)	-38.3 (-198, 121)
Sm-PFOS	-34.9 (-117, 46.9)	-38.3 (-135, 57.9)	-32.7 (-131, 65.4)	-88.3 (-213, 36.6)	-37.0 (-207, 133)	7.1 (-171, 185)
PFHxS	3.3 (-80.2, 86.9)	13.1 (-75.0, 101)	4.7 (-102, 112)	-14.0 (-135, 107)	-1.7 (-149, 145)	19.2 (-124, 162)
PFNA	-102 (-208, 4.3)	35.0 (-48.0, 118)	-84.3 (-229, 60.1)	-185 (-341, -29.9)	77.0 (-18.8, 173)	100 (18.4, 182)
PFDA	14.2 (-25.3, 53.6)	-3.8 (-47.3, 39.8)	18.7 (-27.6, 65.0)	-12.5 (-70.6, 45.5)	-2.0 (-87.1, 83.1)	16.8 (-60.0, 93.5)
WQS	-59.3 (-181, 62.5)	-78.7 (-219, 61.3)	-87.3 (-262, 87.5)	-191 (-393, 10.6)	-26.1 (-183, 131)	13.7 (-177, 204)
	Birth weight for Gestational Age Z-Score					
	All Offspring (n=130)		Male Offspring (n=74)		Female Offspring (n=56)	
PFAS	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)

PFAS = per- and polyfluoroalkyl substances; CI = Confidence Interval

[a]IQR (ng/mL) for n-PFOS=2.8, n-PFOA=1.2, Sm-PFOS=1.0, PFHxS = 0.70, PFNA = 0.40, PFDA = 0.10

[b]Robust Regression Analysis

[c]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw

Table S3.1 (Continued). Associations between maternal serum PFAS (per IQR[a] increase for individual PFAS, or per quartile increase in WQS PFAS mixture index) and gestational age at birth (days), birth weight (grams), and birth weight for gestational age z-score (points) for participants of the TESIE birth outcomes study, central North Carolina, 2009–2011

	Birth weight for Gestational Age Z-Score					
	All Offspring (n=130)		Male Offspring (n=74)		Female Offspring (n=56)	
PFAS	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)	Unadjusted β (95% CI)	Adjusted[c] β (95% CI)
n-PFOS	-0.10 (-0.28, 0.07)	-0.11 (-0.29, 0.07)	-0.11 (-0.29, 0.08)	-0.13 (-0.33, 0.06)	0.09 (-0.32, 0.50)	0.11 (-0.34, 0.56)
n-PFOA	-0.03 (-0.25, 0.19)	-0.02 (-0.27, 0.22)	0.05 (-0.23, 0.32)	0.04 (-0.30, 0.37)	-0.13 (-0.50, 0.23)	-0.05 (-0.46, 0.37)
Sm-PFOS	-0.04 (-0.20, 0.13)	-0.05 (-0.25, 0.15)	-0.01 (-0.19, 0.17)	-0.03 (-0.26, 0.20)	-0.05 (-0.44, 0.34)	0.04 (-0.43, 0.51)
PFHxS	-0.03 (-0.20, 0.13)	-0.03 (-0.21, 0.14)	0.006 (-0.18, 0.19)	-0.003 (-0.21, 0.20)	-0.09 (-0.42, 0.25)	-0.09 (-0.46, 0.29)
PFNA	0.11 (-0.05, 0.27)	0.07 (-0.09, 0.24)	0.08 (-0.16, 0.32)	-0.04 (-0.29, 0.22)	-0.18 (-0.56, 0.20)	0.01 (-0.46, 0.48)
PFDA	0.05 (-0.04, 0.13)	0.003 (-0.09, 0.09)	0.05 (-0.03, 0.14)	-0.01 (-0.12, 0.09)	0.04 (-0.15, 0.24)	0.05 (-0.15, 0.24)
WQS	-0.09 (-0.30, 0.12)	-0.03 (-0.29, 0.23)	-0.11 (-0.39, 0.16)	-0.11 (-0.44, 0.23)	-0.07 (-0.41, 0.27)	-0.009 (-0.42, 0.40)

PFAS = per- and polyfluoroalkyl substances; CI = Confidence Interval

[a]IQR (ng/mL) for n-PFOS=2.8, n-PFOA=1.2, Sm-PFOS=1.0, PFHxS = 0.70, PFNA = 0.40, PFDA = 0.10

[b]Robust Regression Analysis

[c]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw

Table S3.2. Sensitivity Analysis: Associations between maternal serum PFAS (per IQR[a] increase for individual PFAS, or per quartile increase in WQS PFAS mixture index) and gestational age at birth (days), birth weight (grams), and birth weight for gestational age z-score (points), comparing all participants to those that had serum samples collected during the 1st trimester for participants of the TESIE birth outcomes study, central North Carolina, 2009–2011

	Gestational Age at Birth					
	All Offspring[1]		Male Offspring[3]		Female Offspring[5]	
	All Participants[b]	1st Trimest Serum[b]	All Participants[b]	1st Trimest Serum[b]	All Participants[b]	1st Trimest Serum[b]
PFAS	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
n-PFOS	-0.30 (-1.7, 1.1)	-0.27 (-2.2, 1.7)	0.18 (-1.5, 1.9)	0.15 (-2.3, 2.6)	-2.5 (-5.8, 0.76)	-2.5 (-6.6, 1.7)
n-PFOA	-2.2 (-4.2, -0.25)	-4.0 (-6.7, -1.4)	-3.6 (-6.6, -0.70)	-5.6 (-9.3, -2.0)	-2.8 (-5.9, 0.19)	-3.6 (-8.0, 0.68)
Sm-PFOS	-0.44 (-2.1, 1.2)	-0.46 (-2.3, 1.4)	-0.59 (-2.6, 1.4)	-0.97 (-3.3, 1.4)	-2.8 (-6.3, 0.67)	-2.5 (-7.1, 2.1)
PFHxS	0.47 (-0.98, 1.9)	0.83 (-0.89, 2.6)	0.19 (-1.6, 2.0)	0.10 (-2.1, 2.3)	1.6 (-1.3, 4.5)	1.4 (-2.6, 5.4)
PFNA	-0.08 (-1.4, 1.3)	-0.63 (-2.6, 1.3)	-2.2 (-5.1, 0.78)	-5.3 (-9.6, -0.88)	0.29 (-1.5, 2.0)	-0.88 (-4.8, 3.1)
PFDA	0.11 (-0.62, 0.84)	-0.14 (-1.1, 0.83)	0.23 (-0.69, 1.2)	-0.58 (-1.8, 0.63)	-0.78 (-2.3, 0.75)	-1.5 (-3.6, 0.69)
WQS	-3.2 (-6.1, -0.31)	-3.0 (-6.2, 0.26)	-6.2 (-11.1, -1.3)	-6.8 (-12.1, -1.4)	-0.82 (-4.3, 2.6)	-1.7 (-6.8, 3.5)
	Birth weight					
	All Offspring[2]		Male Offspring[4]		Female Offspring[6]	
	All Participants[b]	1st Trimest Serum[b]	All Participants[b]	1st Trimest Serum[b]	All Participants[b]	1st Trimest Serum[b]
PFAS	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
n-PFOS	-48.4 (-135, 38.7)	-14.5 (-125, 95.5)	-89.2 (-196, 17.4)	-40.9 (-174, 91.8)	-89.2 (-196, 17.4)	-40.9 (-174, 172)
n-PFOA	-79.2 (-196, 37.9)	-104 (-249, 42.2)	-134 (-314, 45.5)	-146 (-335, 43.0)	-38.3 (-198, 121)	-26.1 (-240, 196)
Sm-PFOS	-38.3 (-135, 57.9)	-17.6 (-121, 85.7)	-88.3 (-213, 36.6)	-67.1 (-186, 51.6)	7.1 (-171, 185)	52.0 (-157, 143)
PFHxS	13.1 (-75.0, 101)	41.0 (-55.3, 137)	-14.0 (-135, 107)	-45.1 (-173, 83.1)	19.2 (-124, 162)	-27.0 (-197, 261)
PFNA	35.0 (-48.0, 118)	29.7 (-79.0, 138)	-185 (-341, -29.9)	-82.2 (-298, 134)	100 (18.4, 182)	86.6 (-22.8, 188)
PFDA	-3.8 (-47.3, 39.8)	15.9 (-38.3, 70.2)	-12.5 (-70.6, 45.5)	35.6 (-32.7, 104)	16.8 (-60.0, 93.5)	84.4 (-3.0, 91.8)
WQS	-78.7 (-219, 61.3)	-34.2 (-203, 135)	-191 (-393, 10.6)	-218 (-448, 11.6)	13.7 (-177, 204)	25.6 (-181, 232)

PFAS = per- and polyfluoroalkyl substances; CI = Confidence Interval;

[a]IQR (ng/mL) for n-PFOS=2.8 and 2.7, n-PFOA=1.2 and 1.4, Sm-PFOS=1.0 and 1.0, PFHxS = 0.70 and 0.70, PFNA = 0.40 and 0.50, PFDA = 0.10 and 0.10 for all and 1st trimester serum participants, respectively

[b]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw

[1]n=134 for All participants and 90 for participants with serum collected in the 1st trimester; [2]n=130 for All participants and 88 for participants with serum collected in the 1st trimester

[3]n=75 for All male participants and 49 for male participants with serum collected in the 1st trimester; [4]n=74 for All male participants and 48 for male participants with serum collected in the 1st trimester
[5]n=59 for All female participants and 40 for female participants with serum collected in the 1st trimester; [6]n=56 for All female participants and 40 for female participants with serum collected in the 1st trimester

Table S3.2 (Continued). Sensitivity Analysis: Associations between maternal serum PFAS (per IQR[a] increase for individual PFAS, or per quartile increase in WQS PFAS mixture index) and gestational age at birth (days), birth weight (grams), and birth weight for gestational age z-score (points), comparing all participants to those that had serum samples collected during the 1st trimester for participants of the TESIE birth outcomes study, central North Carolina, 2009–2011

	Birth weight for Gestational Age Z-Score					
	All Offspring[2]		Male Offspring[4]		Female Offspring[6]	
	All Participants[b]	1st Trimest Serum[b]	All Participants[b]	1st Trimest Serum[b]	All Participants[b]	1st Trimest Serum[b]
PFAS	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
n-PFOS	-0.11 (-0.29, 0.07)	-0.001 (-0.22, 0.22)	-0.13 (-0.33, 0.06)	-0.05 (-0.32, 0.25)	0.11 (-0.34, 0.56)	0.13 (-0.12, 0.63)
n-PFOA	-0.02 (-0.27, 0.22)	0.02 (-0.29, 0.32)	0.04 (-0.30, 0.37)	0.03 (-0.38, 0.53)	-0.05 (-0.46, 0.37)	0.04 (-0.59, 0.60)
Sm-PFOS	-0.05 (-0.25, 0.15)	0.03 (-0.18, 0.23)	-0.03 (-0.26, 0.20)	-0.04 (-0.28, 0.23)	0.04 (-0.43, 0.51)	0.08 (-0.57, 0.31)
PFHxS	-0.03 (-0.21, 0.14)	0.07 (-0.12, 0.26)	-0.003 (-0.21, 0.20)	-0.01 (-0.26, 0.21)	-0.09 (-0.46, 0.29)	-0.13 (-0.48, 0.65)
PFNA	0.07 (-0.09, 0.24)	0.12 (-0.10, 0.34)	-0.04 (-0.29, 0.22)	0.07 (-0.38, 0.45)	0.01 (-0.46, 0.48)	0.003 (-0.50, 0.59)
PFDA	0.003 (-0.09, 0.09)	0.03 (-0.08, 0.14)	-0.01 (-0.12, 0.09)	0.11 (-0.03, 0.21)	0.05 (-0.15, 0.24)	0.14 (-0.38, 0.63)
WQS	-0.03 (-0.29, 0.23)	0.05 (-0.28, 0.37)	-0.11 (-0.44, 0.23)	-0.19 (-0.60, 0.21)	-0.009 (-0.42, 0.40)	0.18 (-0.32, 0.68)

PFAS = per- and polyfluoroalkyl substances; CI = Confidence Interval;
[a]IQR (ng/mL) for n-PFOS=2.8 and 2.7, n-PFOA=1.2 and 1.4, Sm-PFOS=1.0 and 1.0, PFHxS = 0.70 and 0.70, PFNA = 0.40 and 0.50, PFDA = 0.10 and 0.10 for all and 1st trimester serum participants, respectively
[b]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw
[1]n=134 for All participants and 90 for participants with serum collected in the 1st trimester; [2]n=130 for All participants and 88 for participants with serum collected in the 1st trimester
[3]n=75 for All male participants and 49 for male participants with serum collected in the 1st trimester; [4]n=74 for All male participants and 48 for male participants with serum collected in the 1st trimester
[5]n=59 for All female participants and 40 for female participants with serum collected in the 1st trimester; [6]n=56 for All female participants and 40 for female participants with serum collected in the 1st trimester

Table S3.3. Sensitivity Analysis: Associations between maternal serum PFAS (per IQR[a] increase for individual PFAS, or per quartile increase in WQS PFAS mixture index) and birth weight (grams), comparing models adjusted and not adjusted for gestational age at birth for participants of the TESIE birth outcomes study, central North Carolina, 2009–2011

	Birth Weight[b]		
	All Offspring (n=130)	**Male Offspring (n=74)**	**Female Offspring (n=56)**
PFAS	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
n-PFOS	-48.4 (-135, 38.7)	-89.2 (-196, 17.4)	-89.2 (-196, 17.4)
n-PFOA	-79.2 (-196, 37.9)	-134 (-314, 45.5)	-38.3 (-198, 121)
Sm-PFOS	-38.3 (-135, 57.9)	-88.3 (-213, 36.6)	7.1 (-171, 185)
PFHxS	13.1 (-75.0, 101)	-14.0 (-135, 107)	19.2 (-124, 162)
PFNA	35.0 (-48.0, 118)	-185 (-341, -29.9)	100 (18.4, 182)
PFDA	-3.8 (-47.3, 39.8)	-12.5 (-70.6, 45.5)	16.8 (-60.0, 93.5)
WQS	-78.7 (-219, 61.3)	-191 (-393, 10.6)	13.7 (-177, 204)
	Birth Weight[b] Additionally Adjusted for Gestational Age at Birth		
	All Offspring (n=130)	**Male Offspring (n=74)**	**Female Offspring (n=56)**
PFAS	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
n-PFOS	-38.1 (-113, 36.7)	-59.2 (-139, 20.8)	55.9 (-136, 248)
n-PFOA	-2.4 (-108, 104)	11.9 (-133, 157)	-13.0 (-191, 165)
Sm-PFOS	-15.3 (-98.3, 67.7)	-17.7 (-112, 76.4)	33.0 (-166, 232)
PFHxS	-14.3 (-87.6, 59.0)	-7.3 (-92.0, 77.5)	-47.4 (-212, 117)
PFNA	27.5 (-42.3, 97.4)	-38.2 (-154, 77.3)	-28.8 (-228, 171)
PFDA	0.15 (-37.3, 37.6)	-8.5 (-52.0, 35.0)	16.9 (-67.0, 101)
WQS	-9.8 (-125, 106)	-53.2 (-212, 106)	-9.6 (-181, 161)

PFAS = per- and polyfluoroalkyl substance; CI = Confidence Interval

[a]IQR (ng/mL) for n-PFOS=2.8, n-PFOA=1.2, Sm-PFOS=1.0, PFHxS = 0.70, PFNA = 0.40, PFDA = 0.10

[b]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw

Table S3.4. Sensitivity Analysis: Associations between maternal serum PFAS (per IQR[a] increase for individual PFAS, or per quartile increase in WQS PFAS mixture index) and gestational age at birth (days), birth weight (grams), and birth weight for gestational age z-score (points), comparing models with individual PFAS and mutually adjusted for all PFAS for participants of the TESIE birth outcomes study, central North Carolina, 2009–2011

	Gestational Age at Birth					
	All Offspring (n=134)		Male Offspring (n=75)		Female Offspring (n=59)	
	Individual PFAS[b]	All PFAS[b]	Individual PFAS[b]	All PFAS[b]	Individual PFAS[b]	All PFAS[b]
PFAS	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
n-PFOS	-0.30 (-1.7, 1.1)	-0.41 (-2.6, 1.8)	0.18 (-1.5, 1.9)	1.6 (-1.8, 4.9)	-2.5 (-5.8, 0.76)	-1.2 (-5.9, 3.5)
n-PFOA	-2.2 (-4.2, -0.25)	-3.6 (-6.2, -0.93)	-3.6 (-6.6, -0.70)	-4.2 (-9.5, 0.97)	-2.8 (-5.9, 0.19)	-5.0 (-10.9, 0.98)
Sm-PFOS	-0.44 (-2.1, 1.2)	0.07 (-2.5, 2.7)	-0.59 (-2.6, 1.4)	-1.1 (-5.0, 2.9)	-2.8 (-6.3, 0.67)	-1.7 (-6.4, 3.1)
PFHXS	0.47 (-0.98, 1.9)	1.3 (-0.32, 3.0)	0.19 (-1.6, 2.0)	1.7 (-0.75, 4.1)	1.6 (-1.3, 4.5)	2.2 (-0.54, 5.0)
PFNA	-0.08 (-1.4, 1.3)	0.58 (-0.97, 2.1)	-2.2 (-5.1, 0.78)	-1.7 (-6.6, 3.2)	0.29 (-1.5, 2.0)	3.9 (-2.3, 10.0)
PFDA	0.11 (-0.62, 0.84)	0.44 (-0.41, 1.3)	0.23 (-0.69, 1.2)	0.16 (-0.93, 1.2)	-0.78 (-2.3, 0.75)	-0.06 (-2.0, 1.9)
	Birth Weight					
	All Offspring (n=130)		Male Offspring (n=74)		Female Offspring (n=56)	
	Individual PFAS[b]	All PFAS[b]	Individual PFAS[b]	All PFAS[b]	Individual PFAS[b]	All PFAS[b]
PFAS	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
n-PFOS	-48.4 (-135, 38.7)	-91.1 (-223, 40.3)	-89.2 (-196, 17.4)	-145 (-347, 57.5)	-89.2 (-196, 17.4)	56.3 (-203, 316)
n-PFOA	-79.2 (-196, 37.9)	-176 (-336, -15.5)	-134 (-314, 45.5)	-227 (-558, 105)	-38.3 (-198, 121)	-167 (-460, 126)
Sm-PFOS	-38.3 (-135, 57.9)	28.1 (-123, 179)	-88.3 (-213, 36.6)	11.6 (-226, 249)	7.1 (-171, 185)	-17.2 (-283, 248)
PFHXS	13.1 (-75.0, 101)	54.4 (-43.2, 152)	-14.0 (-135, 107)	66.0 (-84.1, 216)	19.2 (-124, 162)	28.6 (-130, 187)
PFNA	35.0 (-48.0, 118)	97.3 (4.7, 190)	-185 (-341, -29.9)	147 (-157, 452)	100 (18.4, 182)	88.1 (-167, 343)
PFDA	-3.8 (-47.3, 39.8)	20.0 (-29.5, 69.5)	-12.5 (-70.6, 45.5)	23.5 (-43.7, 90.7)	16.8 (-60.0, 93.5)	17.0 (-88.9, 123)
	Birth weight for Gestational Age Z-Score					
	All Offspring (n=130)		Male Offspring (n=74)		Female Offspring (n=56)	
	Individual PFAS[b]	All PFAS[b]	Individual PFAS[b]	All PFAS[b]	Individual PFAS[b]	All PFAS[b]
PFAS	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
n-PFOS	-0.11 (-0.29, 0.07)	-0.22 (-0.51, 0.06)	-0.13 (-0.33, 0.06)	-0.27 (-0.61, 0.07)	0.11 (-0.34, 0.56)	0.28 (-0.34, 0.90)
n-PFOA	-0.02 (-0.27, 0.22)	-0.12 (-0.47, 0.22)	0.04 (-0.30, 0.37)	0.11 (-0.44, 0.66)	-0.05 (-0.46, 0.37)	0.21 (-0.63, 1.0)
Sm-PFOS	-0.05 (-0.25, 0.15)	0.10 (-0.22, 0.42)	-0.03 (-0.26, 0.20)	0.15 (-0.28, 0.57)	0.04 (-0.43, 0.51)	-0.09 (-0.74, 0.56)
PFHXS	-0.03 (-0.21, 0.14)	0.02 (-0.18, 0.22)	-0.003 (-0.21, 0.20)	0.006 (-0.26, 0.27)	-0.09 (-0.46, 0.29)	-0.09 (-0.47, 0.30)
PFNA	0.07 (-0.09, 0.24)	0.14 (-0.05, 0.33)	-0.04 (-0.29, 0.22)	0.0002 (-0.35, 0.35)	0.01 (-0.46, 0.48)	-0.46 (-1.3, 0.37)
PFDA	0.003 (-0.09, 0.09)	0.03 (-0.08, 0.13)	-0.01 (-0.12, 0.09)	0.02 (-0.11, 0.14)	0.05 (-0.15, 0.24)	0.04 (-0.22, 0.30)

