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Gestational and Childhood Exposure to Per- and Polyfluoroalkyl Substances and Cardiometabolic Risk at Age 12 Years

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1. Introduction

Exposure to environmental chemicals during fetal development, a critical period of heightened susceptibility and programming, may increase the risk of obesity and cardiometabolic disease later in life (Braun 2016; Braun et al. 2016; Braun and Gray 2017; Heindel and Blumberg 2018; Janesick and Blumberg 2016; Navas-Acien et al. 2006; Trasande et al. 2018). Of particular concern is exposure to per- and polyfluoroalkyl substances (PFAS), a class of endocrine disrupting chemicals used in some oil/water-resistant coatings, industrial processes, food packaging, cleaning/personal care products, and firefighting foams (Buck et al. 2011; European Food Safety Authority 2008; Organisation for Economic Co-operation and Development 2018). PFAS are almost universally detected among pregnant women, infants and children, and readily cross the placenta to potentially affect the developing fetus (Apelberg et al. 2007b; Braun et al. 2016; Høyer et al. 2015; Jain 2013; Johnson et al. 2014; Maisonet et al. 2012; Manzano-Salgado et al. 2015; Woodruff et al. 2011). Some PFAS have long biological half-lives in humans (3.8–7.3 years) (Olsen et al. 2007). PFAS are routinely detected in food and drinking water in the United States (U.S.) due to their release from landfills, airports, fire training areas, and manufacturing facilities (Agency for Toxic Substances and Disease Registry 2017). Numerous communities (>6 million residents) nationwide have perfluorooctanoate (PFOA) and/or perfluorooctane sulfonate (PFOS) - contaminated drinking water in excess of the Environmental Protection Agency health advisory level of 70 ng/L (Guelfo and Adamson 2018; Hu et al. 2016; The United States Environmental Protection Agency 2018)

Early life PFAS exposure may increase cardiometabolic risk later in life. Compelling evidence from experimental animal and epidemiological studies suggests that gestational PFAS exposure may increase obesity risk (Braun et al. 2016; Halldorsson et al. 2012; Hines et al. 2009; Høyer et al. 2015; Johnson et al. 2014; Maisonet et al. 2012; Mora et al. 2017). Rodent studies suggest that perinatal or early postnatal PFAS exposure may increase insulin levels, impair glucose tolerance, alter lipid homeostasis, and increase leptin levels in offspring (Hines et al. 2009; Lv et al. 2013; Steenland et al. 2010; Tan et al. 2013; Wan et al.

2014; Zhao et al. 2011). A potential mechanism underlying the above-mentioned associations is that PFAS have a similar chemical structure to fatty acids and can activate peroxisome proliferator-activated receptors (PPAR) α and γ to disturb glucose metabolism, lipid metabolism, and energy homeostasis (Berger et al. 2005; Staels and Fruchart 2005; Takacs and Abbott 2007).

Cardiometabolic risk factors are a cluster of conditions – elevated abdominal obesity, dyslipidemia, disturbed glucose and insulin metabolism, and high blood pressure – that increase the risk of developing cardiovascular disease and type 2 diabetes, which are both among the leading causes of death worldwide and in the U.S. (Heron 2018; Isomaa et al. 2001; Lakka et al. 2002; Liese et al. 1998; Watson 2007; World Health Organization 2018). Cardiometabolic risk has origins in early life and tracks from childhood into adulthood (Bao et al. 1994; Bao et al. 1995; Barker 2000; Chen et al. 2000; Costa-Silva et al. 2016; Hales and Barker 2013; Webber et al. 1991). Cardiometabolic risk factors tend to cluster together (Anderson et al. 2016; Brambilla et al. 2007; Jousilahti et al. 1994). While metabolic syndrome, a dichotomous measure, is often used to predict the cardiometabolic risk in adults (Alberti et al. 2009), continuous cardiometabolic risk summary scores in adolescents and young adults predict later life cardiovascular disease risk and may detect more subtle or earlier manifestations of cardiometabolic disease (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011; Kelly et al. 2011).

Some prospective studies have examined the impact of early life PFAS exposure on children's cardiometabolic risk; however, the findings were inconclusive in terms of particular PFAS and distinctive cardiometabolic risk factors (Alderete et al. 2019; Domazet et al. 2016; Fleisch et al. 2017; Halldorsson et al. 2012; Lin et al. 2020; Maisonet et al. 2015; Manzano-Salgado et al. 2017; Mora et al. 2018; Shelly et al. 2019; Warembourg et al. 2019). Most studies did not comprehensively study overall cardiometabolic risk, only examining some components separately. Only one study to date has examined overall cardiometabolic risk associated with early life PFAS exposure, and found that perfluorononanoate (PFNA) was associated with higher cardiometabolic risk scores in Spanish children at age 4 years (Manzano-Salgado et al. 2017). However, that study did not assess glucose/insulin homeostasis. Thus, prior studies may not accurately estimate the influence of PFAS exposure on children's overall cardiometabolic risk. In addition, most previous studies focused on PFAS exposure during gestation and did not examine potential periods of heightened susceptibility during childhood.

To better understand the potential influence of gestational and childhood PFAS exposure on cardiometabolic risk in children, we investigated the associations of repeated measures of gestational and childhood serum PFAS concentrations with two different cardiometabolic risk summary scores based on traditional or novel cardiometabolic risk factors in adolescents using data from a cohort of children with higher gestational PFOA exposure.

2. Materials and Methods

2.1. Study Participants

We used data from a longitudinal pregnancy and birth cohort, the Health Outcomes and Measures of the Environment (HOME) Study. The HOME Study recruited pregnant women from Cincinnati, Ohio between 2003 and 2006, and conducted follow-up visits with the mothers and their children through age 12 years (Braun et al. 2017). The inclusion criteria included: 18 years old; 16±3 weeks of gestation; living in the Cincinnati, Ohio area in a home built before 1978; no diagnosis of diabetes, schizophrenia, bipolar disorder, or cancer; no history of HIV infection; and not taking any medications for thyroid disorders or seizure. Of 1,263 eligible women, 468 agreed to participate in the study, and 421 actually participated in the study and had live singleton births. More details regarding the HOME Study eligibility criteria, recruitment, and follow up were published elsewhere (Braun et al. 2017). A total of 221 mother-child pairs who had at least one serum PFAS concentration measurement during gestation or childhood, assessment of at least one individual cardiometabolic risk factor at age 12 years, and relevant covariate data were included in the current analysis.

The institutional review boards (IRBs) at Cincinnati Children's Hospital Medical Center (CCHMC) and participating delivery hospitals approved the HOME Study protocols. Brown University and the Centers for Disease Control and Prevention (CDC) IRBs deferred to the CCHMC IRB. All mothers provided informed consent for themselves and their children at all visits; children provided informed assent at the age 12 year visit.

2.2. PFAS Exposure Assessment

Trained phlebotomists collected maternal, umbilical cord, and child blood samples at gestation, delivery, and ages 3, 8, and 12 years via venipuncture. Gestational serum PFAS concentrations were measured at 16 weeks of pregnancy for 86% of women; when 16-week blood samples were unavailable, 26-week (9.5%) or maternal delivery samples (4.5%) were used. After separating serum from whole blood, the samples were stored at -80 °C until PFAS quantification. The CDC laboratory staff quantified serum concentrations of PFOA, PFOS, PFNA, and perfluorohexane sulfonate (PFHxS) using online solid phase extraction coupled to high performance liquid chromatography-isotope dilution tandem mass spectrometry (Kato et al. 2011). PFAS concentrations were measured in a 100 µL serum aliquot diluted with formic acid and fortified with isotopically-labeled PFAS internal standards (Kato et al. 2011; Kuklenyik et al. 2005). Each analytic batch included reagent blanks and low- and high-concentration quality control materials that were evaluated using standard statistical probability rules. The limits of detection (LOD) for PFAS were ~0.1 to 0.2 ng/mL. Concentrations below the LOD were replaced with the LOD/ 2 (Hornung and Reed 1990). Serum PFAS concentrations (ng/mL) were log₂-transformed in statistical analyses. We standardized the concentrations of each PFAS by its interquartile range (IQR) across visits to make effect sizes comparable across different PFAS (Buckley et al. 2016).

