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Associations of cord plasma per- and polyfluoroalkyl substances (PFAS) with neonatal and child body composition and adiposity: The GUSTO study

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ABSTRACT

Background: The influence of prenatal exposure to per- and poly- fluoroalkyl substances (PFAS) on birth size and offspring adiposity is unclear, especially for the newer, shorter-chained replacement PFAS.

Methods: In the GUSTO multi-ethnic Singaporean mother-offspring cohort, 12 PFAS were measured in 783 cord plasma samples using ultra-performance-liquid chromatography-tandem-mass-spectrometer (UPLC-MS/MS). Outcomes included offspring anthropometry, other indicators of body composition/metabolic health, and MRI-derived abdominal adiposity (subset) at birth and 6 years of age. PFAS were modeled individually, in categories of long-chain and short-chain PFAS, and as scores of three principal components (PC) derived using PC analysis (PC1, PC2, and PC3 reflect predominant exposure patterns to "very-long-PFAS", "long-PFAS", and "short-PFAS", respectively). Associations with outcomes were assessed using multivariable linear regressions, adjusted for important covariates such as maternal sociodemographic and lifestyle factors.

Results: Overall, cord PFAS levels showed either no or positive associations (mostly for long-chain PFAS) with birth weight, length and head circumference. In general, PFAS were associated with higher neonatal abdominal adiposity, driven by shorter-chain PFAS. Perfluoroheptanoic acid (PFHpA) was associated with higher volumes of superficial subcutaneous adipose tissue (sSAT) (3.75 [1.13, 6.37] mL per SD increase in PFAS) and internal adipose tissue (IAT) (1.39 [0.41, 2.38] mL). Higher levels of perfluorobutanesulfonic acid (PFBS), short-chain PFAS, and PC3 were associated with higher IAT volume (β range 1.22–1.41 mL/SD, all $P < 0.02$), especially

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in girls. Higher PC3 score was additionally associated with higher sSAT (3.12 [0.45, 5.80] mL) volume. At age 6 years, most observed associations did not persist. No consistent associations were observed between PFAS and whole-body adiposity measures.

Conclusions: Fetal exposure to emerging short-chain PFAS was associated with higher abdominal adiposity at birth but not at age 6 years. Further research is needed to replicate the findings and to determine if these effects may reappear beyond early childhood. Population exposure to newer PFAS and consequent health impact must be monitored.

1. Introduction

Adverse birth and childhood outcomes, such as low birth weight and childhood obesity, constitute major public health challenges globally and impose a substantial healthcare burden (Sahoo et al., 2015; Negrato and Gomes, 2013). Over recent past decades, there has been a dramatic worldwide increase in the prevalence of overweight and obesity among children and adolescents aged 5–19 years old, from just 4 % in 1975 to over 18 % in 2016 (Obesity and overweight, n.d.). These adverse early life events not only increase risks of short-term morbidity and mortality but also contribute to worse health outcomes in adulthood according to the Developmental Origins of Health and Diseases (DOHaD) paradigm (Lakshman et al., 2012; Poston et al., 2022). Although genetics plays a role, the proportion of variance in these conditions explained by genetic variation is generally low (Locke et al., 2015). Thus, it remains a priority to identify modifiable environmental factors that can affect birth and childhood adiposity outcomes to implement effective public health interventions.

Per- and poly- fluoroalkyl substances (PFAS) are a group of synthetic chemicals characterized by at least one fully fluorinated carbon atom in an alkyl chain. PFAS are widely used in industrial manufacturing due to their resistance to water, grease, oil, and heat, leading to their use in products such as stain- and water- repellent carpeting and fabrics, fire-fighting foams, cookware, and food packaging. The widespread use of PFAS, along with their stable chemical structure and long half-life (ranging from months to years depending on chain length (Xu et al., 2020)), have all contributed to their almost ubiquitous presence in our modern environment. Due to their well-documented toxicity affecting immunity, reproduction, development, lipid and insulin regulation, thyroid, liver and kidney function, and cancer risk (reviewed in Fenton et al., 2021), increasing human exposure to PFAS through consumer products, the environment, and food (e.g., seafood) and food packaging is a major public health concern. Previous research studies have led to the phase-out of many legacy PFAS, mainly the longer-chain ones such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), with a ban imposed in an increasing number of countries. These legacy PFAS have been replaced by a range of newer (mostly shorter-chain) PFAS thought to be of lower toxicity due to their shorter half-lives. However, emerging research suggests that this may not be the case. For instance, it has been recently shown that short-chain PFAS are not only extremely persistent but also highly mobile (Li and MacDonald, 2022; Brendel et al., 2018) due to their low absorption potential; they are also harder to remove from the water and environment with current technology compared to their longer chain counterparts (Brendel et al., 2018).

While PFAS have been extensively studied in relation to health outcomes in general populations, their impact on maternal and child health remains inconsistent and unclear. In particular, research on the long-term effects of fetal exposure to PFAS on birth outcomes and childhood health is limited. Although PFOA and PFOS have been relatively well-studied, there is a scarcity of research on the impact of the newer short-chain PFAS on birth size and offspring adiposity. Given the differing exposure patterns of PFAS across regions (Sunderland et al., 2019), it is also crucial to gather evidence from a variety of geographical locations. To address this research gap, our study aims to investigate the influence of 12 PFAS, including newer replacement PFAS, on birth size and offspring adiposity in a multi-ethnic Asian mother-offspring cohort. We hypothesized that prenatal exposure to newer replacement PFAS, similar to legacy PFAS, may negatively influence birth and offspring anthropometric measurements and adiposity.