PFAS = per- and polyfluoroalkyl substances; CI = Confidence Interval

[a]IQR (ng/mL) for n-PFOS=2.8, n-PFOA=1.2, Sm-PFOS=1.0, PFHxS = 0.70, PFNA = 0.40, PFDA = 0.10
[b]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw

Table S3.5. Sensitivity Analysis: Associations between maternal serum PFAS (per quartile increase in WQS PFAS mixture index) and gestational age at birth (days), birth weight (grams), and birth weight for gestational age z-score (points), comparing WQS components set as negative and positive for participants of the TESIE birth outcomes study, central North Carolina, 2009–2011

	Gestational Age at Birth		
	All Offspring (n=134)	**Male Offspring (n=75)**	**Female Offspring (n=59)**
PFAS	**Adjusted[a] β (95% CI)**	**Adjusted[a] β (95% CI)**	**Adjusted[a] β (95% CI)**
WQS β = Negative	-3.2 (-6.1, -0.31)	-6.2 (-11.1, -1.3)	-0.82 (-4.3, 2.6)
WQS β = Positive	-0.87 (-3.8, 2.1)	-2.1 (-6.6, 2.4)	1.3 (-1.7, 4.4)
	Birth Weight		
	All Offspring (n=130)	**Male Offspring (n=74)**	**Female Offspring (n=56)**
PFAS	**Adjusted[a] β (95% CI)**	**Adjusted[a] β (95% CI)**	**Adjusted[a] β (95% CI)**
WQS β = Negative	-78.7 (-219, 61.3)	-191 (-393, -10.6)	13.7 (-177, 204)
WQS β = Positive	-33.9 (-184, 116)	-149 (-376, 78.8)	33.1 (-163, 230)
	Birth weight for Gestational Age Z-Score		
	All Offspring (n=130)	**Male Offspring (n=74)**	**Female Offspring (n=56)**
PFAS	**Adjusted[a] β (95% CI)**	**Adjusted[a] β (95% CI)**	**Adjusted[a] β (95% CI)**
WQS β = Negative	-0.03 (-0.29, 0.23)	-0.11 (-0.44, 0.23)	-0.009 (-0.42, 0.40)
WQS β = Positive	0.04 (-0.22, 0.30)	0.06 (-0.31, 0.43)	0.08 (-0.32, 0.47)

PFAS = per- and polyfluoroalkyl substances; CI = Confidence Interval

[a]Adjusted for mother's age at delivery, race, education, parity, body mass index at last menstrual period, prenatal smoking, and gestational age at blood draw

CHAPTER FOUR: Predictors of Per- and Polyfluoroalkyl Substances (PFAS) Concentrations in Children's Serum from the Toddlers Exposure to Semi-Volatile Organic Compounds in Indoor Environments (TESIE) Study

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Abstract

Background

Per- and polyfluoroalkyl substances (PFAS) are a group of widely used chemicals that are resistant to stains, grease, water, and other agents. Many persist within both indoor and outdoor environments leading to human exposure. We examined environmental, demographic, and behavioral predictors of serum PFAS concentrations in children aged three to six years enrolled in a North Carolina-based prospective cohort study.

Methods

Mothers from the Newborn Epigenetics STudy (NEST) (n=73) and their 3 to 6 year old children (n=84) enrolled in the Toddlers Exposure to Semi-Volatile Organic Chemicals (SVOCs) in Indoor Environments (TESIE) study. Maternal prenatal serum samples were collected during pregnancy (median 11.1 weeks gestation) (2009-2011). During home visits (2014-2016), we collected data on child, maternal, and housing characteristics via questionnaire and also collected dust, handwipe, and child serum samples. A subset of participants were asked to wear silicone wristbands for 7 days (n=26) and/or to have a sorbent-impregnated passive air sampler (SIP) placed in their home for 21 days (n=17). We used multivariable robust regression models to estimate associations of child serum PFAS concentrations with predictors.

Results

Children that ate out (e.g., restaurant or take-out foods) at least once per week averaged 0.41 ng/mL (95% CI=0.03, 0.79) higher serum PFOA concentrations than those that ate

out less frequently. Those that ate microwave popcorn more than once per month averaged 0.14 ng/mL (95% CI=0.004, 0.27) higher serum PFHxS concentrations than those that ate less. Compared to children that drank primarily well water, children that drank municipal water averaged 0.58 ng/mL higher serum concentrations of PFOA (95% CI=0.05, 1.1). PFAS detected in maternal serum was positively associated with several PFAS detected in child serum, including: PFHxS (β=0.13, 95% CI=0.01, 0.26) and n-PFOS (β=0.10, 95% CI=0.02, 0.19). PFAS detected in air was positively associated with several PFAS detected in child serum, including: MeFOSE in air and child serum PFHxS (β=0.21, 95% CI=0.08, 0.35), PFOS (β=2.2, 95% CI=1.7, 2.8), n-PFOS (β=1.6, 95% CI=1.1, 2.1), and Sm-PFOS (β=0.64, 95% CI=0.55, 0.73); and EtFOSE in air and child serum Sm-PFOS (β=3.6, 95% CI=1.5, 5.8).

Discussion

We found that several behaviors and characteristics in children, their mothers, and their home environments influenced child serum PFAS concentrations. Eating habits, drinking water source, maternal serum PFAS concentrations, and PFAS air concentrations inside the home were predictive of child serum PFAS concentrations. Taken together, our results suggest that exposure to PFAS is multi-faceted.

Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of over 4,500 chemicals that have been produced since the mid-twentieth century (Z. Wang et al., 2017). Because of their chemical and physical properties, PFAS are added to materials to make them resistant to stains, grease, water, and other agents, and they are widely used in consumer and industrial products such as firefighting foams, food packaging, non-stick cookware, carpet, and textiles (Schultz et al., 2003). Many PFAS persist within the environment and bioaccumulate, with estimated human elimination half-lives of years for some PFAS (ATSDR, 2018). PFAS have also been detected in ground and surface water used as sources of drinking water (Schultz et al., 2003).

Because of their widespread use, certain PFAS are ubiquitous in indoor and outdoor environments. People are exposed to them through hand-to-mouth transfer and inhalation or ingestion of contaminated air, food, water, or dust (ATSDR, 2018; Balk et al., 2019; Barton et al., 2020; Boronow et al., 2019; Brantsæter et al., 2013; Daly et al., 2018; Fraser et al., 2012; Hansen et al., 2016; Hu et al., 2019; Pitter Gisella et al., n.d.; Poothong et al., 2020; Schultz et al., 2003; Timmermann et al., 2019). Additionally, PFAS can cross the placental barrier and are present in breast milk, exposing fetuses and infants (ATSDR, 2018; Manzano-Salgado et al., 2015). Occupational studies have demonstrated that workers in facilities that use or manufacture PFAS have the highest exposure levels; however, PFAS are ubiquitous in human serum from the general population of the United States (ATSDR, 2018; Schultz et al., 2003). Epidemiological studies indicate that exposure to some PFAS is associated with negative health outcomes

in humans, including cholesterol-, thyroid-, liver-, asthma-, immune-, reproductive-, and fertility-related impacts (ATSDR, 2018).

Some previous studies have found that child characteristics such as history of breastfeeding, BMI, age, fast food consumption frequency, and whether or not they slept in a room with carpeting or a rug were predictive of concentrations of certain PFAS in serum or plasma (Harris et al., 2017; Kingsley et al., 2018; Winkens et al., 2017). Additionally, mothers' prenatal plasma or serum PFAS concentrations, age, race, parity, and educational achievement, along with family and census tract income have been found in some studies to be predictive of children's plasma or serum concentrations of certain PFAS (Harris et al., 2017; Kingsley et al., 2018).

Since young children are still developing, they may be more susceptible to the negative health impacts associated with PFAS exposure than adults. Sources of exposure in children are generally less understood than among adults; it is therefore important to better characterize predictors of children's serum PFAS concentrations. We aimed to identify predictors of serum PFAS concentrations in children aged three to six years enrolled in a North Carolina-based prospective cohort study. We examined associations with maternal prenatal serum, house dust, and handwipe PFAS concentrations along with housing, drinking water, demographic, and behavioral characteristics. In a smaller subsample of the study population, we also examined associations between child serum PFAS concentrations and PFAS detected in air and silicone wristbands worn by the participants.

Methods

Study participants

Figure 4.1 displays a flow chart for the study population and the varying sample sizes for the biological and environmental samples that we used to estimate predictors of child serum PFAS concentrations. Individuals previously participating in the Newborn Epigenetics STudy (NEST) were approached and asked to participate in the Toddlers Exposure to Semi-Volatile Organic Chemicals (SVOCs) in Indoor Environments (TESIE) study. The NEST study enrolled 2,595 pregnant women aged 18 years or older who received prenatal care at the Duke University Division of Maternal and Fetal Medicine between 2005 and 2011. The women were asked to participate in a prospective study examining associations between prenatal factors, epigenetic modifications, and health outcomes in their offspring (Hoyo et al., 2011). Mothers in the NEST study were administered demographic and exposure-related questionnaires and provided prenatal serum samples (median 11.1 weeks gestation; range 5.6 to 29.6 weeks) that were archived. The racial and ethnic distribution within the NEST study included approximately 27% non-Hispanic white, 40% non-Hispanic black, and 29% Hispanic participants.

Two hundred and three NEST study participant children aged 3 to 6 years were recruited from 190 homes into the TESIE study between 2014 and 2016 through mailed letters, emails, and follow-up phone calls as previously described (Hoffman et al., 2018). TESIE researchers conducted a home visit with each child participant to collect further information. Ninety TESIE participants provided blood samples during home visits and

were included in our current study. As several sets of siblings were included in the TESIE dataset, a single sibling from each of four sets of two siblings and one set of three siblings was randomly selected to participate in our study while the others were excluded, leaving 84 participants. At home visits we collected the children's height and weight, house dust and handwipe samples, and information on child and home environment characteristics through direct observation and questionnaires (Hoffman et al., 2018). We asked a subset of TESIE participants to wear silicone wristbands (n=33) and/or to have passive air monitors placed in their homes (n=17), which were collected at home visits. Only 26 participants returned their wristbands at the end of the sampling period. Mothers provided informed consent for their child's participation in TESIE and for use of their data from the original NEST study. The Duke University Institutional Review Board approved human subject protocols.

Serum Collection and Analysis

Certified phlebotomists collected maternal serum samples at prenatal appointments (median 16.6 weeks gestation, range 4.9 to 38.1 weeks gestation, during 2009-2011) and child samples at home visits (median 4.4 years, range 3.2 to 6.1 years, during 2014-2016) in serum separator tubes. We processed and stored serum samples at -20º C at Duke University until they were shipped to the Division of Laboratory Sciences at the Centers for Disease Control and Prevention (CDC) for analysis. As previously described, serum was analyzed for PFAS using an on-line solid-phase extraction method coupled with high-performance liquid chromatography-tandem mass spectrometry

(Hoffman et al., 2018; Kuklenyik et al., 2005). Sera samples were analyzed for 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid (EtFOSAA), 2-(N-methyl-perfluorooctane sulfonamide) acetic acid (MeFOSAA), perfluorodecanoic acid (PFDA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), total perfluorooctanoic acid (PFOA), linear and branched PFOA (n-PFOA and Sb-PFOA, respectively), total perfluorooctane sulfonatic acid (PFOS), linear and branched PFOS (n-PFOS and Sm-PFOS, respectively), and perfluorooctane sulfonamide (PFOSA). The limit of detection (LOD) for all PFAS was 0.1 ng/mL; values below the LOD were replaced with LOD/2 for statistical analyses (range 0% to 100% of samples <LOD for children and 0% to 100% of samples <LOD for mothers).

Handwipe Collection and Analysis

TESIE researchers collected handwipes during home visits with child participants using cotton twill wipes (4 x 4 in., MG Chemicals) pre-cleaned and wrapped in aluminum foil as previously described by Stapleton et al.[22] The wipes were soaked with 3 mL isopropyl alcohol and used by gloved researchers to wipe the entire surface of both hands and between each finger of the child participants. Once collected, the handwipes were wrapped in aluminum foil and stored at -20º C until analysis. Laboratory analysis was previously described[23], briefly, handwipes were spiked with internal standards, including 13C 6:2 FTOH, 13C 8:2 FTOH, deuterated MeFOSE, and deuterated EtFOSE, extracted by sonication, concentrated, and cleaned. The samples were concentrated to ~1 mL and analyzed using gas chromatography-mass spectrometry (GC/MS). Recovery of the

internal standards was assessed and field blanks (n=14) were analyzed for quality assurance and quality control. Method detection limits (MDLs) were calculated as 3 times the standard deviation of the levels in the field blanks; values below the MDL were replaced with the value LOD/2 for statistical analyses.

Dust Collection and Analysis

Participants were asked not to vacuum their home for two days prior to home visits. At home visits, TESIE researchers used an Eureka Mighty Mite vacuum that included a cellulose thimble within the hose attachment to vacuum the entire exposed floor area of the main living room, as previously described.[24] To prevent cross-contamination, the vacuum hose was cleaned with soap and water and solvent rinsed with methanol between home visits.[23] The thimbles containing house dust were wrapped in aluminum foil and stored at -20º C until analysis. Laboratory analysis was previously described[25]; briefly, dust samples were sieved prior to extraction and extracted similarly to the handwipes. Lab blanks and house dust standard reference material (n=5 each; SRM 2585 National Institute of Standards and Technology (NIST), Gaithersburg, MD) were analyzed with each batch for quality assurance and quality control and are reported in Hall et al. 2020. Method detection limits (MDLs) were calculated as 3 times the standard deviation of the levels in the lab blanks; values below the MDL were replaced with the value LOD/2 for statistical analyses.

Wristband Collection and Analysis

During the second half of the study, child participants in the TESIE study were given silicone wristbands to wear as personal sampling devices for seven days. As previously described[26], commercially available child-sized silicone wristbands (24hourwristbands.com, Houston, TX) were cleaned and dried in a fume hood, wrapped in aluminum foil, and placed in labeled 40 mL amber jars. The children were asked to wear the silicone wristbands continuously for seven days during all activities, including sleeping and bathing. After seven days, wristbands were wrapped in aluminum foil at home, placed back in the amber jars, and returned to our laboratory where they were stored at -20º C until analysis. Twenty-six of the wristbands were returned (the remainder (n=7) were not returned). To analyze the wristbands, they were cut using solvent-rinsed scissors, spiked with internal standards, extracted and the extracts were concentrated. The concentrated extracts were filtered to remove large particles, cleaned, concentrated to ~1 mL and analyzed by GC/MS. Recovery of internal standards was assessed along with field blanks and lab blanks for quality assurance and quality control. Method detection limits (MDLs) were calculated as 3 times the standard deviation of the levels in the field blanks; values below the MDL were replaced with the value LOD/2 for statistical analyses.

Passive Air Sampler Collection and Analysis

A smaller, convenience sample of willing participants (n=17) had passive air samplers placed in their homes during the study. At home visits, polyurethane foam

passive air samplers sorbent-impregnated with XAD-4 resin (SIPs), as previously described[27,28], were placed at least 1 meter off the ground in an area that was not likely to be disturbed in the main living room of the participants' homes. The SIPs were left undisturbed in the home and collected after 21 days and then stored at -20° C until analysis. SIPs were extracted, concentrated, cleaned, and analyzed by GC/MS. To convert the total amount of PFAS measured on the SIPs (ng) to air concentrations (ng/m^3), we divided the total by the estimated air volume sampled during the time period the SIPs were in participants' homes. We assumed that participants' homes had an indoor temperature of 22° C for the duration of the 21 days that they were sampled. Prior to this study, we conducted a small calibration study for the SIPs in a home over the course of 21 days. Due to changing air concentrations and a small number of data points in our calibration study, estimated air volumes used in this study were based on previous studies[18,27,28], although our estimate of the air sampling rates were similar in magnitude to those previously estimated in the literature (e.g. 3.4 m^3/day vs. 3.6 m^3/day 8:2 FTOH). Estimated air volumes were as follows: 6:2 FTOH=65 m^3, 8:2 FTOH=76 m^3, 10:2 FTOH=73 m^3, EtFOSE=76 m^3, MeFOSE=75 m^3.