2.3. Adolescent Cardiometabolic Risk Outcomes

All cardiometabolic risk factors were measured at the 12-year follow-up visit (Braun et al. 2020). We obtained an overnight-fasting blood sample from adolescents via venipuncture. Using a combination of valid and reliable immunoassays, we measured serum glucose, insulin, triglycerides, high density lipoprotein (HDL), leptin and adiponectin concentrations. Trained laboratory technicians in the Cincinnati Children's Hospital Medical Center NIH-funded Clinical Translational Research Center Core Laboratory conducted all assays. The coefficient of variations for leptin and adiponectin were 11.1% and 13.1%, respectively. We calculated homeostatic model assessment for insulin resistance (HOMA-IR) using standard formulas - $\text{HOMA-IR} = \text{fasting insulin (mIU/L)} \times \text{fasting glucose (mg/dL)} / 405$, with higher values of HOMA-IR representing more severe insulin resistance (Matthews et al. 1985). We also calculated triglyceride to HDL ratio and adiponectin to leptin ratio. We took 3 sitting blood pressure measurements from adolescents, each one minute apart, using a Dinamap Pro100 automated monitor and previously described methods (Gillman and Cook 1995; Perloff et al. 1993). For statistical analyses, we excluded the first measure of blood pressure and took the average of the second and third measures (Lacruz et al. 2017). We measured iliac waist circumference around a horizontal plane defined by the iliac crests. Cross-sectional area of fat inside abdominal cavity (cm^2) were measured using dual x-ray absorptiometry (DXA, Hologic Horizon densitometer) (Wang et al. 2010). Whole body DXA scans were analyzed using the National Health and Nutrition Examination Survey (NHANES) body composition analysis option.

We constructed two different continuous cardiometabolic risk summary scores with one based on traditional cardiometabolic risk factors and the other based on novel cardiometabolic risk factors. We calculated the traditional cardiometabolic risk score by summing standardized z-scores for glucose, insulin, triglycerides, HDL (multiplied by -1), the mean of systolic blood pressure and diastolic blood pressure, and waist circumference (Väistö et al. 2014). The novel cardiometabolic risk score was calculated by summing standardized z-scores for HOMA-IR, triglyceride to HDL ratio, adiponectin to leptin ratio (multiplied by -1 , higher adiponectin to leptin ratio is associated with more favorable cardiometabolic outcome), systolic blood pressure, and cross-sectional area of fat inside abdominal cavity. Higher cardiometabolic risk scores indicate higher cardiometabolic risk. We calculated sex-, age-, and height- standardized blood pressure z-scores and percentiles according to the nationally-based childhood blood pressure database in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011; National Institutes of Health National Heart, Lung, and Blood Institute, 2005). We additionally standardized these blood pressure z-scores to our study participants for consistency and comparability across individual components of the cardiometabolic risk score. For other components without representative U.S. references, we calculated age- and sex-standardized z-scores according to our own study participants. To do so, we ran linear regression models of each individual cardiometabolic risk component as the dependent variable, and age and sex as predictors. We then standardized the residuals to derive the age- and sex-specific z-scores (Eisenmann 2008). Insulin, triglycerides, waist circumference, HOMA-IR, triglycerides to HDL ratio, adiponectin to

leptin ratio, and the cross-sectional area of fat inside the abdominal cavity were not normally distributed (right-skewed) and thus were log₂-transformed before standardization.

2.4. Covariate Assessment

We used the previous literature and directed acyclic graphs to identify potential confounders that may be associated with both PFAS exposure and adolescent cardiometabolic risk, but not causal intermediates or colliders (Supplemental Figures S1–S2). Trained interviewers administered standardized questionnaires at baseline to assess maternal age, education, parity, maternal prenatal fish intake frequency, at the postpartum visit to assess children's race, and at the 3-year visit to assess breastfeeding duration. We abstracted data on child sex from hospital medical charts. We used self-reported height and weight (or imputed weight if missing) to calculate pre-pregnancy body mass index (BMI) (van der Laan et al. 2007). We used the average of the log₁₀-transformed serum cotinine concentrations measured at 16- and 26-weeks of gestation to assess gestational tobacco smoke exposure. At the 12-year visit, we provided adolescents with standardized instructions for them to self-evaluate their pubertal stage (stages I–V) based on pubic hair growth in a private room with full-length mirror. We assessed adolescents' physical activity level by administering the validated Physical Activity Questionnaire for Older Children and calculating the activity summary score (Kowalski et al. 1997). Trained research staff at the NIH-funded Clinical Translational Research Center Bionutrition Core collected three 24-hour food recalls (2 weekdays and 1 weekend day) from adolescents. We analyzed food recalls using the Nutrition Data Systems for Research software and foods database (University of Minnesota, MN) and calculated Healthy Eating Index scores (2010) - a measure of diet quality in terms of conformance with federal dietary guidance (Guenther et al. 2013; University of Minnesota Nutrition Coordinating Center).

2.5. Statistical Analyses

We first explored the distribution of serum PFAS concentrations at each visit by calculating univariate statistics. We then calculated the Pearson correlation coefficient for gestational and cord serum PFAS concentrations and the intraclass correlation coefficients (ICC) of childhood PFAS concentrations. We also calculated the Pearson correlation coefficient for traditional and novel cardiometabolic risk scores. Additionally, we calculated mean traditional and novel cardiometabolic risk scores by strata of the key covariates. Further, we calculated univariate statistics for traditional and novel cardiometabolic risk scores and individual components, stratified by sex.

2.5.1. Main Analyses.—We used the multiple informant method to estimate covariate-adjusted associations of gestational and childhood serum PFAS concentrations at each visit (gestation, birth, ages 3, 8, and 12 years) with adolescents' cardiometabolic risk scores and individual cardiometabolic risk components at age 12 years. Details on the multiple informant method have been previously described (Buckley et al. 2019; Jackson-Browne et al. 2018; Li et al. 2019; Sanchez et al. 2011; Stacy et al. 2017). Briefly, the multiple informant model utilizes generalized estimating equations to jointly estimate the exposure-outcome association for each exposure period, and tests whether the estimates for exposure-outcome association are equal across all exposure periods (Buckley et al. 2019; Jackson-

Browne et al. 2018; Li et al. 2019; Sanchez et al. 2011; Stacy et al. 2017). The multiple informant method can be used when there are repeated and sparsely sampled environmental exposure measures at different time points and information gathered from multiple sources is used to measure the same construct (Sanchez et al. 2011).

We estimated the difference in cardiometabolic risk outcomes per IQR increase in log₂-transformed serum concentrations of a specific PFAS (e.g., PFOA, PFOS, PFNA, PFHxS) for each time period. The two differently constructed cardiometabolic risk scores (traditional and novel cardiometabolic risk scores) and each of the individual cardiometabolic risk components (glucose, insulin, triglycerides, HDL, mean of systolic and diastolic blood pressure, waist circumference; and HOMA-IR, triglyceride to HDL ratio, adiponectin to leptin ratio, systolic blood pressure, cross-sectional area of fat inside abdominal cavity) were examined separately as outcomes. Insulin, triglycerides, waist circumference, HOMA-IR, triglycerides to HDL ratio, adiponectin to leptin ratio, and the cross-sectional area of fat inside the abdominal cavity were not normally distributed (right-skewed) and thus were log₂-transformed to satisfy normality assumptions.