Predictor Data

At the home visit, parents were asked to complete questionnaires containing information about child, parent, housing, and water characteristics. Children's height and weight were measured by trained study personnel. In addition to the maternal serum, handwipe, dust, wristband, and air samples, we considered potential predictors of child

serum PFAS, including the following characteristics of the child: sex, age at serum collection, history of breastfeeding, body mass index (BMI), frequency of hand washing, frequency of eating out and eating microwave popcorn, time spent at home or in the car, and the season that the child's serum sample was collected (determined using the week of home visit). We considered the following maternal characteristics: age at child participant's birth, race, parity at the time of the child's birth, education, and whether the mother was married or cohabitating. Finally, we considered the following water and housing-related characteristics: whether the home was supplied with municipal water or well water; use of any type of water filter (e.g., whole house, refrigerator, pitcher); consumption of usually bottled, usually tap, or a mixture of both types of water; type of home the child lived in (i.e., mobile home or trailer, apartment, one family attached house, or one family detached house); year the home was built; number of years living in the current home; carpeting in the child's bedroom, room where child most often played, and/or living room; and frequency of vacuuming per month.

Statistical Analyses

PFAS detected in >65% of participants were included in analyses. We examined univariate distributions of PFAS measured in all samples to assess normality. We calculated descriptive statistics of covariates and PFAS measured in all media. We compared the geometric mean PFAS concentrations from children in our study to child participants aged 3 to 5 years in the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of U.S. citizens, collected between 2013

and 2014, the closest available ages and years of collection to when our study children's samples were collected (CDC, 2019). We compared serum PFAS concentrations from maternal participants of our study to those of female NHANES participants aged 19 to 40 years measured between 2009 and 2010 (n=364), the closest available years to when our maternal serum samples were collected (CDC, 2019). We calculated Spearman correlations between PFAS measured in child serum and PFAS in maternal serum, handwipes, dust, wristbands, and air. Statistical significance was set at $p<0.05$.

Shapiro-Wilk tests were used to assess normality of the outcome, children's serum concentrations, none of which were normally or log-normally distributed. Additionally, there were some outliers of concern in the data set; we therefore used robust regression models with the MM estimation method (SAS, 2008) to estimate associations of child serum PFAS concentrations with predictors. This method can withstand a high proportion of outliers and maintain its robustness, and has higher statistical efficiency than some other methods of dealing with outliers (SAS, 2008). All variables were modeled as continuous untransformed variables.

Predictor variables were added one at a time to multivariable models and adjusted for a set of core variables: child sex, breastfeeding history, child BMI, maternal race (non-Hispanic black and Hispanic versus non-Hispanic white), maternal parity at the time of the child's birth (nulliparous versus parous), and maternal education at the time the child's serum was drawn. Due to small sample sizes, multivariable models estimating associations between child serum PFAS and air or wristband PFAS concentrations were adjusted for maternal race only, since it was the strongest predictor of child serum PFAS

concentrations.

Some participants had missing data on breastfeeding duration (4.8%), maternal parity (4.8%), and whether the mother was married or cohabitating (1.2%). We used multiple imputation with 10 imputations using the robust regression method in the proc mi procedure in SAS(SAS, 2015) to impute these missing data, and then combined results using proc mianalyze based on Rubin's rule(Rubin, 2004). We performed all statistical analyses using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC).

Results

Participant characteristics

Participant, housing, and water characteristics are presented in **Table 4.1**. Children in our study were 3 to 6 years (mean 4.4 years) of age. Approximately 61% of child participants were male. Approximately half (51%) of the children in our study had breastfed for three or more months. For 50% of the children, guardians reported that they ate out more than one time per week, and 44% of children ate microwave popcorn more than one time per month. Mothers in our study ranged in age from 19 to 40 years (mean 29.7 years). Approximately 45% of mothers self-identified as non-Hispanic white, 42% as non-Hispanic black, and 11% as Hispanic. Most mothers (60%) in our study had at least one previous pregnancy when the child participant was born. The majority of maternal serum samples were collected during the 1st trimester (58%). Most participants reported drinking municipal (87%) versus well (13%) water, and most participants obtained drinking water from Durham, NC (73%) rather than from other water sources (26%).

PFAS detection and correlations

Table 4.2 displays concentrations of PFAS detected in child and maternal serum samples compared to those detected in the U.S. population from the NHANES study. PFOS had the highest geometric mean serum concentration among both children and mothers, 2.6 and 6.0 ng/mL, respectively. Geometric mean child serum PFAS

concentrations in our study were similar or slightly lower than those detected in U.S. children aged 3 to 5 years from NHANES. When we compared females aged 19 to 40 from the NHANES study to prenatal serum samples from mothers in our study, we found that geometric mean serum PFAS concentrations were fairly similar.

PFAS concentrations in child serum samples were moderately to highly positively correlated with each other (r_s=0.37 to 0.99), all of which reached statistical significance ($p<0.05$) (Table S4.1). Linear and total PFOA were highly correlated with each other (r_s=0.97), and linear and branched PFOS were highly correlated with total PFOS (r_s=0.99 and 0.91, respectively) and with each other (r_s=0.86). PFHxS was moderately to highly correlated with total, linear, and branched PFOS (*rs*=0.72, 0.69, and 0.78, respectively) and with total and linear PFOA (r_s=0.60 and 0.65, respectively). Linear and branched PFOA were moderately to highly correlated with total PFOS (r_s=0.67 and 0.71, respectively), linear PFOS (*rs*=0.66 and 0.70, respectively), and branched PFOS (r_s=0.68 and 0.70, respectively).

In general, prenatal maternal serum PFAS concentrations were weakly to moderately positively correlated with child serum concentrations (r_s=0.02 to 0.32). (**Table S4.2**). Correlations between maternal and child PFHxS (r_s=0.27), PFOA (r_s=0.30), n-PFOA (r_s=0.30), PFOS (r_s=0.25), n-PFOS (r_s=0.28), and Sm-PFOS (r_s=0.23) all reached statistical significance.

PFAS detected and measured in environmental samples are presented in **Table 4.3**. 6:2 FTOH had the highest geometric mean concentration in handwipe, wristband,

and air samples (78.0 ng/wipe, 167 ng/g, and 3.2 ng/m^3, respectively), while 8:2 FTOH had the highest geometric mean concentration in dust samples (1,512 ng/g).

Correlations between child serum PFAS and environmental samples are listed in **Table S4.3**. PFAS in handwipes and dust were generally weakly correlated with child serum PFAS concentrations (r_s=-0.18 to 0.15 for handwipes and r_s=-0.11 to 0.24 for dust). PFAS detected in wristbands were slightly more correlated with child serum PFAS (either positively or negatively) than with handwipes and dust (r_s=-0.24 to 0.41). PFAS detected in air samples were the most highly correlated of our environmental samples with child serum PFAS (r_s=-0.02 to 0.64) with several, including PFOS in serum and MeFOSE in air (r_s=0.49), reaching statistical significance. However, some of the highest correlations between PFAS in child serum and air samples were between PFAS in serum that could not be derived from the correlated compounds in air, such as PFHxS in serum and 6:2 and 8:2 FTOH in air (r_s=0.64 and 0.50, respectively) and PFOA in serum and EtFOSE in air (r_s=0.49).

Predictors of child serum PFAS concentrations

Based on results from regression models investigating associations between child serum PFAS concentrations and the core set of predictor variables (i.e., child sex, breastfeeding history, child BMI, maternal race, maternal parity, maternal education), the strongest predictor of child serum PFAS concentration was maternal race (**Figure 4.2a and Table S4.1**). Compared to non-Hispanic white mothers, children of non-Hispanic

black mothers had lower concentrations of PFHxS (β=-0.20 ng/mL, 95% CI=-0.36, -0.04), PFOA (β=-0.46 ng/mL, 95% CI=-0.89, -0.03), n-PFOA (β=-0.49 ng/mL, 95% CI=-0.87, -0.12), PFOS (β=-0.71 ng/mL, 95% CI=-1.4, -0.08), n-PFOS (β=-0.53 ng/mL, 95% CI=-1.1, -0.01), and Sm-PFOS (β=-0.19 ng/mL, 95% CI=-0.34, -0.04) ($p<0.05$ for all listed PFAS). Associations were not as clear for children with Hispanic mothers compared to those with non-Hispanic white mothers, likely due to the relatively small number of participants with Hispanic mothers (n=9). Compared to females, male children generally had lower serum PFAS concentrations, with PFNA having the most precise effect estimate; on average, males had 0.11 ng/mL lower serum PFNA concentrations than females (95% CI=-0.21, -0.02).

None of the other core model variables strongly predicted child serum PFAS concentrations. However, the data suggest that children that had ever breastfed generally had higher concentrations of serum PFAS than children that had never breastfed (range: 0.09 ng/mL [95% CI=-0.04, 0.35] to 0.65 ng/mL [95% CI=-0.14, 1.4] higher). Children whose mothers were nulliparous prior to their birth generally had higher serum PFAS concentrations than those whose mothers had had a previous child (range: 0.01 ng/mL [95% CI=-0.09, 0.12] to 0.39 ng/mL [95% CI=-0.23, 1.0] higher). Also, children whose mothers had less than some college education generally had lower concentrations of serum PFAS than those whose mothers completed at least some college (range: -0.32 ng/mL [95% CI=-1.2, 0.53] to 0.01 ng/mL [95% CI=-0.22, 0.25]).

Children that ate out one or more times per week had, on average, 0.41 ng/mL (95% CI=0.03, 0.79) and 0.32 ng/mL (95% CI=-0.01, 0.65) higher serum PFOA and n-

PFOA concentrations compared to those that ate out less frequently (**Figure 4.2c and Table S4.4**). Children that ate microwave popcorn more than one time per month had higher serum PFHxS concentrations (β=0.14 ng/mL, 95% CI=0.004, 0.27) than those that ate less microwave popcorn. Generally, the season that the child's serum was collected did not appear to be associated with serum PFAS concentrations; however, serum that was collected in the fall had 0.61 ng/mL higher concentrations of PFOA compared to serum that was collected in the winter (95% CI=0.13, 1.1). Compared to children that drank primarily well water, children that drank municipal water averaged 0.58 ng/mL higher serum concentrations of PFOA (95% CI=0.05, 1.1) (**Figure 4.2b2 and Table S4.4**). Other characteristics were generally not associated with child serum PFAS concentrations.

Some PFAS measured in prenatal maternal serum samples were associated with child serum samples (**Figure 4.2c and Table S4.4**). PFHxS detected in maternal serum was positively associated with PFHxS in child serum (β=0.13, 95% CI=0.01, 0.26); PFOA in maternal serum was positively associated with n-PFOA in child serum (β=0.17, 95% CI=0.001, 0.34); and n-PFOS in maternal serum was positively associated with both PFOS (β=0.11, 95% CI=0.01, 0.21) and n-PFOS (β=0.10, 95% CI=0.02, 0.19) in child serum.

We found that several PFAS detected in air were predictive of child serum PFAS (**Figure 4.2 and Table S4.5**). MeFOSE detected in air was positively associated with PFHxS (β=0.21 ng/mL, 95% CI=0.08, 0.35), PFOS (β=2.2 ng/mL, 95% CI=1.7, 2.8), n-PFOS (β=1.6 ng/mL, 95% CI=1.1, 2.1), and Sm-PFOS (β=0.64 ng/mL, 95% CI=0.55,

0.73) in child serum. EtFOSE in air was positively associated with Sm-PFOS (β=3.6 ng/mL, 95% CI=1.5, 5.8) in child serum. Some of the positive associations between PFAS in child serum and air samples that reached statistical significance were between compounds in air that are not precursors of those found in serum, such as MeFOSE detected in air and PFNA (β=0.08 ng/mL, 95% CI=0.02, 0.15), PFOA (β=0.54 ng/mL, 95% CI=0.13, 0.94) and n-PFOA (β=0.49 ng/mL, 95% CI=0.16, 0.83) in child serum; EtFOSE in air and PFOA (β=15.6 ng/mL, 95% CI=5.1, 26.1) and n-PFOA (β=12.4 ng/mL, 95% CI=2.7, 22.2) in child serum; 6:2 FTOH (β=0.01 ng/mL, 95% CI=0.001, 0.02), 8:2 FTOH (β=0.04 ng/mL, 95% CI=0.02, 0.06), and 10:2 FTOH (β=0.12 ng/mL, 95% CI=0.02, 0.21) in air and PFHxS in child serum.

Generally, PFAS detected in handwipes and dust (**Table S4.4**) were not predictive of child serum PFAS, nor were PFAS detected in wristbands (**Table S4.5**). It is possible that with a larger sample size of wristbands we may have seen a stronger association between MeFOSE in wristbands and PFOS (β=263 ng/mL, 95% CI=-62.2, 239) and/or n-PFOS (β=231 ng/mL, 95% CI=-27.0, 490) in child serum.

Discussion

In our child participants (aged 3-6 years) sampled between 2014 and 2016 in central North Carolina, we found evidence that, similar to previous study findings, both food and water were predictors of child serum PFOA concentrations. Consumption of municipal water compared to well water in this region of North Carolina was a stronger

predictor (29% higher) of serum concentrations than eating out one or more times per week (compared to eating out less). We also found that those that ate microwave popcorn more frequently had higher concentrations of PFHxS than those that ate it once or less per month. Certain demographic factors were predictive of PFAS exposure: children with non-Hispanic black mothers had lower serum concentrations of several PFAS than those with non-Hispanic white mothers, and male children generally appeared to have lower serum concentrations of PFAS than female children, though only PFNA reached statistical significance. Prenatal maternal serum and air concentrations of certain PFAS were good predictors of several PFAS in children's serum, although other environmental predictors did not appear to be associated.

Based on the results of the environmental samples we collected, we found that participants were exposed to a number of different PFAS (**Table 4.2**). In handwipes, wristbands, and air, 6:2 FTOH was the PFAS with the highest geometric mean concentration, while 8:2 FTOH was the PFAS with the highest geometric mean concentration in dust, which is similar to findings from previous studies that included environmental samples (Fraser et al., 2012, 2013). As observed in previous studies, a number of different PFAS were detected in both maternal and child serum (**Table 4.2**), with PFOS having the highest serum concentrations in both mothers and children (Calafat et al., 2007; Harris et al., 2017; Hu et al., 2018; Kingsley et al., 2018; Sagiv et al., 2015). Mothers, whose serum samples were collected during an earlier time period than children's serum samples, generally had higher geometric mean concentrations of PFAS than children, with the exception of PFOA and n-PFOA, which had similar

concentrations in both children's and maternal serum. This is reflective of other studies that have found that certain PFAS concentrations have decreased over time, that children in the same age range as our study tend to have lower concentrations of many PFAS than adults, and that PFAS concentrations generally increase with age (Barton et al., 2020; Hu et al., 2018; Pitter Gisella et al., n.d.).

Although we did not ask specifically what type(s) of food participants consumed, we found that children that ate out more frequently had 0.41 ng/mL higher concentrations of PFOA than those that ate out less. PFAS have been commonly used as oil- and water-resistant paper and cardboard coatings for fast-food paper and cardboard containers and in microwave popcorn bags (Begley et al., 2005, 2008; Tittlemier et al., 2007). Previous studies have observed that people that consumed fast food recently and/or frequently had higher concentrations of PFAS, including: PFOA, PFNA, PFDA, PFHxS, PFOS, and MeFOSAA in their bodies than those that ate it less frequently (Boronow et al., 2019; Harris et al., 2017; Susmann et al., 2019). We observed that children that ate microwave popcorn more frequently had higher concentrations of perfluorosulfonic acids (range 0.07 to 0.40 ng/mL), with PFHxS reaching statistical significance compared to those that did not eat it as frequently, which is similar to some previous findings (Susmann et al., 2019). Unlike other study findings that people who regularly and/or recently consumed microwave popcorn had higher concentrations of serum PFOA and PFNA (Susmann et al., 2019; Wu et al., 2015), we did not observe higher concentrations of perfluorinated carboxylic acids with more frequent microwave popcorn consumption.

We found that drinking water was a predictor of PFOA exposure in our study participants. Almost three quarters of the children in this study resided in Durham, which uses water from Lake Michie and Little River Reservoir as sources of drinking water. This surface water may have a higher potential for contamination from PFAS in runoff water than ground water from wells in this region. Previous studies have found that drinking water is an important predictor of PFAS exposure, with those that drank water from a highly PFAS-contaminated source having higher serum concentrations of PFAS compared to those with non-contaminated water sources (Barton et al., 2020; Boronow et al., 2019; Daly et al., 2018; Hu et al., 2019; Pitter Gisella et al., n.d.). Whether or not the child drank mostly bottled water and/or the use of a water filter did not appear to affect child serum PFAS concentrations in our study, although some previous studies have found that those that drank only bottled water or a mix of bottled, well, and tap water had lower concentrations of certain PFAS compared to those that drank only tap water (Barton et al., 2020; Pitter Gisella et al., n.d.). This may be due in part to the fact that we did not have a large enough sample size to separate out different types of water filters, some of which may be more effective of reducing PFAS concentrations than others (Herkert et al., 2020).

Maternal race was a strong predictor of PFAS exposure with children of non-Hispanic white mothers having higher concentrations of PFHxS, PFOA, n-PFOS, PFOS, n-PFOS, and Sm-PFOS. Similarly, previous studies have found that race is an important predictor of PFAS exposure (Boronow et al., 2019), and that children of non-Hispanic black mothers have lower concentrations of certain PFAS than those of non-Hispanic

white mothers (Harris et al., 2017; Kingsley et al., 2018). Although some previous studies found that Hispanic participants had lower serum concentrations of certain PFAS than non-Hispanic white participants (Barton et al., 2020), we did not find a strong difference in serum concentrations between children of non-Hispanic white and Hispanic mothers, perhaps due to the inclusion of only a very small number of children with Hispanic mothers in our study (n=9).

We found evidence that male children had lower serum concentrations of PFNA than females, but did not find strong evidence that concentrations of other PFAS differed by sex. In the HOME study, males sampled at age 3 and 8 generally had lower concentrations of PFAS than females, though none reached statistical significance (Kingsley et al., 2018). In contrast, some other studies have found that males, in adolescence and adulthood, generally have higher concentrations of certain PFAS than females (Barton et al., 2020; Hu et al., 2018; Pitter Gisella et al., n.d.; Wu et al., 2015). Unlike previous study findings that PFAS is present in breastmilk (Jin et al., 2020; Mogensen et al., 2015; Nyberg et al., 2018), that breastfeeding is predictive of PFAS levels in infancy (Harris et al., 2017; Kingsley et al., 2018; Mogensen et al., 2015; Wu et al., 2015), and that maternal PFAS concentrations decrease with increased breastfeeding duration (Brantsæter et al., 2013), we did not find a large difference in serum PFAS concentrations between children that ever breastfed compared to those that never breastfed, perhaps due to the low number of participants that never breastfed in our study (n=12). We did not observe an association between child BMI and PFAS serum concentrations among our study participants; one previous study found that children with

a higher BMI had lower concentrations of certain PFAS (Harris et al., 2017), while another found that certain PFAS were highest among obese adults compared to those with a lower BMI (Brantsæter et al., 2013). Despite previous studies that found an association between maternal parity and maternal and/or child serum samples (Brantsæter et al., 2013; Kingsley et al., 2018; Pitter Gisella et al., n.d.; Sagiv et al., 2015; Shu et al., 2018), our study found that maternal parity was only weakly associated with child serum PFAS concentrations. Unlike previous study findings that maternal educational attainment was positively associated with certain PFAS exposures in child and/or maternal serum (Brantsæter et al., 2013; Harris et al., 2017), we did not find strong evidence of an association between child serum PFAS and maternal education. Although we did not collect information on household income, which was found to be predictive of certain PFAS exposures in previous studies (Brantsæter et al., 2013; Harris et al., 2017), information on educational attainment is often reflective of socioeconomic status. We did not observe a difference in child serum PFAS associated with maternal age, unlike some previous studies (Harris et al., 2017; Kingsley et al., 2018). Finally, we found that children whose serum was collected in the fall had higher concentrations of PFOA than those that were sampled in the winter, though we did not observe any other seasonal differences in serum concentrations. Though exposure to some compounds has been shown in previous studies to vary by season (D. Wang et al., 2019), the estimated elimination half-life of PFOA is years; thus there may not be a true difference in associations between child serum collected in the fall versus the winter and this may be a spurious result.

We found that certain maternal PFAS serum concentrations, measured while the child participants were *in utero,* were still associated with child serum PFAS at age 3 to 6 years. Specifically, prenatal PFHxS was associated with child PFHxS, prenatal PFOA was associated with child n-PFOA, and prenatal n-PFOS was associated with child PFOS. Previous studies have also found that certain prenatal serum samples were associated with corresponding PFAS in child serum samples years later (Harris et al., 2017). Based on a review of previous literature (ATSDR, 2018), the estimated half-life of those PFAS in humans is 4.7 to 35 years for PFHxS, 2.1 to 10.1 years for PFOA, and 3.1 to 27 years for PFOS. Thus, some of the PFASs measured in child serum are likely attributable to prenatal exposure, while some may reflect a shared environment (Fraser et al., 2012; Makey et al., 2017).

We found an association between PFAS in air and child serum PFHxS, PFOA, n-PFOA, PFOS, n-PFOS, and Sm-PFOS concentrations, which is similar to previous study findings that have examined associations between PFAS detected in serum and air in adults (Beesoon et al., 2012; Fraser et al., 2012; Makey et al., 2017; Poothong et al., 2020), and the first to our knowledge to observe these associations in children. Previous studies have demonstrated associations between serum concentrations and environmental exposures to PFAS and their precursors through inhalation of contaminated indoor air (presumably derived from products in home and/or office environments) (Balk et al., 2019; Beesoon et al., 2012; Fraser et al., 2012; Poothong et al., 2020). This is indicative that the home environment is an important route of exposure to PFAS. Some of the PFAS precursors detected in air in our study are associated with derivatives of those compounds

(e.g., MeFOSE in air and PFHxS and PFOS in serum), however other PFAS precursors detected in air were associated with PFAS that are not derivatives of those compounds (e.g., MeFOSE and EtFOSE in air and PFOA and n-PFOA in serum, and 8:2 FTOH and 10:2 FTOH in air and PFHxS in serum). The latter results may be due to the fact that PFAS derivatives detected in child serum were all correlated with each other.

We did not find strong evidence of an association between child serum and PFAS detected in handwipes, dust, or wristbands. Despite our results, inhalation and ingestion of contaminated dust has been suggested in some studies to be a source of environmental PFAS exposure (Balk et al., 2019; Beesoon et al., 2012; Poothong et al., 2020), though the association is not as clear in other studies (Fraser et al., 2013; Wu et al., 2015). As a potential source of exposure to PFAS, some previous studies have found that having carpet in the home (Hu et al., 2018), particularly if treated for stain-resistance (Beesoon et al., 2012; Boronow et al., 2019), and/or sleeping in a room with a carpet or rug is predictive of certain PFAS exposures (Harris et al., 2017); however we did not find evidence of this in our study. There have been fewer studies exploring potential dermal and hand-to-mouth routes of PFAS exposure by examining associations between PFAS detected on handwipes and serum samples; however, one such study found that PFDS, which we did not measure in our study, detected in handwipes was correlated with serum concentrations (Poothong et al., 2020).

Strengths and limitations

A strength of our study is that it is the first, to our knowledge, to examine multiple PFAS exposure pathways (maternal serum, water, demographics, BMI, behavior, and environmental samples), in children. We also examined many different PFAS in both environmental media and serum samples. Finally our study population is fairly diverse, which allows us to generalize our results to a wider population, since many previous studies have been conducted in relatively homogeneous populations (e.g. (Harris et al., 2017; Kingsley et al., 2018; Sagiv et al., 2017)).

A limitation of this study is the relatively small sample size; a larger study population would likely have given us a clearer picture of predictors of child serum PFAS concentrations and increased the precision of associations that we observed in our analyses. For example, only a fraction of the participants wore wristbands or had air samplers placed in their homes. Socioeconomic status is complicated; we collected information about maternal race and education, but not household income, an important predictor of PFAS exposure (Brantsæter et al., 2013; Harris et al., 2017; Sagiv et al., 2017). The dietary information that we collected was limited; we asked about the frequency of eating out, but did not ask the type(s) of restaurants or foods that participants were eating, which are predictors of PFAS exposure based on other studies (Boronow et al., 2019; Brantsæter et al., 2013; Hansen et al., 2016; Hu et al., 2018; Lin et al., 2020; Pitter Gisella et al., n.d.; Poothong et al., 2020; Timmermann et al., 2019; Wu et al., 2015). We did not ask any questions about personal care product use, another potential source of PFAS exposure (Boronow et al., 2019). Drinking water can be an

important source of PFAS exposure (Boronow et al., 2019; Daly et al., 2018; Hu et al., 2019; Pitter Gisella et al., n.d.). Although we asked participants if they mostly drank tap, bottled, or a mix of both types of water and whether they had well or city water, we did not collect any water samples, which would have given us information on actual participant-level PFAS exposures from drinking water. Finally, care is needed in the interpretation of our results as the models may not be causal.

Conclusion

In our relatively diverse population of children aged 3 to 6 years sampled between 2014 and 2016, we found that frequency of eating out and eating microwave popcorn, maternal race, drinking water source, maternal serum and air PFAS concentrations were predictive of certain PFAS detected in child serum samples. Future studies should examine predictors of PFAS in air, collect water samples to further examine drinking water as a source of exposure, and evaluate child PFAS exposures in a larger study population.

Figure 4.1. Study population and sample sizes for serum and environmental samples

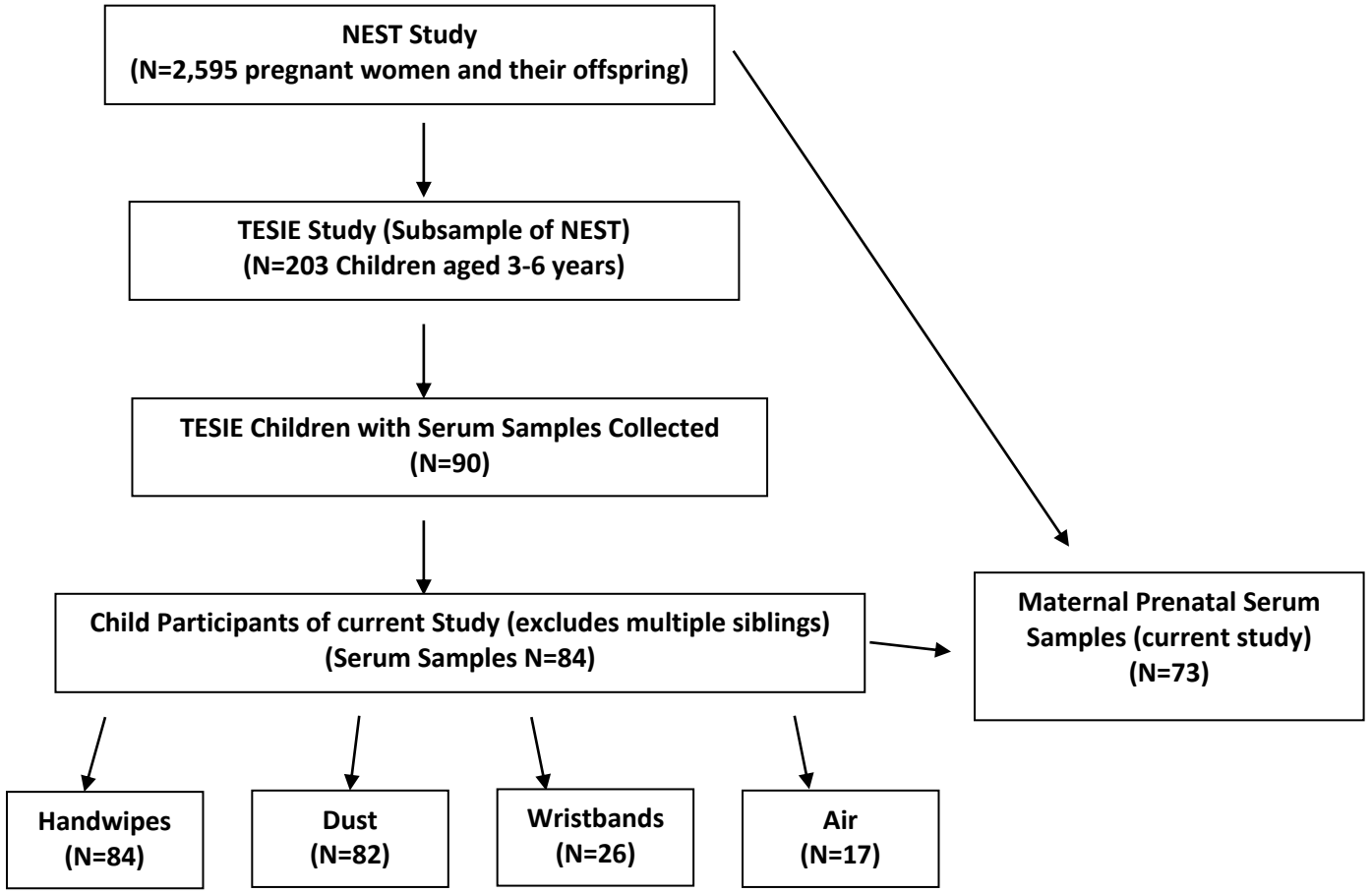


Table 4.1. Characteristics of Study Participants (n=84 Mother/Child Pairs)

Child Characteristics		Maternal Characteristics	
	Mean +/- SD or N (%)		Mean +/- SD or N (%)
Child's Age at Blood Draw (years)	4.4 +/- 0.56	Maternal Age at Delivery	29.7 +/- 5.7
Sex		Maternal Race/Ethnicity	
Male	51 (60.7)	Non-Hispanic White	38 (45.2)
Female	33 (39.3)	Non-Hispanic Black	35 (41.7)
Breastfeeding Duration		Hispanic	9 (10.7)
Never	12 (14.3)	Other	2 (2.4)
Ever	68 (81.0)	Maternal Parity	
≥3 Months	43 (51.2)	0	30 (35.7)
Missing	4 (4.8)	≥1	50 (59.5)
BMI (Percentile)		Missing	4 (4.8)
Underweight/Normal (<85th)	59 (70.2)	Maternal Education During Pregnancy	
Overweight (85-<95th)	16 (19.1)	<High School	15 (17.9)
Obese (≥95th)	9 (10.7)	HS Diploma or GED	16 (19.1)
Hours Spent Inside the Home Per Day		Some College	14 (16.7)
≤12	22 (26.2)	College Degree or Higher	39 (46.4)
13-18	46 (54.8)	Maternal Education at Child Sampling	
≥19	16 (19.0)	<High School	11 (13.1)
Time Spent Inside a Car Per Day		HS Diploma or GED	11 (13.1)
≤30 minutes	35 (41.7)	Some College	17 (20.2)
31 minutes to 1 hour	27 (32.1)	Associate's Degree or Higher	45 (53.6)
>1 hour	22 (26.2)	Mother Married or Cohabitating	
Frequency of Hand Washing Per day		No	23 (27.4)
1-2	6 (7.1)	Yes	60 (71.4)
3-6	51 (60.7)	Missing	1 (1.2)
≥7	27 (32.1)	Gestational Age at Blood Draw	
Frequency of Eating Out		1st Trimester	49 (58.3)
<1 time a week	42 (50.0)	2nd Trimester	30 (35.7)
1-2 times a week	25 (29.8)	3rd Trimester	5 (6.0)
≥3 times a week	17 (20.2)		
Frequency of Eating Microwave Popcorn			
<1 time a month	47 (56.0)		
1-3 times a month	23 (27.4)		
≥4 times a month	14 (16.7)		
Season Sampled			
Winter	18 (21.4)		
Spring	19 (22.6)		
Summer	21 (25.0)		
Fall	26 (31.0)		

Table 4.1 (Continued). Characteristics of Study Participants (n=84 Mother/Child Pairs)

Housing Characteristics		Drinking Water Characteristics	
	Mean +/- SD or N (%)		Mean +/- SD or N (%)
Housing Type		Drinking Water Type	
Mobile Home or Trailer	1 (1.2)	Usually Tap	29 (34.5)
Apartment	22 (26.2)	Usually Bottled	25 (29.8)
One Family Attached House	5 (6.0)	A Mix of Tap and Bottled	30 (35.7)
One Family Detached House	56 (66.7)	Well or City Water	
Year Home Was Built		City	73 (86.9)
Before 1959	6 (7.1)	Well	11 (13.1)
1960-1977	16 (19.0)	Water Company	
1978-1999	19 (22.6)	Durham	61 (72.6)
2000 to present	21 (27.8)	Other than Durham	22 (26.2)
Don't know	22 (25.6)	Missing	1 (1.2)
Number of Years Family in Home		House Water Filter	
<2 Years	22 (26.2)	Yes	8 (9.5)
2-5.5 Years	34 (40.5)	No	40 (47.6)
6-9 Years	21 (25.0)	Missing	36 (42.9)
≥10 Years	7 (8.3)	Faucet Water Filter	
Carpet in Child's Bedroom		Yes	6 (7.1)
Yes	61 (72.6)	No	78 (92.9)
No	23 (27.4)	Refrigerator Water Filter	
Carpet in Child's Play Room		Yes	22 (26.2)
Yes	47 (56.0)	No	29 (34.5)
No	37 (44.0)	Missing	33 (37.1)
Carpet in Living Room		Pitcher Water Filter	
Yes	37 (44.0)	Yes	9 (10.7)
No	47 (56.0)	No	39 (46.4)
Number of Times Vacuum		Missing	36 (42.9)
None	13 (15.5)	Unknown Water Treatment	
1-3 Times a Month	16 (19.0)	Yes	2 (2.4)
4-6 Times a Month	19 (22.6)	No	45 (53.6)
>6 Times a Month	36 (42.9)	Missing	37 (44.0)
		Any Water Filter or Treatment	
		Yes	40 (47.6)
		No	44 (52.4)

Table 4.2. Descriptive statistics for PFAS in serum samples

MATRIX AND COMPOUND	N (%) DETECT	GEOMETRIC MEAN	MINIMUM	MEDIAN	MAXIMUM	NHANES[B] GEOMEAN
CHILD SERUM[A] (NG/ML) N=84						
ETFOSAA	1 (1.2)	N/A	<LOD	<LOD	0.80	N/A
MEFOSAA	35 (41.7)	N/A	<LOD	<LOD	3.4	N/A
PFDA	49 (58.3)	N/A	<LOD	0.20	1.1	0.10 (<LOD, 0.13)
PFHXS	84 (100)	0.71	0.20	0.70	10.0	0.72 (0.62, 0.83)
PFNA	83 (98.8)	0.42	<LOD	0.40	1.4	0.76 (0.63, 0.93)
PFOA	84 (100)	1.7	0.40	1.8	4.0	2.0 (1.8, 2.3)
N-PFOA	84 (100)	1.5	0.40	1.6	3.9	1.9 (1.6, 2.2)
SB-PFOA	43 (51.2)	N/A	<LOD	0.10	1.7	N/A
PFOS	84 (100)	2.6	0.20	3.0	20.0	3.4 (3.0, 3.8)
N-PFOS	83 (98.8)	2.0	<LOD	2.0	20.0	2.2 (2.0, 2.5)
SM-PFOS	82 (97.6)	0.51	<LOD	0.50	3.0	1.0 (0.87, 1.2)
PFOSA	0 (0.0)	N/A	<LOD	<LOD	<LOD	N/A
MATERNAL SERUM[A] (NG/ML) N=73						
ETFOSAA	0 (0.0)	N/A	<LOD	<LOD	<LOD	N/A
MEFOSAA	19 (26.0)	N/A	<LOD	<LOD	1.0	0.15 (0.06, 0.25)
PFDA	67 (91.8)	0.26	<LOD	0.20	1.0	0.23 (0.14, 0.33)
PFHXS	73 (100)	0.90	0.20	0.90	3.6	0.87 (0.78, 0.96)
PFNA	73 (100)	0.79	0.30	0.70	2.1	0.97 (0.87, 1.1)
PFOA	73 (100)	1.8	0.70	2.0	6.6	2.2 (2.1, 2.3)
N-PFOA	73 (100)	1.7	0.60	1.8	6.4	N/A
SB-PFOA	28 (38.4)	N/A	<LOD	<LOD	0.30	N/A
PFOS	73 (100)	6.0	1.1	6.1	29.0	5.6 (5.5, 5.7)
N-PFOS	73 (100)	4.5	1.0	4.6	21.0	N/A
SM-PFOS	73 (100)	1.4	0.10	1.4	7.8	N/A
PFOSA	0 (0.0)	N/A	<LOD	<LOD	<LOD	N/A

N/A: Not calculated - proportion of results below limit of detection was too high to provide a valid result; [a]Limit of detection (LOD) = 0.1 ng/mL

[b]Child Serum Data compared to NHANES data for children aged 3-5 years (n=181) 2013-2014; Maternal Serum Data Compared to NHANES data for females of all aged 19-40 years (n=364) 2009-2010