The multiple informant model included visit, PFAS x visit, and covariates, allowing us to test whether PFAS-cardiometabolic risk associations differed by exposure period. The null hypothesis is that the associations are the same across all time periods, and we considered those with heterogeneity p-values <0.05 as evidence that at least one of the PFAS-cardiometabolic risk association differed from the rest. In all multiple informant models, we adjusted for mother's age, education, parity, pre-pregnancy BMI, gestational serum cotinine concentrations; and child's age, sex, race, and pubertal stage. For childhood PFAS exposure only, we also adjusted for breastfeeding duration.

2.5.2. Secondary Analyses.—First, we used the three-way visit x PFAS x sex interaction term p-value from our multiple informant models to determine if the PFAS-cardiometabolic risk associations across visits differed by sex; a *P* value for this term <0.05 was considered as evidence for interaction. Second, we graphically examined the dose-response relations using 3-knot restricted cubic polynomial splines for select associations between PFAS and novel cardiometabolic risk scores (Desquilbet and Mariotti 2010). Third, we jointly adjusted for PFOA and PFHxS concentrations measured at gestation or birth in the model to assess potential confounding (post hoc analysis). Finally, we specified a weighted quantile sum (WQS) regression model to examine gestation exposure to PFAS mixture (i.e., PFOA, PFOS, PFNA, and PFHxS) in association with adolescent's novel cardiometabolic risk score (Czarnota et al. 2015). The WQS regression model constructs a weighted index within a set of correlated exposures (e.g., PFAS mixture) and estimates its overall association with the outcome. The weights that the model assigns to the individual exposure reflect the relative variable importance of the individual exposure (Czarnota et al. 2015). We implemented WQS regression in an iterative fashion (N=1,000 iterations) within a parallel-processing computing environment to capture weight uncertainty (Tanner et al. 2019). In each iteration, we randomly sampled 40% of the observations to estimate weights that maximized the association across B=100 bootstrap sub-samples. We used the remaining 60% of the observations to fit a linear regression model to estimate a standardized coefficient that assessed the exposure-outcome association.

2.5.3. Sensitivity Analyses.—To account for the influence of pubertal stage on the outcome, we examined the associations between PFAS and the age-, sex-, and pubertal stage-standardized novel cardiometabolic risk scores. Further, we conducted sensitivity analyses by additionally adjusting for child's Healthy Eating Index 2010 total scores, physical activity summary scores, and maternal prenatal fish intake frequency (once a week vs. < once a week), or removing pubertal stage from the covariate adjustment set since the presence or directionality of the associations of these covariates with PFAS exposure or outcome is unclear. We performed all analyses using SAS version 9.4 (SAS Institute Inc., U.S.).

3. Results

Gestational serum PFAS concentrations were generally higher than childhood PFAS concentrations. Children's PFAS concentrations peaked at age 3 years and were lowest at age 12 years (Supplemental Table S1). Gestational serum PFAS concentrations were highly correlated with cord serum PFAS concentrations (Pearson's r ranges 0.78–0.96). The ICCs of childhood PFAS concentrations were 0.4. PFAS concentrations of women and children in our cohort are comparable to those of pregnant women and children in other studies, except that gestational and cord serum PFOA concentrations were somewhat higher in our cohort, possibly due to the elevated drinking water PFOA levels in the Ohio River that was contaminated by a West Virginia fluoropolymer plant (Andersen et al. 2013; Apelberg et al. 2007a; Apelberg et al. 2007b; Casas et al. 2013; Darrow et al. 2013; Emmett et al. 2006; Fei et al. 2010; Frisbee et al. 2009; Fromme et al. 2010; Grandjean et al. 2012; Halldorsson et al. 2012; Hamm et al. 2010; Inoue et al. 2004; Jain 2013; 2018; Javins et al. 2013; Kato et al. 2009; Kim et al. 2011; Lee et al. 2013; Monroy et al. 2008; Schecter et al. 2012; Whitworth et al. 2012; Ye et al. 2018).

The mean \pm standard deviation (SD) of traditional and novel cardiometabolic risk scores were 0.1 ± 3.4 and 0 ± 3.4 , respectively. The traditional and novel cardiometabolic risk scores were highly correlated (Pearson's $r=0.93$). On average, mean traditional and novel cardiometabolic risk scores were higher among adolescents who were non-Hispanic Black, not breastfed, at more advanced pubertal stage, or were born to mothers with less education (high school education), actively smoked during pregnancy, or had higher pre-pregnancy BMI ($> 30 \text{ kg/m}^2$) (Table 1). Among the 221 adolescents included in our analysis, individual cardiometabolic risk components were measured among 184–221 adolescents, with adiponectin to leptin ratio measured among 184 adolescents and blood pressure and waist circumference measured among 221 adolescents (Table 2). Compared to males, females had lower adiponectin to leptin ratio and smaller cross-sectional area of fat inside abdominal cavity, and higher insulin, HOMA-IR, and waist circumference.

After adjusting for covariates, the association of serum PFOA concentrations with the traditional cardiometabolic risk score differed across visits (P for heterogeneity=0.04), with serum PFOA concentrations at gestation and birth being positively associated with traditional cardiometabolic risk scores (Figure 1, Supplemental Tables S2–S3). In particular, with 1-IQR increase in \log_2 -transformed gestational and cord serum PFOA concentrations, traditional cardiometabolic risk scores increased 0.5 SDs (95% confidence interval [CI]=

−0.3, 1.3) and 1.0 SDs (95%CI=−0.1, 2.0), respectively. Associations of serum PFHxS concentrations with traditional cardiometabolic risk scores were uniformly positive across visits (P for heterogeneity=0.56), but were stronger at gestation and birth (gestational β =0.5, 95%CI=−0.2, 1.2; cord β =0.7, 95%CI=−0.1, 1.6). These positive associations of gestational and cord PFOA and PFHxS concentrations with traditional cardiometabolic risk scores were mainly driven by their positive associations with insulin, waist circumference, and mean of systolic and diastolic blood pressure (PFHxS only). Generally, gestational and childhood serum PFOS and PFNA concentrations were not associated with traditional cardiometabolic risk scores, except that PFOS and PFNA at age 3 years were associated with lower traditional cardiometabolic risk scores. Serum PFOS concentrations at ages 3, 8 and 12 years was associated with higher HDL levels.

After adjusting for covariates, the association of serum PFOA concentrations with novel cardiometabolic risk scores differed across visits (P for heterogeneity=0.03), with only serum PFOA concentrations at gestation and birth having significantly positive associations with novel cardiometabolic risk scores (gestational β =0.8, 95%CI=0.0, 1.6; cord β =0.9, 95%CI=−0.1, 1.9) (Figure 2, Supplemental Tables S2–S3). The positive associations for gestational PFOA were primarily driven by HOMA-IR (β =0.3; 95%CI=0.1, 0.5) and adiponectin/leptin ratio (β =−0.5; 95%CI=−1.0, 0.0). Serum PFHxS concentrations with novel cardiometabolic risk scores were uniformly positive across visits (P for heterogeneity=0.57) and were again stronger for gestational and cord PFHxS concentrations (gestational β =0.9, 95%CI=0.2, 1.6; cord β =0.9, 95%CI=0.1, 1.7). These associations were driven by similar individual components as PFOA, as well as systolic blood pressure and cross-sectional area of fat inside the abdominal cavity. Gestational and childhood serum PFOS and PFNA concentrations were in general not associated with novel cardiometabolic risk scores, except that PFOS and PFNA at age 3 years were associated with lower novel cardiometabolic risk scores.

The associations between PFAS concentrations and cardiometabolic risk across visits in general did not differ by sex (Supplemental Figures S3–S4 and Table S4). The dose-response relation of gestational and cord PFOA concentrations with novel cardiometabolic risk scores were close to non-linear (inverted U-shape), although not at a statistically significant level (non-linearity p -values were 0.05 and 0.19, respectively). We observed linear increases in adolescents' novel cardiometabolic risk scores with increasing gestational and cord serum concentrations of PFHxS (non-linearity p -values were 0.41 and 0.67, respectively) (Supplemental Figure S5). When we jointly adjusted for gestational or cord serum PFOA and PFHxS concentrations, the associations were slightly attenuated. Gestational or cord PFOA was more strongly associated with insulin and HOMA-IR than PFHxS, whereas gestational and cord PFHxS was more strongly associated with waist circumference than PFOA (Supplemental Figure S6). When examining the aggregate impact of the four PFAS using WQS regression, an IQR increase in the weighted gestational PFAS index was positively associated with the novel cardiometabolic risk score (β =0.23, 95%CI=0.18, 0.29). PFOA and PFHxS (relative weights=0.80 and 0.16, respectively) contributed largely to these associations compared to PFOS and PFNA (relative weights=0.01 and 0.03, respectively) (Figure 3). The results were not substantially different from our main analysis when we used the age-, sex-, and pubertal stage-adjusted novel

cardiometabolic risk scores, additionally adjusted for Healthy Eating Index 2010 total scores, physical activity summary scores, maternal prenatal fish intake frequency, or removed pubertal staging from the covariate adjustment set.

4. Discussion

Using data from a pregnancy and birth cohort, we examined the associations of repeated measures of serum PFAS concentrations from gestation to age 12 years with adolescents' cardiometabolic risk at age 12 years. Gestational and cord PFOA and PFHxS concentrations were positively associated with both cardiometabolic risk scores. The positive associations with traditional cardiometabolic risk scores were driven by insulin, waist circumference, and mean systolic and diastolic blood pressure (PFHxS only); associations with novel cardiometabolic risk scores were primarily driven by HOMA-IR, adiponectin to leptin ratio, systolic blood pressure (PFHxS only), and cross-sectional area of fat inside abdominal cavity (PFHxS only).

PFAS are structurally similar to fatty acids, and thus may alter fatty acid metabolism and lipid synthesis in the liver (Pilz et al. 2006). With their similar structure, PFAS can act as agonists of PPAR α and γ , key regulators of metabolic functions in both rodents and humans (Berger et al. 2005; Staels and Fruchart 2005; Takacs and Abbott 2007). Thus, one potential mechanism is that PFAS may disturb glucose metabolism, lipid metabolism, and energy homeostasis by activating PPAR α and γ (Berger et al. 2005; Staels and Fruchart 2005; Takacs and Abbott 2007). PFAS also interfere with the signaling pathways of the thyroid hormones, which play a key role in regulating metabolism (Lau et al. 2007; Mullur et al. 2014). In addition, PFAS exposure increase oxidative stress, which in turn contributes to metabolic dysfunction (Liu et al. 2007; Mahjoub and Masrou-Roudsari 2012). Evidence from an experimental study suggests that *in utero* PFOA exposure, but not adult exposure, was associated with mid-life overweight in mice, suggesting that gestation is a unique period of heightened susceptibility to PFOA exposure (Hines et al. 2009). Besides obesity, early life PFAS exposure may also be associated with other cardiometabolic risk factors. Rodent studies suggest that perinatal or early postnatal exposure to PFOA, PFOS and PFHxS increases insulin and leptin levels, and impairs glucose tolerance in offspring (Hines et al. 2009; Lv et al. 2013; Steenland et al. 2010; Tan et al. 2013; Wan et al. 2014; Zhao et al. 2011). Early life PFAS exposure may also disrupt lipid metabolism and induce hepatotoxic effects (Kennedy et al. 2004; Lau et al. 2007; White et al. 2011), as well as increase oxidative stress and impair vasodilation, which in turn could increase blood pressure (Ceriello 2008; Huang et al. 2013; Panaretakis et al. 2001; Wielsøe et al. 2015).

Because pediatric cardiometabolic risk factors tend to cluster, continuous cardiometabolic risk scores may be an important outcome that can be measured before adult disease onset and provide opportunities for disease prevention (Anderson et al. 2016; Brambilla et al. 2007; Jousilahti et al. 1994). However, despite the growing use of continuous cardiometabolic risk summary score in pediatrics, there is currently no validated or harmonized consensus definition (Eisenmann 2008; Kamel et al. 2018; Sovio et al. 2013). Thus, we constructed cardiometabolic risk scores that included either traditional or relatively novel cardiometabolic risk markers. Our novel risk score is likely a better predictor of

subsequent cardiometabolic risk. For example, HOMA-IR, which plays an essential role in initiating and perpetuating the pathologic manifestations of metabolic syndrome, is a robust surrogate measure of insulin resistance (Antuna-Puente et al. 2011; Lann and LeRoith 2007; Matthews et al. 1985). Growing evidence supports that triglyceride to HDL ratio and adiponectin to leptin ratio are closely related to insulin resistance and metabolic syndrome, and are good predictors of cardiovascular disease and type 2 diabetes risk or mortality (Ayina et al. 2017; Chen et al. 2020; Cordero et al. 2008; Dai et al. 2019; Frithioff-Bøjsøe et al. 2020; Frühbeck et al. 2018; Inoue et al. 2006; Kim et al. 2019; López-Jaramillo et al. 2014; McLaughlin et al. 2005; Vega et al. 2014). Fasting HOMA-IR (compared to fasting insulin) and triglycerides to HDL ratio (compared to triglycerides and HDL individually) had higher predictive values when assessing metabolic syndrome in adolescents (Chu et al. 2019; Piña-Aguero et al. 2018). Systolic blood pressure is a major risk factor for cardiovascular disease in later life (Strandberg and Pitkala 2003). Finally, we directly measured visceral fat, which is an important predictor of cardiometabolic risk (Nakamura et al. 1994; Snijder et al. 2006; Zhang et al. 2015).

Only one previous study has examined the associations between early life PFAS exposure and children's cardiometabolic risk scores, reporting that gestational exposure to PFNA, but not PFOA, PFOS, or PFHxS, was positively associated with cardiometabolic risk in Spanish children at age 4 years (Manzano-Salgado et al. 2017). In contrast, in our cohort, gestational PFOA and PFHxS concentrations were positively associated with cardiometabolic risk scores. The cardiometabolic risk score calculated in the Spanish study included waist circumference, blood pressure, HDL, and triglycerides, but not markers of glucose-insulin homeostasis, which is typically used to define metabolic syndrome (Alberti et al. 2009). Thus, the findings may not comprehensively estimate the potential impact of gestational PFAS on children's cardiometabolic risk at age 4 years. The inconsistent findings between the Spanish study (INMA) and ours may also be partly due to differences in gestational PFOA concentration distributions. Gestational PFOA concentrations were higher in our cohort, perhaps because of contamination from a West Virginia fluoropolymer plant (IQR: HOME: 3.7–7.2 ng/mL; INMA: 1.6–3.3 ng/mL) (Emmett et al. 2006; Frisbee et al. 2009). However, we observed that the association between gestational PFOA and novel cardiometabolic risk score was linear and positive at the lower range of PFOA concentrations. Therefore, it is unlikely the inconsistent findings were solely due to the different distributions of gestational PFOA concentrations. In addition, the age difference of outcome assessment may also partly explain the discrepancy in results, where some unfavorable cardiometabolic risk factors have not yet manifested at age 4 years.