Table 4.3. Descriptive statistics for PFAS in environmental samples

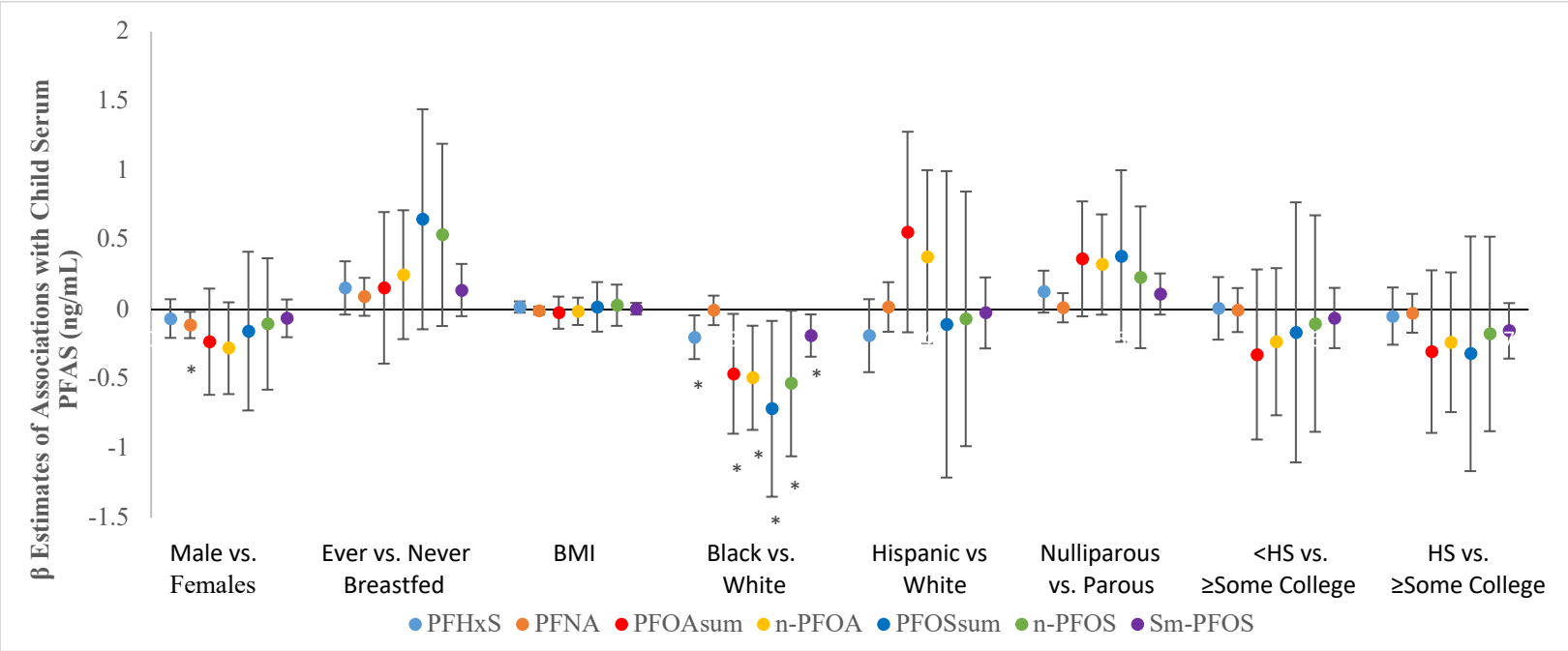
MATRIX AND COMPOUND	N (%) DETECT	GEOMETRIC MEAN	MINIMUM	MEDIAN	MAXIMUM
HAND WIPE (NG/WIPE) N=84					
6:2 FTOH	80 (95.2)	78.0	<MDL	75.5	10,629
8:2 FTOH	60 (71.4)	15.3	<MDL	19.4	150
ETFOSE	57 (67.9)	1.3	<MDL	1.5	38.2
MEFOSE	45 (53.6)	0.89	<MDL	0.63	2,209
DUST (NG/G) N=82					
6:2 FTOH	78 (95.1)	548	<MDL	594	29,464
8:2 FTOH	82 (100)	1,512	97.3	1,342	44,222
ETFOSE	14 (17.1)	N/A	<MDL	<MDL	366
MEFOSE	15 (18.3)	N/A	<MDL	<MDL	7,981
6:2 DIPAP	82 (100)	122	1.1	119	34,360
8:2 DIPAP	31 (37.8)	N/A	<MDL	<MDL	5,128
PFBS	1 (1.2)	N/A	<MDL	<MDL	473
PFBA	9 (11.0)	N/A	<MDL	<MDL	502
PFHPA	12 (14.6)	11.1	<MDL	<MDL	713
PFHXA	79 (96.3)	10.0	<MDL	9.6	1,382
PFHXS	52 (63.4)	1.3	<MDL	1.2	187
PFNA	82 (100)	4.2	0.26	3.3	208
PFOA	82 (100)	10.6	0.67	10.3	2,354
PFOS	73 (89.0)	5.4	<MDL	5.1	892
WRISTBANDS (NG/G) N=26					
6:2 FTOH	25 (96.2)	167	<MDL	208	3,688
8:2 FTOH	17 (65.4)	27.3	<MDL	26.0	107
10:2 FTOH	23 (88.5)	7.2	<MDL	9.4	61.3
ETFOSE	24 (92.3)	1.0	<MDL	1.2	14.9
MEFOSE	24 (92.3)	1.4	<MDL	1.6	6.7
6:2 DIPAP[C]	24 (100)	13.3	0.11	14.3	437
8:2 DIPAP[C]	22 (91.7)	1.8	<MDL	1.9	52.9
PFBS[C]	2 (8.3)	N/A	<MDL	<MDL	0.35
PFBA[C]	0 (0.0)	N/A	<MDL	<MDL	<MDL
PFHPA[C]	2 (8.3)	N/A	<MDL	<MDL	0.34
PFHXA[C]	5 (20.8)	N/A	<MDL	<MDL	0.34
PFDA[A]	13 (54.2)	N/A	<MDL	0.26	0.34
PFHXS[A]	2 (8.3)	N/A	<MDL	<MDL	0.34
PFNA[A]	16 (66.7)	0.08	<MDL	0.06	0.34
PFOA[A]	5 (20.8)	N/A	<MDL	<MDL	0.15
PFOS[A]	9 (37.5)	N/A	<MDL	<MDL	0.56
AIR (NG/M^3) N=17					
6:2 FTOH	13 (76.5)	3.2	<MDL	3.3	49.6
8:2 FTOH	17 (100)	2.3	0.06	3.3	13.2
10:2 FTOH	13 (76.5)	0.74	<MDL	0.99	3.5

ETFOSE	13 (76.5)	0.03	<MDL	0.03	0.67
MEFOSE	17 (100)	0.21	0.01	0.20	4.0

N/A: Not calculated - proportion of results below method detection limit to provide a valid result; [c]n= 24

Figure 4.2. Associations and Confidence Intervals from Robust Regression Models for Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

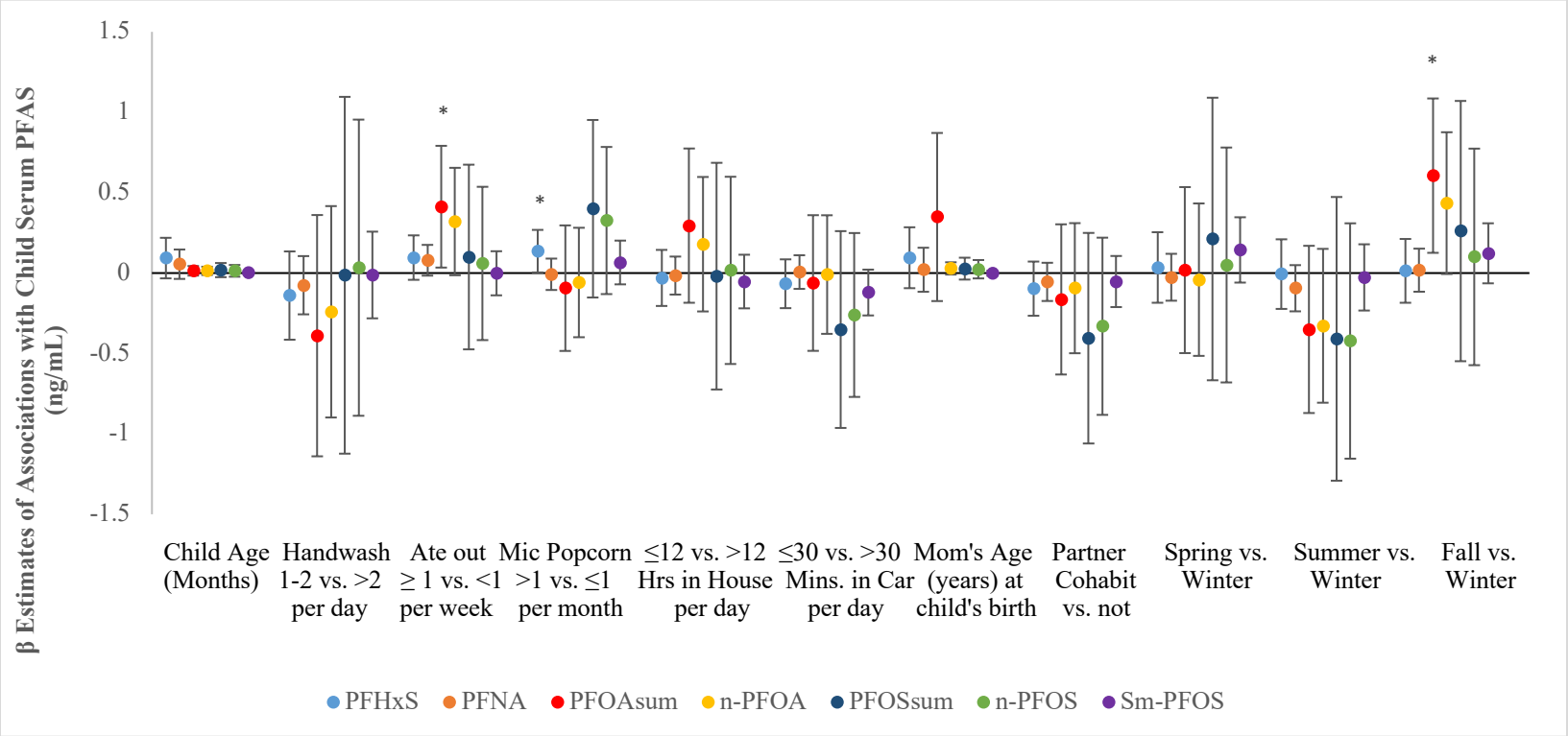
a. Core Model: sex, breastfeeding, child BMI, race, parity, and education (mutually adjusted)



*Statistically significant ($p<0.05$)

Figure 4.2 (Continued). Adjusted Associations† and Confidence Intervals from Robust Regression Models for Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

b1. Predictors, analyzed one at a time†

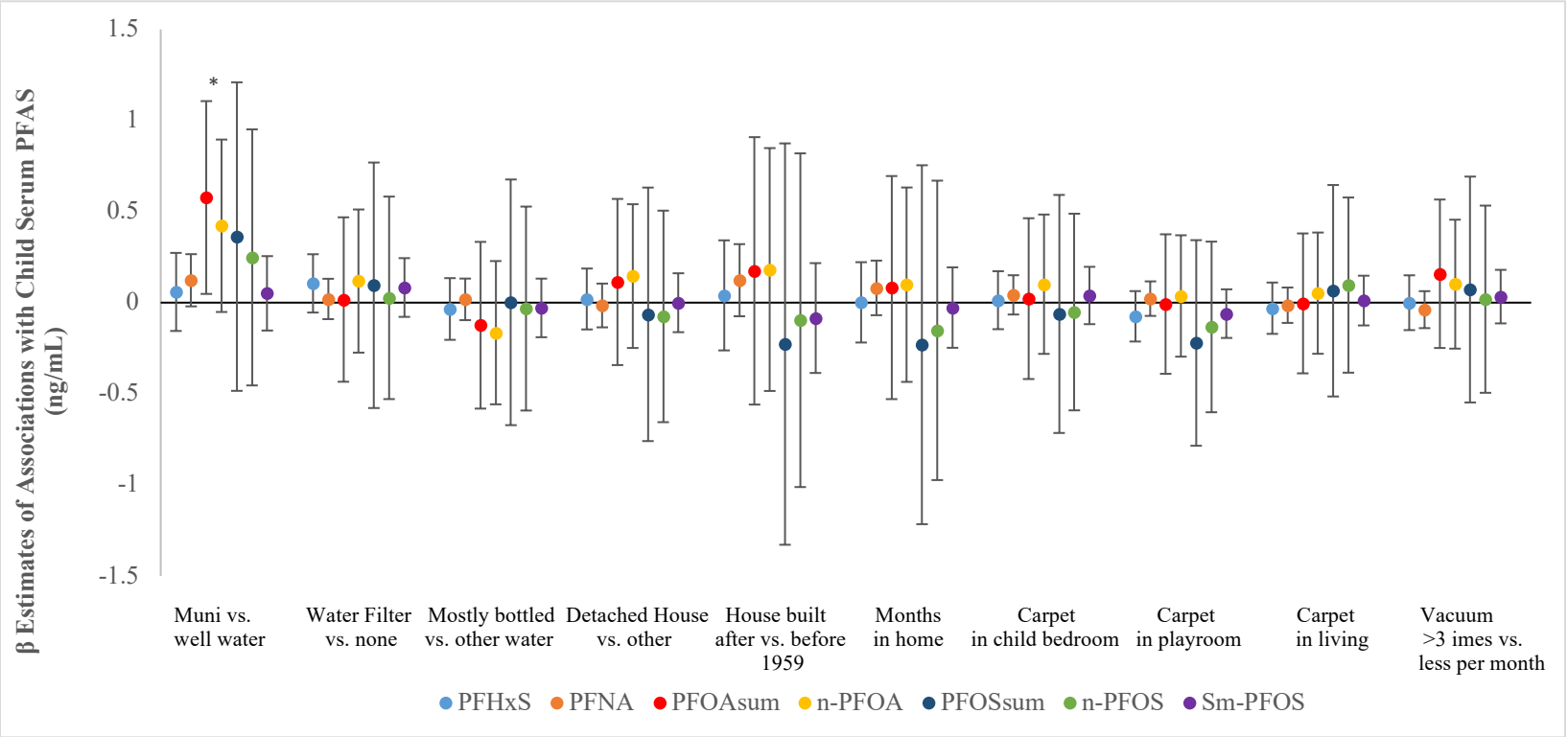


†Adjusted for core variables: sex, breastfeeding, child BMI, race, parity, and education

*Statistically significant ($p<0.05$)

Figure 4.2 (Continued). Adjusted Associations† and Confidence Intervals from Robust Regression Models for Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

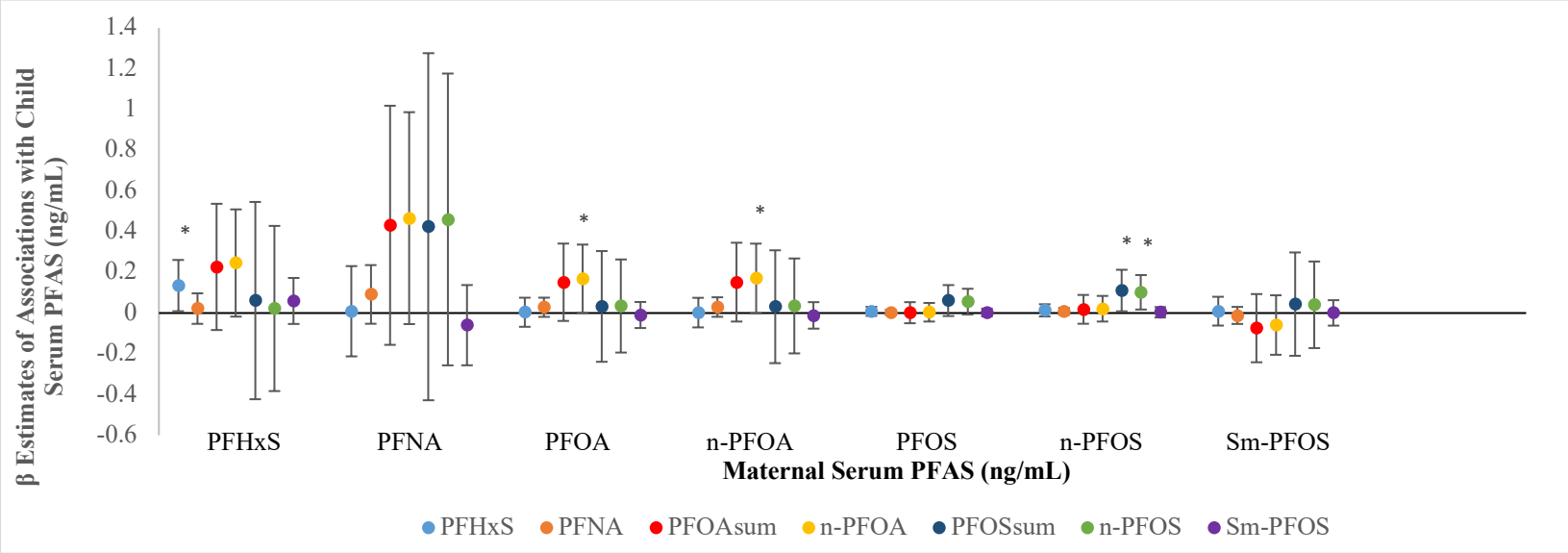
b2. Predictors, analyzed one at a time†



†Adjusted for core variables: sex, breastfeeding, child BMI, race, parity, and education
*Statistically significant ($p<0.05$)