We found that gestational and cord PFOA and PFHxS concentrations were positively associated with insulin and HOMA-IR in adolescents at age 12 years. Consistent with our findings, a Danish Study found that gestational PFOA concentrations were positively associated with insulin in young adults aged 20 years (Halldorsson et al. 2012). In contrast, a study using data from the Project Viva cohort (based in Boston, Massachusetts, U.S.) reported that gestational PFAS (including PFOA, PFOS, PFNA, and PFHxS) were not associated with HOMA-IR in mid-childhood (median age: 7.7 years) (Fleisch et al. 2017); the distribution of gestational plasma PFOA concentrations in the Project Viva cohort was comparable to that in our cohort. The Project Viva (1999–2002) and HOME Study (2002–

2006) cohorts enrolled participants several years before the US Environmental Protection Agency PFOA Stewardship Program, which asked the eight major leading companies in the PFAS industry to commit to reducing PFOA emissions. Thus, the participants in these two studies presumably had higher PFOA exposure. The differences in study design and participant demographics (e.g., children's age, family socioeconomic status) between the two studies may explain the inconsistent findings.

Gestational and childhood PFAS were generally not associated with triglycerides, HDL, or triglyceride to HDL ratio in our study. The Spanish study found that gestational PFHxS, but not PFOA, PFOS, or PFNA were positively associated with triglycerides at age 4 years (Manzano-Salgado et al. 2017). In our study, gestational PFHxS was marginally associated with higher triglycerides at age 12 years, although the 95% CI included the null. Another study using data from the Project Viva cohort reported that gestational PFAS were not associated with triglycerides or HDL in mid-childhood (median age: 7.7 years) (Mora et al. 2018). Many cross-sectional studies reported that higher PFOA concentrations are associated with unfavorable lipid profiles, including higher total cholesterol and low-density lipoprotein cholesterol in both children and adults (Frisbee et al. 2010; Matilla-Santander et al. 2017; Mora et al. 2018; Nelson et al. 2010; Skuladottir et al. 2015). It is unclear why we did not observe this association in our cohort.

We found that gestational PFOA and PFHxS were associated with higher leptin levels and lower adiponectin to leptin ratio. Consistently, the Danish study also found that gestational PFOA were associated with higher leptin levels and leptin to adiponectin ratio in adults at age 20 years (Halldorsson et al. 2012). The Project Viva study found null associations of gestational PFAS with leptin or adiponectin levels in mid-childhood (Fleisch et al. 2017). Similarly, a study in the Faroe Islands reported that gestational PFAS were associated with neither leptin nor adiponectin concentrations at age 13 years (Shelly et al. 2019). However, the latter two studies only examined the impact of gestational PFAS on individual adipocytokines but not the ratio of the two adipocytokines. It is noteworthy that individual adipocytokines may not be a good predictor of cardiometabolic risk. Growing evidence shows that adiponectin to leptin ratio (or leptin to adiponectin ratio) is a better predictor of insulin resistance and cardiometabolic risk in children than individual adipocytokines (Ayina et al. 2017; Frithioff-Bøjsøe et al. 2020; Frühbeck et al. 2018; Inoue et al. 2006; López-Jaramillo et al. 2014).

Gestational and childhood exposure to PFHxS, but not to PFOA, PFOS, or PFNA was associated with adolescents' blood pressure in our study. Gestational PFHxS was not associated with blood pressure in the Spanish (INMA) study (Manzano-Salgado et al. 2017). It is noteworthy that the adolescents in our cohort have lower average blood pressure than the U.S. general population at the same age range (possibly partly due to overnight fasting), which may to some extent reduce the generalizability of our findings. Regardless, two previous studies have examined childhood blood pressure in associations with gestational exposure to PFOA, PFOS, or PFNA, and reported findings consistent with ours (Manzano-Salgado et al. 2017; Warembourg et al. 2019).

We found that gestational PFOA and PFHxS were both positively associated with waist circumference, and gestational PFHxS was also positively associated with cross-sectional area of fat inside abdominal cavity. Consistently, two other studies reported that gestational PFOA was positively associated with adolescents' waist circumference (Halldorsson et al. 2012; Mora et al. 2017). In contrast, the Spanish study found that gestational PFAS were not associated with waist circumference at age 7 years. Gestational PFOA was positively associated with waist circumference, but not with cross-sectional area of fat inside abdominal cavity. Our findings on PFOA are not contradictory. The cross-sectional area of fat inside abdominal cavity we measured using DXA is a direct measure of visceral fat. In contrast, waist circumference is an indirect method to assess central adiposity and cannot disentangle visceral fat from abdominal subcutaneous fat (Bigornia et al. 2013; Bosy-Westphal et al. 2010). Given that this is the first study to date that examined the associations between early life PFAS and directly measured visceral fat, future studies are needed to confirm our findings.

PFOS and PFNA at 3 years old were associated with decreased cardiometabolic risk in our cohort, and these associations were driven by several components such as HDL, triglycerides, HOMA-IR, and adiponectin to leptin ratio. No previous studies have examined the impact of PFOS and PFNA at age 3 years on children's cardiometabolic risk, and thus we do not have a basis for comparison. However, and to some extent consistent with our findings, in Project Viva mid-childhood PFOS was associated with increased HDL and decreased triglycerides, as well as mid-childhood PFOS and PFNA were associated with decreased HOMA-IR (Mora et al. 2018). Future studies are needed to confirm these findings and investigate the underlying mechanisms.

Few studies have examined the impact of gestational PFAS mixtures on adolescent's cardiometabolic risk, and thus we do not have a basis for comparison. In our WQS analysis, PFAS mixture was positively associated with the novel cardiometabolic risk score, with gestational PFOA and PFHxS as the more important variables contributing to this association. This finding is consistent with our findings from single PFAS analysis where gestational PFOA and PFHxS were positively associated with the cardiometabolic risk.

We did not observe sex-specific patterns of associations between PFAS and cardiometabolic risk in our cohort. Most previous studies either did not examine or did not observe effect measure modification by sex (Alderete et al. 2019; Domazet et al. 2016; Fleisch et al. 2017; Halldorsson et al. 2012; Lin et al. 2020; Maisonet et al. 2015; Manzano-Salgado et al. 2017; Mora et al. 2018; Shelly et al. 2019; Warembourg et al. 2019). Two studies found slightly stronger associations in girls (Halldorsson et al. 2012; Mora et al. 2018). It is noteworthy that most of these studies, including ours, had limited statistical power to study differences by sex so these results need to be interpreted with caution.

There are some strengths and limitations to our study. First, because cardiometabolic risk factors tend to cluster, we used cardiometabolic risk summary scores to assess the influence of PFAS on adolescents' overall cardiometabolic risk. Given that there is currently no consensus on the definition for the score, in addition to constructing a score using traditional cardiometabolic risk factors according to the definition of metabolic syndrome in adults, we

also constructed a score using relatively novel, but likely better predictors to assess risk. However, it is noteworthy that our calculation of cardiometabolic risk score is based on the assumption that each individual component has equal weights/contribution to the overall cardiometabolic risk, which is consistent with current definition of metabolic syndrome. Nonetheless, it is possible that some individual components are more important predictors of cardiometabolic risk than the others, and thus our results need to be interpreted with caution. Second, most previous studies did not examine the influence of childhood PFAS exposure on cardiometabolic risk, or only examined the cross-sectional association between childhood PFAS and cardiometabolic risk. The longitudinal design of our study allowed us to examine the associations of adolescents' cardiometabolic risk with serum PFAS concentrations assessed during multiple periods of susceptibility to the potential effects of PFAS exposure, including gestation and early and middle childhood (Rice and Barone 2000). The multiple informant model enabled us to utilize these repeated PFAS assessments and formally test differences in the associations between PFAS exposure and adolescents' cardiometabolic risk across visits and identify gestation as a potential period of heightened susceptibility (Sanchez et al. 2011). Third, previous studies used maternal gestational PFAS exposure as a proxy for fetal exposure, given that gestational PFAS concentrations were highly correlated with cord blood PFAS concentrations (Manzano-Salgado et al. 2015). However, there is variation in the extent to which each PFAS in maternal blood is transferred to the fetus (Pan et al. 2017). In our study, we measured both gestational and cord serum PFAS concentrations to better assess the fetal PFAS exposure. It is noteworthy that we have fewer cord blood samples than maternal gestational blood samples, and thus the associations for cord blood PFAS were less precise. Fourth, our study had a modest sample size, and the multiple informant model has relatively low power to detect exposure-time period interactions. Regardless, we were still able to detect that associations between PFOA and adolescent cardiometabolic risk scores varied by exposure period. Fifth, we collected a rich set of covariates using valid and reliable measures, which allowed us to adjust for a variety of potential confounders, including diet quality, physical activity, and maternal prenatal fish consumption. However, there may be residual confounding from dietary, and maternal behavioral or lifestyle factors. Diet is one of the major sources of human PFAS exposure and is also associated with cardiometabolic risk, and therefore diet could potentially confound the associations between PFAS exposure and the cardiometabolic risk. Unfortunately, we do not have detailed diet information (consumption of each type of foods) at each exposure period. Future studies are needed to more thoroughly investigate diet as a confounder. There are also possibilities of residual confounding by some less common PFAS or other chemicals that are both correlated with PFOA/PFHxS and associated with cardiometabolic risk. Finally, while multiple comparisons may be a concern in this study, the consistent patterns of gestational and cord serum PFOA and PFHxS associated with both cardiometabolic risk scores and their individual components suggests that these results may not be solely due to chance. The potential concern of false positive results necessitates further replication of our findings.