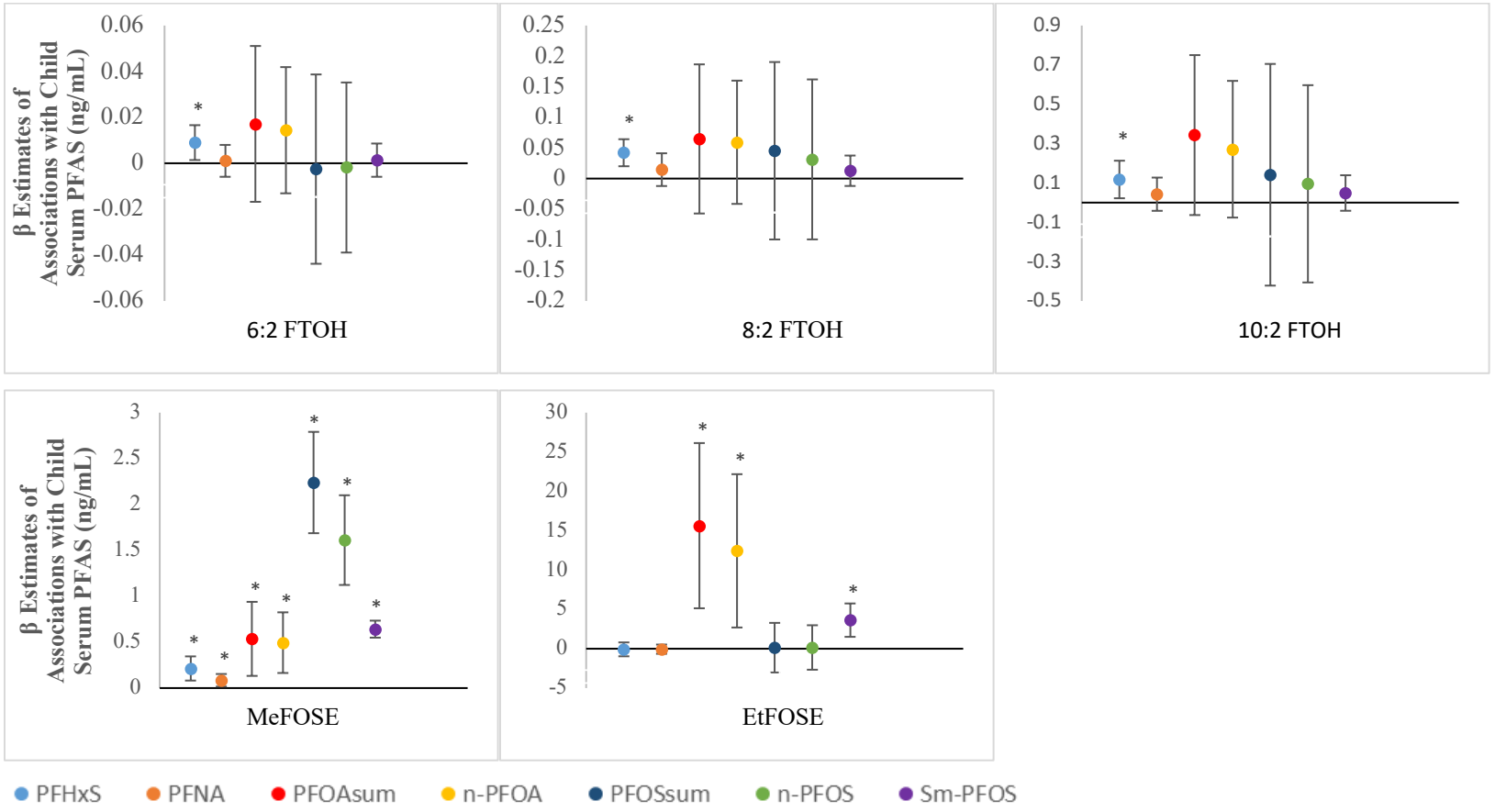
Figure 4.2 (Continued). Adjusted Associations[†] and Confidence Intervals from Robust Regression Models for Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

c. Maternal Serum PFAS[¥], analyzed one at a time[†]



[†]Adjusted for core variables: sex, breastfeeding, child BMI, race, parity, and education
[¥]Maternal PFDA not included in graph
*Statistically significant ($p<0.05$)

Figure 4.3. Adjusted Associations† and Confidence Intervals from Robust Regression Models for PFAS Concentrations in Air (ng/m^3) and TESIE Participant Child Serum Samples



†Adjusted for race

*Statistically significant ($p<0.05$).

Table S4.1. Spearman correlations between PFAS in child serum samples (n=84)

	PFHxS	PFNA	PFOA	n-PFOA	PFOS	n-PFOS	Sm-PFOS
PFHxS	1	0.39*	0.60*	0.65*	0.72*	0.69*	0.78*
PFNA		1	0.55*	0.59*	0.44*	0.46*	0.37*
PFOA			1	0.97*	0.67*	0.66*	0.68*
n-PFOA				1	0.71*	0.70*	0.70*
PFOS					1	0.99*	0.91*
n-PFOS						1	0.86*
Sm-PFOS							1

*p<0.05

Table S4.2. Spearman correlations between PFAS in maternal serum during pregnancy and child serum samples (n=73)

		Child						
		PFHxS	**PFNA**	**PFOA**	**n-PFOA**	**PFOS**	**n-PFOS**	**Sm-PFOS**
Mother	**PFDA**[a]	0.13	0.14	0.28*	0.30*	0.31*	0.31*	0.27*
	PFHxS	0.27*	0.02	0.28*	0.27*	0.16	0.13	0.23
	PFNA	0.17	0.20	0.31*	0.32*	0.23	0.24*	0.15
	PFOA	0.08	0.05	0.30*	0.31*	0.12	0.12	0.11
	n-PFOA	0.06	0.05	0.29*	0.30*	0.11	0.11	0.09
	PFOS	0.19	0.15	0.16	0.20	0.25*	0.25*	0.23
	n-PFOS	0.16	0.18	0.16	0.18	0.27*	0.28*	0.21
	Sm-PFOS	0.24*	0.06	0.14	0.18	0.16	0.14	0.23*

*p<0.05; [a]n=67

Table S4.3. Spearman correlations between PFAS in hand wipes, wristbands, air, dust, and child serum samples

	Child Serum						
	PFHxS	**PFNA**	**PFOA**	**n-PFOA**	**PFOS**	**n-PFOS**	**Sm-PFOS**
Handwipes (n=84)							
6:2 FTOH	0.12	-0.05	-0.07	-0.05	-0.003	-0.01	0.02
8:2 FTOH	0.07	-0.18	-0.08	-0.06	-0.04	-0.05	-0.03
EtFOSE	0.11	-0.14	-0.005	0.02	0.15	0.14	0.12
Dust (n=82)							
6:2 FTOH	0.13	0.19	0.18	0.23*	0.20	0.22	0.16
8:2 FTOH	-0.11	-0.02	0.11	0.11	-0.02	-0.002	-0.06
6:2 diPAP	0.12	0.05	0.02	0.005	0.11	0.09	0.12
PFHxA	0.16	0.04	0.05	0.06	0.09	0.08	0.13
PFNA	0.03	0.07	-0.06	-0.05	-0.02	-0.03	0.01
PFOA	0.22	0.03	0.09	0.12	0.15	0.13	0.24*
PFOS	0.19	-0.006	0.08	0.06	0.16	0.15	0.18
Wristbands (n=26)							
6:2 FTOH	0.11	0.11	-0.18	-0.07	-0.09	-0.11	-0.10
8:2 FTOH	0.11	0.20	-0.14	-0.06	-0.21	-0.24	-0.11
10:2 FTOH	0.17	0.07	-0.17	-0.04	-0.10	-0.13	-0.02
EtFOSE	0.03	-0.13	-0.02	0.04	0.15	0.16	0.06
MeFOSE	0.06	-0.03	0.04	0.13	0.34	0.35	0.22
6:2 diPAP[a]	-0.03	0.10	0.006	0.09	-0.13	-0.13	-0.15
8:2 diPAP[a]	0.07	0.07	-0.07	0.05	-0.17	-0.17	-0.17
PFNA[a]	0.33	-0.08	0.41*	0.33	0.04	0.03	0.22
Air (n=17)							
6:2 FTOH	0.33	-0.02	0.03	0.06	0.04	0.04	0.10
8:2 FTOH	0.64*	0.44	0.34	0.43	0.28	0.28	0.35
10:2 FTOH	0.50*	0.39	0.36	0.44	0.15	0.16	0.25
EtFOSE	0.13	-0.05	0.49*	0.42	0.47	0.42	0.38
MeFOSE	0.20	0.19	0.35	0.30	0.49*	0.44	0.46

*$p<0.05$; [a]n=24

Table S4.4. Adjusted Associations[†] from Robust Regression Models for Multiple Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

	Beta Estimates of Child Serum PFAS Concentration[†] (ng/mL) (95% Confidence Interval)						
Core Model	**PFHxS**	**PFNA**	**PFOA**	**n-PFOA**	**PFOS**	**n-PFOS**	**Sm-PFOS**
Male vs. Female	-0.06 (-0.20, 0.07)	-0.11* (-0.21, -0.02)	-0.23 (-0.61, 0.15)	-0.28 (-0.61, 0.05)	-0.16 (-0.73, 0.42)	-0.10 (-0.58, 0.37)	-0.06 (-0.20, 0.07)
Ever vs. Never Breastfed	0.16 (-0.04, 0.35)	0.09 (-0.04, 0.23)	0.16 (-0.39, 0.70)	0.25 (-0.21, 0.71)	0.65 (-0.14, 1.4)	0.54 (-0.12, 1.2)	0.14 (-0.05, 0.33)
Child BMI	0.02 (-0.02, 0.06)	-0.01 (-0.04, 0.02)	-0.02 (-0.14, 0.09)	-0.01 (-0.11, 0.09)	0.02 (-0.16, 0.20)	0.03 (-0.12, 0.18)	0.01 (-0.04, 0.05)
Non-Hispanic Black vs. Non-Hispanic White	-0.20* (-0.36, -0.04)	-0.01 (-0.11, 0.10)	-0.46* (-0.89, -0.03)	-0.49* (-0.87, -0.12)	-0.71* (-1.4, -0.08)	-0.53* (-1.1, -0.01)	-0.19* (-0.34, -0.04)
Hispanic vs. Non-Hispanic White	-0.19 (-0.45, 0.07)	0.02 (-0.16, 0.20)	0.56 (-0.16, 1.3)	0.38 (-0.24, 1.0)	-0.11 (-1.2, 1.0)	-0.07 (-0.98, 0.85)	-0.02 (-0.28, 0.23)
Nulliparous vs. Parous	0.13 (-0.02, 0.28)	0.01 (-0.09, 0.12)	0.36 (-0.05, 0.78)	0.32 (-0.04, 0.69)	0.39 (-0.23, 1.0)	0.23 (-0.28, 0.74)	0.11 (-0.04, 0.26)
<HS Edu. vs. ≥ Some College	0.01 (-0.22, 0.23)	-0.004 (-0.16, 0.15)	-0.32 (-0.94, 0.29)	-0.23 (-0.76, 0.30)	-0.16 (-1.1, 0.77)	-0.10 (-0.88, 0.68)	-0.06 (-0.28, 0.16)
HS or GED vs. ≥ Some College	-0.05 (-0.25, 0.16)	-0.03 (-0.17, 0.11)	-0.30 (-0.89, 0.28)	-0.24 (-0.74, 0.27)	-0.32 (-1.2, 0.53)	-0.18 (-0.88, 0.52)	-0.15 (-0.35, 0.05)
Covariates							
Child Age	0.01 (-0.003, 0.02)	0.005 (-0.003, 0.01)	0.01 (-0.02, 0.04)	0.01 (-0.01, 0.04)	0.02 (-0.03, 0.06)	0.01 (-0.02, 0.05)	0.002 (-0.01, 0.01)
Child washed their hands 1 to 2 times vs. ≥ 3 times per day	-0.14 (-0.41, 0.13)	-0.08 (-0.26, 0.11)	-0.39 (-1.1, 0.36)	-0.24 (-0.90, 0.42)	-0.01 (-1.1, 1.1)	0.03 (-0.89, 0.95)	-0.01 (-0.28, 0.26)
Child ate out ≥ 1 vs. <1 time per week	0.10 (-0.04, 0.23)	0.08 (-0.02, 0.18)	0.41* (0.03, 0.79)	0.32 (-0.01, 0.65)	0.10 (-0.47, 0.67)	0.06 (-0.41, 0.54)	-0.001 (-0.14, 0.14)
Child ate Microwave Popcorn > 1 vs. ≤ 1 time per month	0.14* (0.004, 0.27)	-0.01 (-0.11, 0.09)	-0.09 (-0.48, 0.30)	-0.06 (-0.40, 0.28)	0.40 (-0.15, 0.95)	0.33 (-0.13, 0.78)	0.07 (-0.07, 0.20)
Child spent 12 or less hrs vs. > 12 hrs in the home per day	-0.03 (-0.20, 0.14)	-0.02 (-0.13, 0.10)	0.29 (-0.18, 0.77)	0.18 (-0.24, 0.60)	-0.02 (-0.72, 0.69)	0.02 (-0.57, 0.60)	-0.05 (-0.22, 0.11)
Child spent 30 or less mins vs. > 30 mins in the car per day	-0.07 (-0.22, 0.09)	0.01 (-0.10, 0.11)	-0.06 (-0.48, 0.36)	-0.009 (-0.38, 0.36)	-0.35 (-0.96, 0.26)	-0.26 (-0.77, 0.25)	-0.12 (-0.26, 0.02)

[†]Adjusted for sex, ever vs. never breastfed, Child BMI, race, maternal parity at birth, and maternal education at the time the child was sampled; *p<0.05

Table S4.4 (Continued). Adjusted Associations[†] from Robust Regression Models for Multiple Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

	Beta Estimates of Child Serum PFAS Concentration[†] (ng/mL) (95% Confidence Interval)						
Covariates	**PFHxS**	**PFNA**	**PFOA**	**n-PFOA**	**PFOS**	**n-PFOS**	**Sm-PFOS**
Mom's age at child birth	0.01 (-0.01, 0.02)	0.002 (-0.01, 0.01)	0.03 (-0.01, 0.07)	0.03 (-0.01, 0.07)	0.03 (-0.04, 0.10)	0.02 (-0.03, 0.08)	-0.001 (-0.02, 0.01)
Partner cohabit vs. not	-0.10 (-0.27, 0.07)	-0.05 (-0.17, 0.06)	-0.16 (-0.63, 0.30)	-0.09 (-0.50, 0.31)	-0.41 (-1.1, 0.25)	-0.33 (-0.88, 0.22)	-0.05 (-0.21, 0.11)
Spring vs. Winter	0.03 (-0.18, 0.25)	-0.03 (-0.17, 0.12)	0.02 (-0.50, 0.53)	-0.04 (-0.52, 0.43)	0.21 (-0.67, 1.1)	0.05 (-0.68, 0.78)	0.14 (-0.06, 0.35)
Summer vs. Winter	-0.01 (-0.22, 0.21)	-0.09 (-0.24, 0.05)	-0.35 (-0.87, 0.17)	-0.33 (-0.81, 0.15)	-0.41 (-1.3, 0.47)	-0.42 (-1.2, 0.31)	-0.03 (-0.23, 0.18)
Fall vs. Winter	0.01 (-0.18, 0.21)	0.02 (-0.12, 0.15)	0.61* (0.13, 1.1)	0.43 (-0.01, 0.88)	0.26 (-0.55, 1.1)	0.10 (-0.57, 0.77)	0.12 (-0.06, 0.31)
Municipal vs. well water	0.06 (-0.16, 0.27)	0.12 (-0.02, 0.27)	0.58* (0.05, 1.1)	0.42 (-0.05, 0.90)	0.36 (-0.48, 1.2)	0.25 (-0.45, 0.95)	0.05 (-0.15, 0.26)
Water filter vs. none	0.11 (-0.05, 0.27)	0.02 (-0.09, 0.13)	0.02 (-0.43, 0.47)	0.12 (-0.27, 0.51)	0.10 (-0.58, 0.77)	0.03 (-0.53, 0.58)	0.08 (-0.08, 0.24)
Mostly bottled vs. other water	-0.03 (-0.20, 0.13)	0.02 (-0.10, 0.13)	-0.12 (-0.58, 0.33)	-0.16 (-0.56, 0.23)	0.002 (-0.67, 0.68)	-0.03 (-0.59, 0.53)	-0.03 (-0.19, 0.13)
Detached house vs. other	0.02 (-0.15, 0.19)	-0.02 (-0.14, 0.10)	0.11 (-0.34, 0.57)	0.15 (-0.25, 0.54)	-0.06 (-0.76, 0.63)	-0.08 (-0.66, 0.51)	-0.0004 (-0.16, 0.16)
House built after 1959 vs. before	0.04 (-0.26, 0.34)	0.12 (-0.07, 0.32)	0.17 (-0.56, 0.91)	0.18 (-0.48, 0.85)	-0.23 (-1.3, 0.87)	-0.10 (-1.0, 0.82)	-0.08 (-0.39, 0.22)
Years in current home	0.0001 (-0.02, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.04, 0.06)	0.01 (-0.04, 0.05)	-0.02 (-0.10, 0.06)	-0.01 (-0.08, 0.06)	-0.002 (-0.02, 0.02)
Child Bedroom Carpet vs. none	0.01 (-0.15, 0.17)	0.04 (-0.07, 0.15)	0.02 (-0.42, 0.46)	0.10 (-0.28, 0.48)	-0.06 (-0.72, 0.59)	-0.05 (-0.59, 0.49)	0.04 (-0.12, 0.20)
Child Play Room Carpet vs. none	-0.08 (-0.21, 0.06)	0.02 (-0.07, 0.12)	-0.01 (-0.39, 0.38)	0.04 (-0.30, 0.37)	-0.22 (-0.79, 0.34)	-0.13 (-0.60, 0.33)	-0.06 (-0.19, 0.07)
Living Room Carpet vs. none	-0.03 (-0.17, 0.11)	-0.01 (-0.11, 0.08)	-0.004 (-0.39, 0.38)	0.05 (-0.28, 0.38)	0.07 (-0.52, 0.65)	0.10 (-0.38, 0.58)	0.01 (-0.13, 0.15)
Vacuum 3 or less vs. 4 or more times per month	-0.0004 (-0.15, 0.15)	-0.04 (-0.14, 0.06)	0.16 (-0.25, 0.57)	0.10 (-0.25, 0.46)	0.07 (-0.55, 0.69)	0.02 (-0.49, 0.53)	0.03 (-0.11, 0.18)

[†]Adjusted for sex, ever vs. never breastfed, Child BMI, race, maternal parity at birth, and maternal education at the time the child was sampled;
*p<0.05

Table S4.4 (Continued). Adjusted Associations[†] from Robust Regression Models for Multiple Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