5. Conclusions

Exposure to PFOA and PFHxS during gestation, compared to childhood, was more strongly associated with unfavorable cardiometabolic risk scores at age 12 years in this cohort of children with higher gestational PFOA exposure. Gestational and childhood PFOS and PFNA exposure were generally not associated with cardiometabolic risk scores at age 12 years. Gestational exposure to the four PFAS was aggregately associated with unfavorable cardiometabolic risk. Future epidemiologic studies investigating the health impacts of early life PFAS exposure should consider using continuous cardiometabolic risk summary scores to assess cardiometabolic risk and confirm our findings. In addition, future epidemiological studies are needed to investigate the impact of other PFAS and PFAS mixture on cardiometabolic risk, and investigate the biological mechanisms underlying these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Gestational PFOA exposure was associated with unfavorable cardiometabolic risk
- Gestational PFHxS exposure was associated with unfavorable cardiometabolic risk
- A novel risk score was used to assess adolescents' cardiometabolic risk

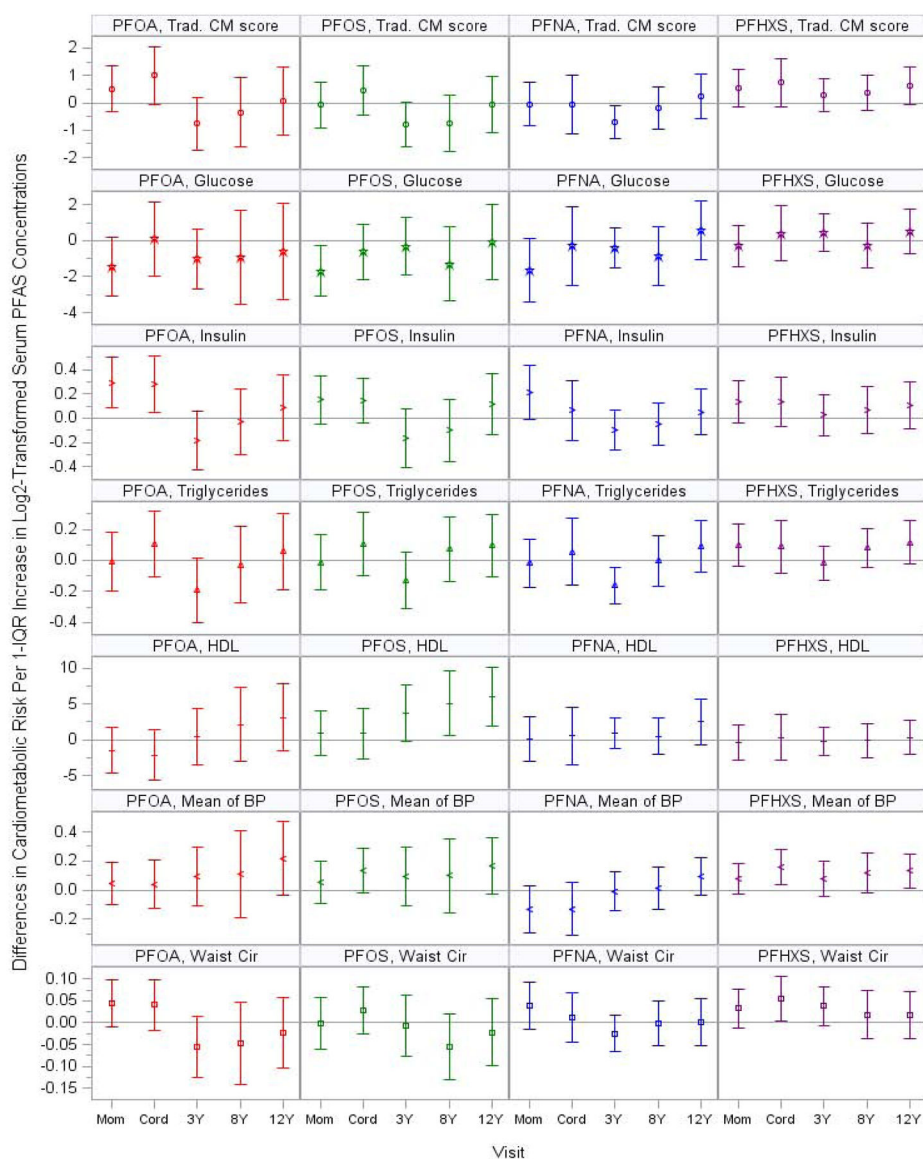


Figure 1.

Adjusted Differences in Traditional Cardiometabolic Risk Scores and the Individual Components with 1-Interquartile Range (IQR) Increase in Log₂-Transformed Serum Per- and Polyfluoroalkyl Substance (PFAS) Concentrations: The HOME Study.

Note: PFOA: perfluorooctanoate; PFOS: perfluorooctane sulfonate; PFNA:

perfluorononanoate; PFHxS: perfluorohexane sulfonate; trad: traditional; CM:

cardiometabolic; HDL: high-density lipoproteins; Mean of BP: mean of systolic and diastolic blood pressure z-scores; Cir: circumference.

The y-axis units were standard deviation for traditional CM score and mean of blood pressure, mg/dL for glucose, triglycerides and HDL, mIU/L for insulin, and centimeter for waist circumference.

Blood Pressure z-scores were sex-, age-, and height- standardized according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.

Traditional CM risk score was the sum of the standardized z-scores for waist circumference, glucose, insulin, triglycerides, HDL (multiplied by -1), and the mean of systolic and diastolic blood pressure.

All models adjusted for visit, visit*PFAS, maternal age, maternal education, maternal pre-pregnancy BMI, gestational serum cotinine concentrations, and parity; and child age, sex, race, and pubertal stage. For childhood PFAS exposure, we also adjusted for breastfeeding duration.

Insulin, triglycerides, and waist circumference were not normally distributed and thus were \log_2 -transformed in the model.

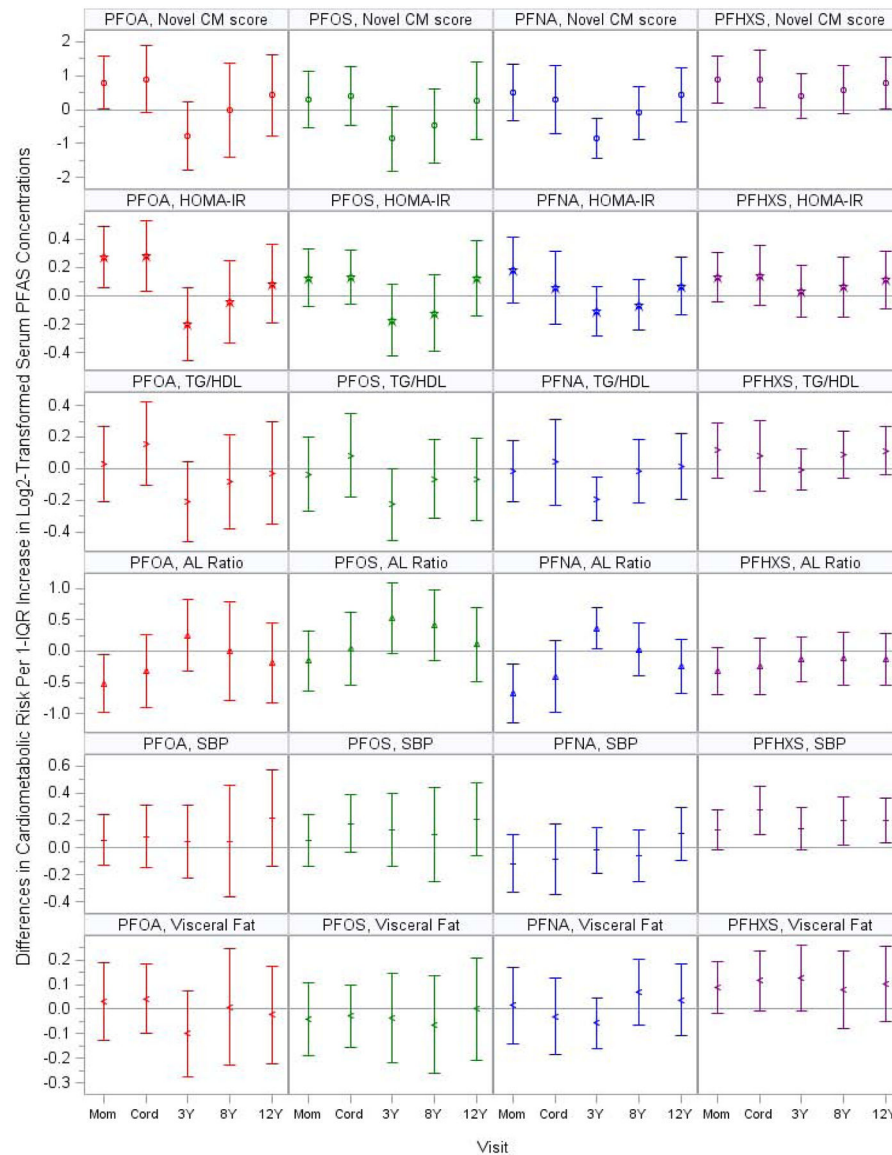


Figure 2.

Adjusted Differences in Novel Cardiometabolic Risk Scores and the Individual Components with 1-IQR Increase in Log₂-Transformed Serum PFAS Concentrations: The HOME Study.

Note: PFOA: perfluorooctanoate; PFOS: perfluorooctane sulfonate; PFNA: perfluorononanoate; PFHxS: perfluorohexane sulfonate; CM: cardiometabolic; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; TG/HDL: triglyceride to high-density lipoproteins ratio; AL: adiponectin to leptin; SBP: systolic blood pressure z-score; visceral fat: cross-sectional area of fat inside the abdominal cavity.

The y-axis units were standard deviation for novel CM score and systolic blood pressure and square centimeters for visceral fat. Blood Pressure z scores were sex-, age-, and height-standardized according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.

Novel CM risk score was the sum of the standardized z-scores for HOMA-IR, triglyceride to HDL ratio, adiponectin to leptin ratio (multiplied by -1), systolic blood pressure, and cross-sectional area of fat inside the abdominal cavity.

All models adjusted for visit, visit*PFAS, maternal age, maternal education, maternal pre-pregnancy BMI, gestational serum cotinine concentrations, and parity; and child age, sex, race, and pubertal stage. For childhood PFAS exposure, we also adjusted for breastfeeding duration.

HOMA-IR, triglyceride to HDL ratio, adiponectin to leptin ratio, and cross-sectional area of fat inside the abdominal cavity were not normally distributed and thus were \log_2 -transformed in the model.

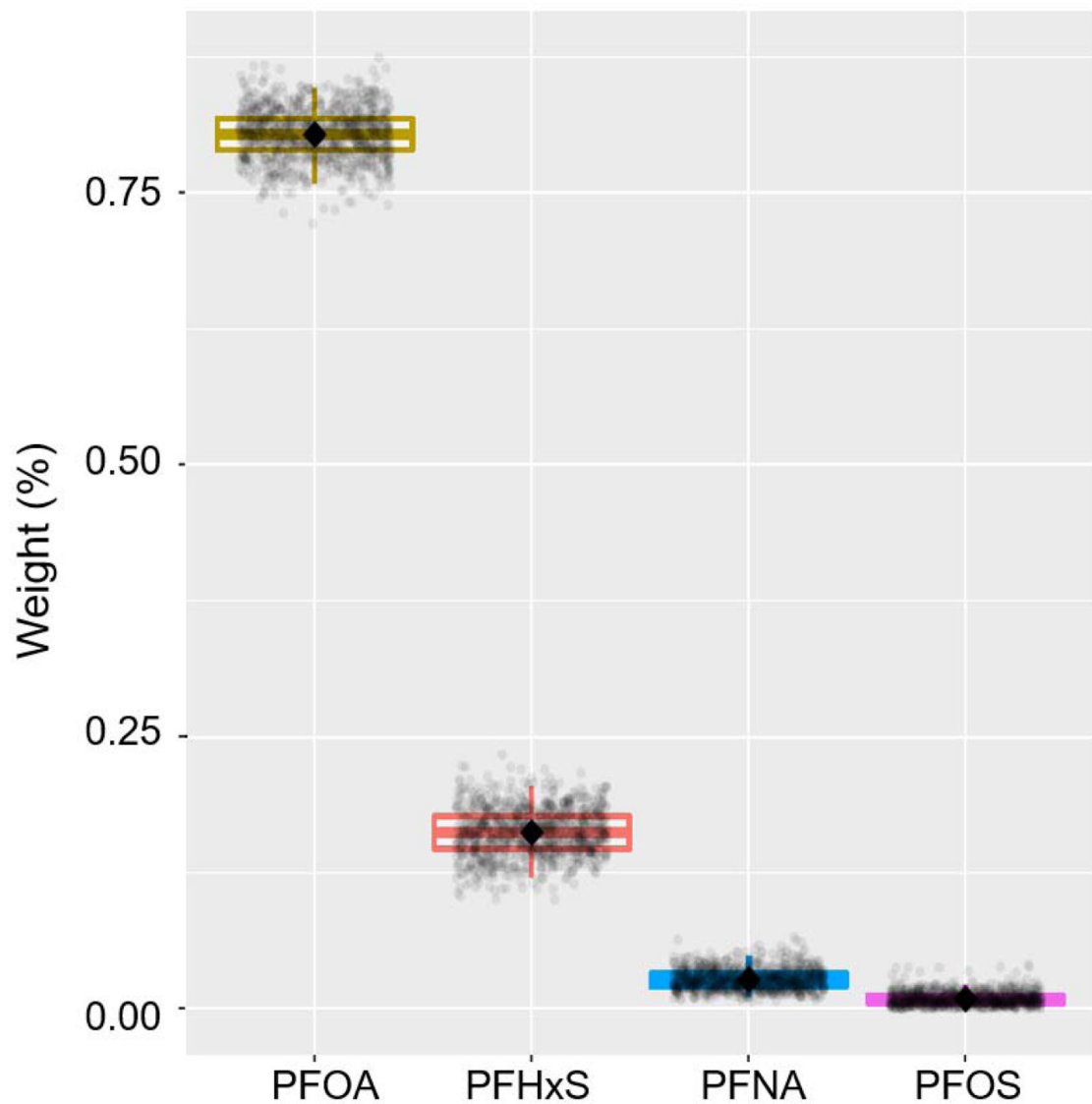


Figure 3.