Beta Estimates of Child Serum PFAS Concentration[†] (ng/mL) (95% Confidence Interval)							
Maternal Serum (ng/mL)	**PFHxS**	**PFNA**	**PFOA**	**n-PFOA**	**PFOS**	**n-PFOS**	**Sm-PFOS**
PFDA	-0.26 (-0.72, 0.21)	0.02 (-0.28, 0.32)	-0.03 (-1.3, 1.3)	-0.03 (-1.1, 1.1)	0.94 (-1.2, 3.1)	0.96 (-0.78, 2.7)	0.11 (-0.36, 0.58)
PFHxS	0.13* (0.01, 0.26)	0.02 (-0.05, 0.10)	0.23 (-0.08, 0.54)	0.25 (-0.02, 0.51)	0.06 (-0.42, 0.55)	0.02 (-0.38, 0.43)	0.06 (-0.05, 0.17)
PFNA	0.01 (-0.21, 0.23)	0.09 (-0.05, 0.24)	0.43 (-0.16, 1.0)	0.47 (-0.05, 0.99)	0.42 (-0.43, 1.3)	0.46 (-0.26, 1.2)	-0.06 (-0.26, 0.14)
PFOA	0.004 (-0.07, 0.08)	0.03 (-0.02, 0.08)	0.15 (-0.04, 0.34)	0.17* (0.001, 0.34)	0.03 (-0.24, 0.30)	0.03 (-0.19, 0.26)	-0.01 (-0.07, 0.05)
n-PFOA	0.002 (-0.07, 0.07)	0.03 (-0.02, 0.08)	0.15 (-0.04, 0.35)	0.17 (-0.001, 0.34)	0.03 (-0.25, 0.31)	0.03 (-0.20, 0.27)	-0.01 (-0.08, 0.05)
PFOS	0.01 (-0.01, 0.03)	0.003 (-0.01, 0.02)	0.002 (-0.05, 0.05)	0.004 (-0.04, 0.05)	0.06 (-0.01, 0.14)	0.06 (-0.01, 0.12)	0.003 (-0.02, 0.02)
n-PFOS	0.01 (-0.02, 0.04)	0.01 (-0.01, 0.03)	0.02 (-0.05, 0.09)	0.02 (-0.04, 0.08)	0.11* (0.01, 0.21)	0.10* (0.02, 0.19)	0.004 (-0.02, 0.03)
Sm-PFOS	0.01 (-0.06, 0.08)	-0.01 (-0.05, 0.03)	-0.07 (-0.24, 0.09)	-0.06 (-0.20, 0.09)	0.04 (-0.21, 0.30)	0.04 (-0.17, 0.25)	0.001 (-0.06, 0.06)
Handwipes (pg/wipe)							
6:2 FTOH	0.11 (-0.02, 0.25)	0.01 (-0.03, 0.04)	0.03 (-0.10, 0.17)	0.04 (-0.07, 0.16)	0.17 (-0.03, 0.36)	0.14 (-0.02, 0.30)	0.03 (-0.02, 0.08)
8:2 FTOH	0.55 (-1.8, 2.9)	-0.40 (-1.9, 1.1)	-2.6 (-8.6, 3.4)	-1.4 (-6.7, 3.9)	-1.3 (-10.4, 7.8)	-1.4 (-9.0, 6.1)	-0.33 (-2.5, 1.8)
EtFOSE	-4.0 (-17.2, 9.2)	-5.4 (-14.2, 3.5)	-9.2 (-45.0, 26.6)	-6.4 (-37.6, 24.8)	8.8 (-44.0, 61.6)	8.3 (-35.6, 52.1)	0.76 (-11.8, 13.3)

[†]Adjusted for sex, ever vs. never breastfed, Child BMI, race, maternal parity at birth, and maternal education at the time the child was sampled;
*p<0.05

Table S4.4 (Continued). Adjusted Associations† from Robust Regression Models for Multiple Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

Beta Estimates of Child Serum PFAS Concentration† (ng/mL) (95% Confidence Interval)							
Dust (pg/g)	**PFHxS**	**PFNA**	**PFOA**	**n-PFOA**	**PFOS**	**n-PFOS**	**Sm-PFOS**
6:2 FTOH	0.003 (-0.01, 0.02)	0.003 (-0.01, 0.01)	0.01 (-0.04, 0.05)	0.009 (-0.03, 0.05)	0.01 (-0.06, 0.07)	0.003 (-0.05, 0.06)	0.003 (-0.01, 0.02)
8:2 FTOH	-0.004 (-0.02, 0.01)	0.003 (-0.004, 0.01)	0.02 (-0.004, 0.05)	0.02 (-0.003, 0.04)	0.01 (-0.04, 0.05)	0.004 (-0.03, 0.04)	0.001 (-0.01, 0.01)
6:2 diPAP	0.008 (-0.01, 0.02)	-0.001 (-0.01, 0.01)	0.001 (-0.05, 0.05)	0.002 (-0.04, 0.04)	0.01 (-0.06, 0.08)	0.01 (-0.04, 0.07)	-0.004 (-0.02, 0.01)
PFHxA	0.10 (-0.30, 0.50)	-0.03 (-0.31, 0.25)	-0.14 (-1.3, 0.99)	-0.14 (-1.1, 0.85)	-0.01 (-1.7, 1.7)	0.21 (-1.2, 1.6)	-0.22 (-0.61, 0.18)
PFNA	-0.89 (-3.2, 1.4)	-0.37 (-2.0, 1.3)	-2.3 (-8.7, 4.2)	-1.9 (-7.5, 3.6)	-0.44 (-10.0, 9.1)	0.69 (-7.2, 8.6)	-0.99 (-3.3, 1.3)
PFOA	0.16 (-0.65, 0.97)	-0.02 (-0.16, 0.12)	-0.07 (-0.61, 0.48)	-0.04 (-0.52, 0.43)	0.06 (-0.74, 0.87)	0.09 (-0.57, 0.76)	-0.02 (-0.22, 0.17)
PFOS	0.13 (-0.32, 0.58)	0.16 (-0.13, 0.46)	0.70 (-0.54, 1.9)	0.61 (-0.50, 1.7)	0.02 (-2.1, 2.1)	0.11 (-1.6, 1.8)	-0.09 (-0.59, 0.42)

†Adjusted for sex, ever vs. never breastfed, Child BMI, race, maternal parity at birth, and maternal education at the time the child was sampled;
*p<0.05

Table S4.5. Adjusted Associations† from Robust Regression Models for Air and Wristband Predictors of PFAS Concentrations in TESIE participant Child Serum Samples

	Beta Estimates of Child Serum PFAS Concentration† (ng/mL) (95% Confidence Interval)						
	PFHxS	**PFNA**	**PFOA**	**n-PFOA**	**PFOS**	**n-PFOS**	**Sm-PFOS**
Air (ng/m^3)							
MeFOSE	0.21* (0.08, 0.35)	0.08* (0.02, 0.15)	0.54* (0.13, 0.94)	0.49* (0.16, 0.83)	2.2* (1.7, 2.8)	1.6* (1.1, 2.1)	0.64* (0.55, 0.73)
EtFOSE	-0.08 (-0.96, 0.80)	-0.06 (-0.64, 0.53)	15.6* (5.1, 26.1)	12.4* (2.7, 22.2)	0.13 (-3.0, 3.3)	0.16 (-2.7, 3.0)	3.6* (1.5, 5.8)
6:2 FTOH	0.01* (0.001, 0.02)	0.001 (-0.01, 0.01)	0.2 (-0.02, 0.05)	0.01 (-0.01, 0.04)	-0.003 (-0.04, 0.04)	-0.002 (-0.04, 0.04)	0.001 (-0.01, 0.01)
8:2 FTOH	0.04* (0.02, 0.06)	0.01 (-0.01, 0.04)	0.06 (-0.06, 0.19)	0.06 (-0.04, 0.16)	0.05 (-0.10, 0.19)	0.03 (-0.10, 0.16)	0.01 (-0.01, 0.04)
10:2 FTOH	0.12* (0.02, 0.21)	0.04 (-0.04, 0.13)	0.34 (-0.06, 0.75)	0.27 (-0.08, 0.62)	0.1 (-0.42, 0.70)	0.10 (-0.41, 0.60)	0.05 (-0.04, 0.14)
Wristbands (pg/g)							
MeFOSE	6.7 (-71.8, 85.3)	-6.7 (-46.0, 32.5)	14.3 (-242 271)	36.5 (-188, 261)	263 (-62.2, 239)	231 (-27.0, 490)	21.8 (-55.2, 98.8)
EtFOSE	-9.9 (-45.8, 26.0)	-8.1 (-26.7, 10.5)	-41.8 (-161, 77.5)	-35.8 (-141, 69.1)	43.6 (-107, 194)	53.5 (-68.4, 175)	-6.9 (-41.7, 28.0)
6:2 FTOH	0.28 (-0.03, 0.59)	0.02 (-0.05, 0.10)	-0.13 (-0.62, 0.35)	-0.10 (-0.52, 0.32)	-0.27 (-0.87, 0.33)	-0.23 (-0.72, 0.25)	-0.05 (-0.19, 0.08)
10:2 FTOH	3.4 (-4.7, 11.5)	0.31 (-3.8, 4.4)	-2.5 (-28.5, 23.5)	3.5 (-19.2, 26.1)	-10.5 (-43.3, 22.3)	-10.3 (-36.8, 16.3)	-0.35 (-7.9, 7.2)
6:2 diPAP	0.74 (-0.22, 1.7)	0.29 (-0.28, 0.86)	1.3 (-1.9, 4.4)	1.4 (-1.4, 4.1)	2.3 (-2.3, 6.8)	1.8 (-2.0, 5.6)	0.40 (-0.56, 1.4)
8:2 diPAP	7.0 (-2.3, 16.3)	-0.22 (-6.0, 5.6)	5.7 (-28.9, 40.3)	8.8 (-21.8, 39.3)	-20.9 (-63.7, 22.0)	-18.1 (-52.9, 16.7)	-2.1 (-12.5, 8.3)

†Adjusted for maternal race

CHAPTER FIVE: CONCLUSION

This research aimed to examine exposures to SVOCs among nail salon workers, pregnant women, and children, and to evaluate effects of prenatal exposure to PFAS on birth outcomes. We conducted analyses utilizing data from a study of female nail salon workers in the Greater Boston Area, from the NEST study, a birth cohort based in central North Carolina, and from the TESIE study, a subset of NEST study offspring. In *Chapter 2*, we examined occupational exposures to phthalates, phthalate alternatives, and OPEs in nail salon workers. In *Chapter 3*, we assessed associations between prenatal exposure to individual and a mixture of PFAS and birth outcomes, including gestational age at birth, birth weight, and birth weight for gestational age z-score. Additionally, we examined predictors of maternal serum PFAS concentrations. In *Chapter 4*, we examined environmental, demographic, and behavioral predictors of child serum PFAS concentrations.

Chapter 2. Exposure of nail salon workers to phthalates, di(2-ethylhexyl) terephthalate, and organophosphate esters: A pilot study

We assessed exposure to SVOCs by quantifying and comparing pre- and post-shift urinary concentrations of phthalates, phthalate alternatives, and OPEs along with levels measured on SWBs worn by nail salon workers during a single work shift. We found evidence that nail salon workers are occupationally exposed to the phthalate alternative DEHTP, with post-shift urinary concentrations of a DEHTP metabolite

(MECPTP) more than triple the concentrations of pre-shift concentrations. This change was moderately correlated with DEHTP levels on SWBs, suggesting an occupational exposure source rather than primarily other exposure sources such as diet that are unlikely to be picked up by SWBs. Although not previously examined in nail salon workers, increases of MECPTP during the day have previously been observed in general populations, however these increases were generally lower than what we observed for our pre- to post-shift change. Concentrations of DEHTP metabolites (MECPTP and MEHHTP) in nail technician post-shift urine samples were also higher than what was observed in US females.

While there was an upward trend for SVOC urinary metabolites from pre- to post-shift in our study, none reached statistical significance, perhaps due to small sample size. Post-shift urinary concentrations from our study participants were generally lower than concentrations from US females from NHANES, with the exception of urinary metabolites of DEHTP, TCEP, and TPHP.

Our pilot study demonstrated relatively high detection frequencies of a number of SVOCs on SWBs after having been worn by nail salon workers for only one shift (e.g., 6 to 11 hours). TPHP concentrations on lapel and wrist SWBs were not correlated, perhaps suggesting that different exposure sources of these compounds are encountered based on contact with skin and surfaces (more likely with wrist SWBs) versus those in the air (more likely with lapel SWBs).

Chapter 3. Per- and polyfluoroalkyl substances serum concentrations in pregnant women from North Carolina: Predictors and associations with birth outcomes

We examined associations between prenatal exposure to individual and a mixture of PFAS based on maternal serum samples collected between 5.6 and 29.6 weeks gestation (mean 12.6 weeks) and gestational age at birth, birth weight, and birth weight for gestational age z-score. In WQS analyses, we observed negative associations between the PFAS mixture index and gestational age at birth among all offspring with the linear isomer of PFOA (n-PFOA) contributing the most to this association. In sex-stratified models, we observed a negative association between the PFAS mixture index and gestational age at birth among male offspring, similarly with n-PFOA contributing most to this association, while the association was not as strong among females. The results for the other birth outcomes for all and sex-stratified analyses were not as clear. While it appears that there is a negative association between PFAS and birth weight among male offspring, we found evidence of confounding by physiology in that association, and that the mechanism of the association between prenatal serum PFAS concentrations and birth weight may in part be through shortened gestational length. Results for the association between maternal serum PFAS concentrations and birth weight for gestational age z-score were mostly null.

We also examined predictors of maternal serum PFAS concentrations. We detected several PFAS in maternal serum samples with PFOS and PFOA having the highest concentrations. As observed in previous studies there was some variability in maternal serum PFAS concentrations between racial/ethnic groups, with non-Hispanic

whites trending towards higher PFAS concentrations than non-Hispanic black and Hispanic mothers. With the exception of those who had a high school diploma or GED, mothers with a college degree or higher tended to have higher serum concentrations of certain PFAS compared to those with less education. Consistent with previous studies, parous mothers in our study had lower concentrations of serum PFAS, on average, than nulliparous mothers, likely due to placental transfer during pregnancy and/or excretion of PFAS through breastmilk. Finally, we observed that PFAS concentrations generally decreased with increasing week of pregnancy during which maternal serum samples were collected, which may be due to plasma volume expansion and increased glomerular filtration rate.

Chapter 4. Predictors of per- and polyfluoroalkyl substances (PFAS) concentrations in children's serum from the Toddlers Exposure to Semi-Volatile Organic Compounds in Indoor Environments (TESIE) Study

We examined environmental, demographic, and behavioral predictors of child serum PFAS concentrations. Based on the results of the environmental samples that we collected, we found that participants were exposed to a number of different PFAS. In handwipes, wristbands, and air, 6:2 FTOH was the PFAS with the highest geometric mean concentration, while 8:2 FTOH was the PFAS with the highest geometric mean concentration in dust. Compared to children's serum samples, which were collected during a later time period than maternal serum samples, maternal serum samples had

higher geometric mean concentrations of PFAS, with the exception of PFOA and n-PFOA, which had similar concentrations in both children's and maternal serum.

We found evidence that both food and water were predictors of child serum PFOA concentrations in our study, with consumption of municipal water compared to well water in the region of North Carolina that participants inhabited being a stronger predictor (29% higher) of serum concentrations than the comparison between children that ate out one or more time per week and those that ate out less. Whether or not the child drank mostly bottled water and/or the use of a water filter did not appear to affect child serum PFAS concentrations in our study, which may be due in part to the fact that we did not have a large enough sample size to separate out different types of water filters, some of which may be more effective at reducing PFAS concentrations than others. We also found that children that ate microwave popcorn more frequently had higher concentrations of PFHxS than those that ate it one or less time per month. Certain demographic factors were predictive of PFAS exposure: children with non-Hispanic black mothers had lower serum concentrations of several PFASs than those with non-Hispanic white mothers, and male children generally appeared to have lower serum concentrations of PFAS than female children, though only PFNA reached statistical significance. Other demographic and behavioral factors were only weakly or not associated with children's serum PFAS concentrations. Finally, we found that prenatal serum and air concentrations of certain PFAS were good predictors of several PFASs in children's serum, although other environmental predictors did not appear to be associated.

Study limitations

Study-specific limitations are discussed in detail in *Chapters 2-4*. A common limitation in all of our studies was a relatively small sample size that limited our statistical power. Additionally a consistent challenge that we encountered with all of our studies was a limitation in data that we gathered from our questionnaires. For example, from previous studies we know that diet is an important route of exposure for many SVOCs (Boronow et al., 2019; Brantsæter et al., 2013; Hansen et al., 2016; Hu et al., 2018; Lin et al., 2020; Pitter Gisella et al., n.d.; Poothong et al., 2020; Sagiv et al., 2015; Timmermann et al., 2019; Wu et al., 2015). Because we did not ask any dietary questions in the study of nail salon workers or in the NEST cohort, and only asked about frequency of eating out and microwave popcorn in the TESIE study, we were not able to exclude diet as a source of exposure to SVOCs among nail salon workers, or examine dietary predictors of maternal and child serum SVOCs in detail. We collected information about maternal race and education in the NEST and TESIE studies, but not household income, an important predictor of SVOC exposure (Brantsæter et al., 2013; Harris et al., 2017; Sagiv et al., 2015, 2017; Wenzel et al., 2018), limiting our ability to control for this variable in our studies. Finally, we did not ask any questions about personal care product use in our studies, another potential source of SVOC exposure based on previous findings (Boronow et al., 2019; Koniecki et al., 2011), which limits our ability to control for this variable in our studies.

In *Chapters 3 and 4* we measured maternal serum PFAS concentrations to characterize prenatal exposure to PFAS. Although the majority of serum samples were

collected early in pregnancy where pregnancy-induced changes in physiology are reduced (>58% during the first trimester of pregnancy in both studies), a potential limitation as discussed in *Chapter 3* is that plasma volume expansion and changes in glomerular filtration rate during pregnancy may lead to exposure misclassification and/or confound the association between prenatal PFAS exposure and birth weight (Bach et al., 2015; Steenland et al., 2018; Verner et al., 2015). We did not measure albumin or creatinine (potential markers for PVE and GFR, respectively) as other studies (e.g., Project VIVA) have done (Sagiv et al., 2017), and thus could not control for those measures.

Study strengths

Strengths of our study of nail salon workers include the use of biomonitoring, demonstration of the use of SWBs, collection of these samples in a sometimes difficult to reach population, and analysis for a wide spectrum of SVOCs. An additional strength is the paired use of biomonitoring and SWB data, which suggested that the increase of urinary DEHTP metabolites was due to occupational exposure rather than other sources such as diet. A major strength of our study examining associations between prenatal PFAS exposure and birth outcomes is the estimation of the effect of a PFAS mixture on birth outcomes, which reduces the potential for mutual confounding by other PFAS and allows us to determine which PFAS contribute most to the PFAS mixture index effect on birth outcomes. A strength of our study characterizing predictors of child serum PFAS is that it is the first, to our knowledge, to examine multiple exposure pathways (maternal serum, water, demographics, BMI, behavior, certain aspects of diet, and environmental

samples) of multiple PFAS exposures, in children. Additionally, both the NEST and TESIE study populations are fairly diverse, which allows us to generalize our results to a wider population, since many previous studies have been conducted in relatively homogenous populations (e.g. (Harris et al., 2017; Kingsley et al., 2018; Sagiv et al., 2017)).