Weighted Quantile Sum Regression Analysis with 1,000 Iterations on Gestational Exposure to PFAS Mixture and Novel Cardiometabolic Risk Score: Relative Weights of Each PFAS (N=168).

Note: each individual dot represents weight for a given PFAS from a single repeated holdout; and box-and-whisker plots describe univariate statistics of the weights from 1,000 repeated holdouts.

PFOA: perfluorooctanoate; PFHxS: perfluorohexane sulfonate; PFNA: perfluorononanoate; PFOS: perfluorooctane sulfonate.

All models adjusted for maternal age, maternal education, maternal pre-pregnancy BMI, gestational serum cotinine concentrations, and parity; and child age, sex, race, and pubertal stage.

Table 1.

Traditional and Novel Cardiometabolic Risk Scores at Age 12 Years According to Covariates among Children from the Health Outcomes and Measures of the Environment (HOME) Study.

	N	Traditional Cardiometabolic Risk Score	N	Novel Cardiometabolic Risk Score
		Mean \pm SD		Mean \pm SD
Overall	186	0.1 \pm 3.4	180	0 \pm 3.4
Child Sex				
Female	97	0 \pm 3.3	96	0 \pm 3.7
Male	89	0.2 \pm 3.4	84	0.1 \pm 3.1
Child Race				
Non-Hispanic White	103	-0.3 \pm 3.5	100	-0.5 \pm 3.5
Non-Hispanic Black	71	0.7 \pm 3.3	69	0.9 \pm 3.3
Other	12	-1.1 \pm 2.7	11	-1.0 \pm 2.4
Child Pubertal Stage				
Stage 1	19	-0.9 \pm 3.9	17	-0.8 \pm 3.5
Stage 2	47	-0.5 \pm 3.5	47	-0.6 \pm 3.7
Stage 3	55	0.2 \pm 3.4	52	0 \pm 3.4
Stage 4	38	1.0 \pm 3.2	38	0.9 \pm 3.4
Stage 5	27	0 \pm 2.7	26	0.4 \pm 2.8
Breastfeeding Duration (Any)				
0 month	35	1.4 \pm 3.0	34	1.1 \pm 3.3
>0–6 months	74	-0.3 \pm 3.0	73	-0.4 \pm 3.1
>6 months	73	-0.5 \pm 3.6	70	-0.2 \pm 3.7
Maternal Age				
18–25 Years	46	0.1 \pm 3.0	45	0.2 \pm 3.0
>25–35 Years	112	-0.1 \pm 3.5	109	-0.1 \pm 3.6
>35 Years	28	0.5 \pm 3.5	26	0.3 \pm 3.6
Maternal Education				
High School or Less	41	1.1 \pm 3.5	41	1.4 \pm 3.2
Tech School/Some College	59	-0.3 \pm 3.4	57	-0.7 \pm 3.7
Bachelor's or More	86	-0.2 \pm 3.3	82	-0.1 \pm 3.2
Pre-Pregnancy BMI (kg/m²)				
<25	96	-0.4 \pm 3.3	92	-0.4 \pm 3.3
25–30	50	-0.3 \pm 3.3	49	-0.3 \pm 3.3
>30	40	1.5 \pm 3.4	39	1.6 \pm 3.5
Gestational Serum Cotinine (ng/ml)				
<0.015 (Unexposed)	56	-0.1 \pm 2.9	51	-0.3 \pm 3.1
0.015–3 (Secondhand)	112	-0.1 \pm 3.5	111	-0.1 \pm 3.6
>3 (Active Smoker)	18	1.7 \pm 3.8	18	1.6 \pm 3.3
Parity				
0	73	-0.6 \pm 3.5	71	-0.5 \pm 3.6
1	62	0.7 \pm 3.4	59	0.5 \pm 3.3

	N	Traditional Cardiometabolic Risk Score	N	Novel Cardiometabolic Risk Score
		Mean \pm SD		Mean \pm SD
2	51	0.3 \pm 3.0	50	0.2 \pm 3.2

Note: We enrolled pregnant women in their second trimester and have conducted two visits (at ~16 week and ~26 week of gestation) to collect maternal baseline information.

Traditional cardiometabolic risk score was the sum of the standardized z-scores for waist circumference, glucose, insulin, triglycerides, high-density lipoproteins (multiplied by -1), and the mean of systolic and diastolic blood pressure.

Novel cardiometabolic risk score was the sum of the standardized z-scores for Homeostatic Model Assessment of Insulin Resistance, triglyceride to high-density lipoproteins ratio, adiponectin to leptin ratio (multiplied by -1), systolic blood pressure, and cross-sectional area of fat inside the abdominal cavity.

SD: standard deviation; BMI: body mass index.

Table 2.

Descriptive Statistics of Cardiometabolic Risk Outcomes among the HOME Study Adolescents at the 12 Year Study Visit: Stratified by Sex (Total N=221).

Measurement	All			Boys			Girls		
	N	Median (25th, 75th)	N	Median (25th, 75th)	N	Median (25th, 75th)	N	Median (25th, 75th)	
Traditional Cardiometabolic (CM) Risk Score	186	0.1 (-2.4, 2.2)	89	0.2 (-2.2, 1.6)	97	0.1 (-2.6, 2.3)			
Glucose (mg/dL)	186	91 (88, 96)	89	93 (89, 98)	97	90 (87, 94)			
Insulin (mIU/L)	187	12 (8.2, 19)	89	10 (6.8, 13)	98	16 (11, 21)			
Triglycerides (mg/dL)	186	75 (59, 100)	89	74 (60, 94)	97	77 (59, 102)			
High Density Lipoprotein (HDL, mg/dL)	186	53 (45, 60)	89	53 (45, 62)	97	52 (45, 58)			
Mean of Systolic and Diastolic Blood Pressure (Z-Score)	221	-0.6 (-0.9, -0.2)	100	-0.5 (-0.9, -0.2)	121	-0.6 (-1.0, -0.2)			
Waist Circumference (Iliac, cm)	221	71 (64, 79)	100	67 (63, 76)	121	72 (66, 82)			
Novel CM Risk Score	180	-0.4 (-2.2, 1.9)	84	-0.2 (-1.8, 1.6)	96	-0.6 (-2.4, 2.6)			
HOMA-IR	186	2.8 (1.9, 4.3)	89	2.4 (1.6, 3.1)	97	3.5 (2.5, 5.2)			
Triglyceride to HDL Ratio	186	1.4 (1.1, 2.1)	89	1.4 (1.0, 1.8)	97	1.4 (1.1, 2.1)			
Adiponectin to Leptin Ratio	184	1.4 (0.6, 4.2)	88	2.3 (0.9, 5.5)	96	1.0 (0.4, 2.5)			
Systolic Blood Pressure (Z-Score)	221	-0.6 (-1.1, -0.1)	100	-0.6 (-1.0, 0.0)	121	-0.6 (-1.1, -0.1)			
Cross-sectional Area of Fat Inside the Abdominal Cavity (cm ²)	214	41 (31, 55)	96	48 (41, 56)	118	34 (26, 52)			

Note: Traditional CM risk score was the sum of the standardized z-scores for waist circumference, glucose, insulin, triglycerides, HDL (multiplied by -1), and the mean of systolic and diastolic blood pressure.

Blood Pressure z-scores were sex-, age-, and height- standardized according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance. HOMA-IR = Fasting insulin (mIU/L) x Fasting glucose (mg/dL)/405.

Novel CM risk score was the sum of the standardized z-scores for HOMA-IR, triglyceride to HDL ratio, adiponectin to leptin ratio (multiplied by -1), systolic blood pressure, and cross-sectional area of fat inside the abdominal cavity.