Public health implications

Results from *Chapter 2* suggest that nail salon workers are occupationally exposed to a number of phthalates, phthalate alternatives, and OPEs. Metabolites of DEHTP showed the largest increase across the work day, with higher urinary metabolite concentrations from nail salon workers than US females. Urinary metabolites of DEHTP have increased in the US over time as DEHTP has replaced some of the more toxic phthalates used in consumer products (Koch et al., 2017; Silva et al., 2019; Zota et al., 2014). A dietary study of DEHTP fed to F-344 rats over 104 weeks found reduced weight gain and exacerbated geriatric retinal degeneration with chronic, high dietary exposure (6,000 or 12,000 ppm) (Deyo, 2008), although very little is known about the health impacts associated with exposures to DEHTP in humans. In the expanding nail salon industry, occupational exposures to phthalate alternatives could have important public health implications highlighting the need for future research on this topic.

Previous studies examining health impacts associated with occupational exposures among nail salon workers are limited, but have largely focused on self-

reported, acute symptoms based on self-report (Harris-Roberts et al., 2011; Roelofs et al., 2008; Shendell et al., 2018). Common symptoms reported by nail salon workers include headaches, musculoskeletal, respiratory, eye, nose, throat, and skin irritation (Harris-Roberts et al., 2011; Roelofs et al., 2008; Shendell et al., 2018). The majority of nail salon workers are female, many of whom are of reproductive age, and therefore prenatal exposures are of public health concern for pregnant women within that industry. A previous study found evidence of adverse birth outcomes, including infants that were small for gestational age, gestational diabetes, and placenta previa among manicurists (T Quach et al., 2015). Studies examining long-term occupational exposure to nail salon workers are lacking, and would help to better determine the public health impacts of working in this industry. Our research demonstrates the need for future studies to examine phthalate alternatives, including DEHTP and other novel SVOC exposures, and to better characterize potential health implications of occupational exposure to these SVOCs among nail salon workers, a vulnerable population in a growing industry.

Chapter 3 adds to the body of literature examining associations between PFAS exposure and birth outcomes. To our knowledge, our study is one of only a handful published that examined the cumulative effect of a mixture of prenatal PFAS on birth outcomes, and one of the first to examine both linear and branched isomers of PFOS and PFOA. In WQS models including all offspring, we observed a negative association between the PFAS mixture index and gestational age at birth with n-PFOA contributing most to this association. Our data suggest gestational age at birth among male offspring may be more susceptible to exposure to multiple PFASs than females. Preterm birth can

increase risk of mortality, and lead to a number of health complication for the premature infant, including respiratory, gastrointestinal, immunologic, central nervous system, hearing and vision problems (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). Although the magnitude of the association that we observed between PFAS exposure and gestational age at birth may not lead to significant health consequences for an individual, there could be significant public health implications on the population level. Our results add to more recent findings that suggest that previous findings of a negative association between PFAS exposure and birth weight may be confounded by changes in physiology during pregnancy (Bach et al., 2015; Steenland et al., 2018; Verner et al., 2015). Our results highlight the importance of examining associations between mixtures of multiple PFAS and birth outcomes rather than individual PFAS to examine cumulative effects and to reduce the potential for mutual confounding by other PFAS. Finally, we found evidence that the mechanism of the association observed between PFAS concentrations and birth weight may partly be through reduced gestational age rather than growth restriction, which should be examined further in future research.

Chapter 4 represents the first study to examine multiple PFAS exposure pathways (maternal serum, water, demographics, BMI, behavior, and environmental samples), in children. This study is also one of the first to examine many different PFAS in both environmental media and serum samples. As observed in previous studies, we found that frequency of eating out and consumption of municipal water in central North Carolina were predictors of child serum PFOA concentrations with drinking water being the

stronger predictor of exposure. This highlights the need to include these predictors in future studies. Similar to some studies, we found that microwave popcorn was predictive of higher serum concentrations of perfluorosulfonic acids (Susmann et al., 2019) (PFSAs), but not perfluorinated carboxylic acids (PFCAs) as observed in other studies (Susmann et al., 2019; Wu et al., 2015). Historically, PFCAs such as PFOA, were more commonly used to coat microwave popcorn bags (Wu et al., 2015); our finding of an association between microwave popcorn consumption and higher serum concentrations of PFSAs (PFHxS in particular), but not PFCAs, perhaps reflects the phase out of PFOA, and a transition to using PFSAs, which should be examined in future studies. Alternatively, an explanation for our observation might be confounding by another dietary source or factor. We observed that air concentrations of certain PFAS were good predictors of several PFASs in children's serum, as observed for adults in previous studies (Fraser et al., 2012). There is a small body of literature examining health impacts associated with PFAS exposure among children. In previous studies, childhood exposure to PFAS has been associated with dyslipidemia, excess adiposity, increased risk of obesity and/or overweight, reduced vaccine response, asthma, impaired renal function, and later age at menarche (Braun, 2017; Rappazzo et al., 2017). Given our findings of widespread exposure to PFAS through multiple pathways, it is likely that PFAS exposure could present a substantial public health concern. Thus, further research on the health implications of childhood exposure to PFAS is necessary to better understand the individual and cumulative effects of these chemicals.

Directions for future research

In *Chapter 2,* one of the phthalate alternatives that we determined that nail salon workers were exposed to was DEHTP. DEHTP is used as a replacement for the phthalate DEHP, and previous literature on DEHTP exposure is limited, but suggests increasing exposure in the US and Europe (Nagorka et al., 2011; Silva et al., 2017, 2019). DEHTP is not a traditional SVOC in nail polish and we do not know the source of the DEHTP in nail salons. Although DEHTP may be present in some nail polishes, we found no evidence for this in a recent nail product study (Young et al., 2018); however it may be present in other personal care products or materials used in nail salons, such as lotions, waxes, or skin scrubbing exfoliants. Further research is necessary to determine the source of occupational DEHTP exposure in nail salon workers. Also, in *Chapter 2,* TPHP concentrations on lapel and wrist SWBs were not correlated, perhaps suggesting that different exposure sources of these compounds are encountered based on contact with skin and surfaces (more likely with wrist SWBs) versus those in the air (more likely with lapel SWBs). More research is needed to understand this difference and its implications for exposure routes.

The replacement of phthalates with alternatives, and the corresponding increased exposure to the latter, is of concern since often we do not fully understand the toxicity of the alternatives (Lakind & Birnbaum, 2010). For example, DEHTP is thought of as a safer alternative to DEHP, a known male reproductive toxicant, since it has not been shown to cause reproductive toxicity (Gray et al., 2000). However, due to the lack of studies examining the health consequences associated with DEHTP exposure in humans

to date, we do not fully understand whether increasing human exposure or long-term exposure to low levels of it will negatively impact human health. TPHP, another replacement chemical found in nail polish, has recently been identified as an endocrine disrupter that may be negatively associated with thyroid function and reproductive health (Carignan et al., 2017; Meeker & Stapleton, 2010; Preston et al., 2017). Future, larger biomonitoring studies of nail salon workers will help to verify and identify phthalates and replacement chemicals of particular concern from changes in formulations to products used in nail salons. These studies should also collect additional 24- to 48-hour post-work shift urine samples to better identify SVOC exposures, and examine associations between occupational exposures and health impacts in nail salon workers.

As discussed in *Chapter 3*, examining associations between mixtures of PFAS and birth outcomes is likely more important than examining associations between birth outcomes and individual PFAS. WQS regression may not be the most appropriate method of assessing the cumulative effect of exposure to PFAS on birth outcomes, given that the assumption that the components all act in the same direction was violated for some of the models. Future studies examining associations between exposure to mixtures of PFAS and birth outcomes should examine using more flexible statistical methods for mixtures, such as Bayesian kernel machine regression. To control for potential confounding by physiology, future studies examining associations between PFAS exposure and birth outcomes should solely collect 1st trimester serum samples, and/or measure albumin or creatinine (potential markers for plasma volume expansion and glomerular filtration rate, respectively).

Collecting additional information from participants would help to better characterize predictors of PFAS exposure in adults and children in future studies. For example, it is well known that diet is an important predictor of PFAS exposure (Boronow et al., 2019; Brantsæter et al., 2013; Hansen et al., 2016; Hu et al., 2018; Lin et al., 2020; Pitter Gisella et al., n.d.; Poothong et al., 2020; Timmermann et al., 2019; Wu et al., 2015), and asking participants to keep a dietary log for several days before serum samples are collected or for more detailed information on diet and frequency of eating foods known to be associated with PFAS exposure would lead to better, more accurate information on dietary predictors. As demonstrated in *Chapter 4* and previous studies (Boronow et al., 2019; Daly et al., 2018; Hu et al., 2019; Pitter Gisella et al., n.d.), drinking water is another important predictor of PFAS exposure. Future studies would benefit from analyses of water samples from individual participant homes and/or municipal water sources. Finally, a larger sample size in future studies would help to better characterize predictors of PFAS exposure in adults and children, particularly with environmental samples such as air and SWB.

As demonstrated in *Chapters 2-4*, nail salon workers, pregnant women, and children are exposed to a number of different SVOCs used commonly in consumer products. As these are all potentially vulnerable populations it is important to focus future studies on better understanding sources of exposure to SVOCs and the potential health impacts associated with those exposures. The future studies outlined above should advance understanding of those issues, and help inform future recommendations of measures to protect public health.

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Young, A. S., Allen, J. G., Kim, U.-J., Seller, S., Webster, T. F., Kannan, K., & Ceballos, D. M. (2018). Phthalate and Organophosphate Plasticizers in Nail Polish: Evaluation of Labels and Ingredients. *Environmental Science & Technology*. https://doi.org/10.1021/acs.est.8b04495

Zegher, Francis de, Devlieger, H., & Eeckels, R. (1999). Fetal Growth: Boys before Girls. *Hormone Research in Paediatrics*, *51*(5), 258–259. https://doi.org/10.1159/000023382

Zota, A. R., Calafat, A. M., & Woodruff, T. J. (2014). Temporal trends in phthalate exposures: Findings from the National Health and Nutrition Examination Survey, 2001-2010. *Environmental Health Perspectives*, *122*(3), 235–241. https://doi.org/10.1289/ehp.1306681

CURRICULUM VITAE

Jessica A. Craig

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EDUCATION

Boston University – Boston, MA — September 2014 to Present
School of Public Health
Doctor of Philosophy Student, Environmental Health
Completed All but Dissertation
Dissertation title: Chemicals in consumer products: health impacts, occupational exposure assessment, and analysis of novel methods to sample selected semi-volatile organic chemicals
Advisor: Thomas F. Webster, DSc

University of Michigan – Ann Arbor, MI — Graduated April 2007
School of Public Health
Master of Public Health, Epidemiology
Thesis title: Sexual dysfunction and the use of hormone therapy in pre-, peri-, and post-menopausal women
Thesis Advisor: MaryFran R. Sowers, PhD

University of Massachusetts – Amherst, MA — Graduated May 2002
College of Food and Natural Resources
Bachelor of Science, Major in Environmental Science with Biology concentration; Minor in Biology

EXPERIENCE

Teaching Assistant — Multiple Semesters 2015 - 2016
Boston University School of Public Health – Boston, MA

- Foundations of Environmental Health (Spring 2015 and Fall 2015)
- Environmental Epidemiology (Fall 2016)

Epidemiologist/Program Manager — October 2009 – July 2014
Alaska Native Tribal Health Consortium (ANTHC), Alaska Native Tribal Epidemiology Center – Anchorage, AK

- Epidemiologist
  - Study design, Survey creation
  - Collect and analyze data (using SAS, SPSS, and Microsoft Excel)
  - Write reports (Regional Health Profiles, Injury Atlas, Etc.)
- Program Manager – promoted September, 2012

    - Responsible for managing an Office of Minority Health American Indian/Alaska Native Health Disparities grant
    - Grant writing, reporting, and management
    - Supervisor, oversee projects
- Program evaluator for ANTHC Methamphetamine and Suicide Prevention Initiative and Doorway to a Sacred Place grants
    - Designed logic models for projects based on desired outcomes
    - Constructed an evaluation plan, and assigned duties to team members
    - Designed phone and Survey Monkey questionnaires and analyzed results
    - Conducted focus groups to obtain feedback
    - Facilitate and complete semi-annual reports
- Conducted a national colorectal cancer (CRC) screening surveillance systems improvement project
    - Wrote a study protocol and designed, pilot tested, and administered a survey instrument to Indian Health Service, Tribal, and Urban facilities nationwide to determine how they manage CRC screening
    - Compiled and analyzed data, wrote and published a report
- Regularly collaborate and interact with Alaska Native tribal health organizations through presentations, meetings, provision of technical assistance, workgroups, and site visits
- Periodically organize and deliver trainings on various topics to tribal and state audiences
- Active member of the Alaska Maternal, Infant, and Child Mortality Review
- Developed regional health profile reports
- Represent organization as:
    - National Tribal Epidemiology Center Health Status Report workgroup member
    - Council of State and Territorial Epidemiologist tribal workgroup member
- Member of Planning Committee and Scientific Program Committee for the World Congress of Epidemiology and Alaska Maternal and Child Health and Immunizations conferences being held in Anchorage in 2014

Centers for Disease Control and Prevention/Council for State and Territorial Epidemiologists Applied Epidemiology Fellow July 2007 – October 2009
New Mexico Department of Health, Environmental Health Epidemiology Bureau – Santa Fe, NM

- Fulfilled a full range of complex epidemiologic and surveillance activities
- Designed a project to assess farmworkers' exposure to pesticides in the New Mexico/Mexico border region
- Contributed to a biomonitoring project to detect depleted uranium in active duty military personnel and veterans
- Led a project to examine microtia/anotia prevalence in New Mexico
- Evaluated NM waterborne disease surveillance
- Participated in a study examining agranulocytosis cases in New Mexico
- Headed an outbreak investigation of Salmonella enteritidis and participated in other foodborne and vector-borne illness investigations
- Served as on-call epidemiologist for both infectious disease and environmental health epidemiology

OTHER EDUCATION

Exchange Program Participant August 2006
Southern Texas Environmental Education and Research Center (STEER) – Laredo, TX

- Four-week elective program through the University of Texas Health Science Center at San Antonio aimed at uniting medicine and public health focusing on environmental factors that affect health
- Gained a broad overview of the health needs and issues on the U.S./Mexico border focusing on underserved populations through classroom and field exercises
- Participated in health fairs, worked with community residents, participated in HIV/AIDS outreach program, and learned how living conditions on both sides of the U.S./Mexico border affect public health

Field Study Participant September – December 2001
School for Field Studies – South Caicos Island

- Increased experience utilizing environmental fieldwork skills
- Conducted a directed research project on juvenile lobster populations
- Tutored in local school assisting children with reading skills
- Increased cultural sensitivity working with the local population
- Actively participated in a United Nations human rights conference

PROFESSIONAL PUBLICATIONS/PRESENTATIONS

Selected Publications and Reports

Craig JA, Ceballos DM, Fruh V, Petropoulos ZE, Allen JG, Calafat AM, Ospina M, Stapleton HM, Hammel S, Gray R, Webster TF (2019). Exposure of Nail Salon Workers to Phthalates, Di(2-ethylhexyl Terephthalate, and Organophosphate Esters: A Pilot Study. *Environmental Science & Technology*, 53(24): 14630-14637.

Ceballos DM, Craig JA, Fu X, Jia C, Chambers D, Chu MT, Fernandez AT, Fruh V, Petropoulos ZE, Allen JG, Vallarino J, Thornburg L, Webster TF (2019). Biological and environmental exposure monitoring of volatile organic compounds among nail technicians in the Greater Boston Area. *Indoor Air*, 29(4): 539-550.

Craig JA, Redwood DG, Provost EM, Haverkamp DS, & Espey DK (2015). Use of tracking and reminder systems for colorectal cancer screening in Indian Health Service and tribal facilities. *IHS Primary Care Provider*, 40(2): 10-17.

Strayer H, Craig J, Asay E, Haakenson A, Provost E (2014). Alaska Native Injury Atlas: An Update, Revised. Anchorage, AK: Alaska Native Tribal Health Consortium Injury Prevention Program and Alaska Native Epidemiology Center. May, 2014.

Craig, Jessica & Hull-Jilly, Deborah (2012). Characteristics of Suicide Among Alaska Native and Alaska non-Native People, 2003-2008. State of Alaska Epidemiology Bulletin, Recommendations and Reports. Volume 15, Number 1.

Brackney, Monica, et al (2009). Agranulocytosis Associated with Cocaine Use - Four States, March 2008 – November 2009. MMWR Morb Mortal Wkly Rep. Dec 18 2009;58(49):1381-1385.

Hagan, Jessica & Moraga-McHaley, Stephanie (2009). Pesticide Exposure of Farmworkers in Dona Ana, Hidalgo, and Luna Counties of New Mexico; A Report Based on Findings from a Survey of 202 Participants.

Hagan, Jessica (2009). Waterborne Disease Surveillance in New Mexico. New Mexico Epidemiology. Volume 2009, Number 1.

Selected Oral Presentations/Trainings Given

Boston University Environmental Health Research Retreat – New Castle, NH October, 2019
Predictors of Per- and Polyfluoroalkyl Substance (PFAS) Concentrations in Three to Six Year Olds – Preliminary Findings. Jessica Craig

International Society of Exposure Science Conference/International Society of Environmental Epidemiology – Ottawa, ON August 2018
PFAS serum concentrations in pregnant women from North Carolina: Predictors and associations with birth outcomes. Jessica Craig, Thomas F. Webster, Kate Hoffman, Allison Phillips, Stephanie Hammel, Amelia Lorenzo, Antonia Calafat, Catherine Hoyo, Susan Murphy, and Heather Stapleton

International Society of Exposure Science Conference – Durham, NC October 2017
Prenatal Exposure to Per- and Polyfluoroalkyl Substances (PFAS) and Associations with Birth Weight. Jessica Craig, Thomas F. Webster, Kate Hoffman, Allison Phillips, Stephanie Hammel, Amelia Lorenzo, Antonia Calafat, Catherine Hoyo, Susan Murphy, and Heather Stapleton

16th Annual Workshop on Brominated and Other Flame Retardants – Toronto, ON May 2016
An Estimate of the Half-Life of Triphenyl Phosphate Associated with Nail Polish Exposure. Jessica Craig

LEADERSHIP EXPERIENCE

Improving Presentations Sessions Facilitator February 2011 – July 2014
ANTHC Department of Community Health Services – Anchorage, AK

- Organized monthly meetings and coordinated speakers to improve presentation skills

Toastmasters International Secretary November 2010 – July 2014
BP Toastmasters Club – Anchorage, AK

- Simultaneously completed Competent Communicator and Competent Leader manuals
- Actively improved speaking skills through giving prepared speeches and participating in impromptu table topics
- Actively advanced leadership skills through acting as club secretary, evaluating speeches, organizing club events, and playing a role in meetings