2. Material and methods

2.1. Study populations

A total of 1450 participants were recruited into the on-going GUSTO mother-offspring cohort study (ClinicalTrials.gov identifier: NCT01174875); the study design has been detailed elsewhere (Soh et al., 2014). Briefly, pregnant women aged 18 years and above were recruited at <14 weeks' gestation from two main public maternity hospitals in Singapore between 2009 and 2010. The Chinese, Malay or Indian participants were Singapore citizens or permanent residents. Women receiving chemotherapy, psychotropic drugs or those with type I diabetes mellitus were excluded. This study was approved by the National Health Care Group Domain Specific Review Board (reference D/09/021) and the SingHealth Centralized Institutional Review Board (reference 2009/280/D). All research was performed in accordance with the relevant guidelines and written informed consent was obtained from all participants upon recruitment.

2.2. Exposure - PFAS analysis

Umbilical cord venous blood was collected immediately following delivery into EDTA tubes. Within 2-hours post-collection, the sample was centrifuged at 1600 g for 10 min at 4 °C to isolate plasma, which was further centrifuged at 16,000 g for 10 min at 4 °C. Next, 4 mL of the plasma was added to a plain tube containing ~15 μL trasylol, and the mixture stored at −80 °C in 0.4 mL aliquots until subsequent batch analyses. 783 umbilical cord plasma samples were available for PFAS analysis. PFAS were analyzed using ultra performance liquid chromatography-tandem mass spectrometer (UPLC-MS/MS). A total of 12 PFAS were measured: 1) short-chain: perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorobutanesulfonic acid (PFBS), and 2) long-chain: perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorohexanesulphonic acid (PFHxS), and perfluorooctanesulfonic acid (PFOS) (see Section 2.5.1 for definitions of short- and long- chain PFAS).

After spiking with 50 μL (200 ng/mL) isotope-labeled standards in methanol, the plasma samples were transferred to a Waters Ostro plate, then mixed with 400 μL of 1 % formic acid/acetonitrile (ACN), and passed through the plate with a vacuum of 10–15″ Hg. The filtrate was collected and concentrated to barely dry with a SpeedVac concentrator at 50 °C under 10 torr vacuum, then reconstituted with 100 μL of methanol. After centrifugation at 3,000 rpm for 15 min, the supernatant was transferred to an insert for instrumental analysis, which was performed on a Waters UPLC I-Class coupled with a Waters Xevo TQ-XS in both positive and negative electrospray ionization. Analytes were separated on a Waters CORTECS C18 column (30 × 2.1 mm, 1.6 μm).

The mobile phase (A) was 0.04 % acetic acid in ACN/Milli-Q water (5/95, v/v) and (B) 0.04 % acetic acid in ACN/Milli-Q water (90/10, v/v). The gradient started at 5 % (B), which was held for 0.5 min, then increased to 90 % in 4 min. After holding at 90 % for 0.3 min, the gradient decreased to the initial condition in 0.2 min, then held for 2 min for re-equilibrium. The oven temperature, flow rate, and injection volume were 45 °C, 0.5 mL/min, and 1 μL, respectively.

Quality assurance. First, two types of QC samples were analyzed, including a sample blank and spiked chemical standards with isotope-labeled internal standards. This was done to ensure there was no cross-contamination of analytes and to check the stability of the instrument during analysis. Then, two analytes from spiked pooling samples (spiked with known chemical standards at high and low concentrations) were analyzed periodically during the analysis to confirm there were no potential matrix effects and to ensure the reliability of the analysis.

2.3. Outcomes

2.3.1. Birth size

Birth weight and gestational age at birth were obtained from medical records. Gestational age was based on a dating ultrasound scan performed in the first trimester. Birth length was measured using a mobile infant mat (SECA model 210, SECA Corp., Hamburg, Germany), and head circumference using a non-stretchable measuring band (SECA 212 Measuring Tape, SECA Corp., Hamburg, Germany) within 72 h after birth by trained research staff using standardized protocols. Duplicate measurements were obtained, which were subsequently averaged.

2.3.2. Neonatal body composition

Neonatal whole-body composition, i.e., fat mass (FM) and fat-free mass (FFM), were measured by air displacement plethysmography (ADP) using The PEA POD Infant Body Composition System Version 3.1.0 (Cosmed, Italy), which was calibrated daily. Neonates were measured with clothing removed while wearing a tight-fitting cap to minimize air trapping in their hair. The neonates were placed on the built-in scale to measure body mass and then inside the chamber for body volume measurements, which required approximately 2 min. Infant percent body fat was computed by software integral to the PEA POD system.

2.3.3. Neonatal abdominal adiposity

Quantification of neonatal abdominal adiposity using magnetic resonance imaging (MRI) within two weeks of delivery in GUSTO has been described in detail elsewhere (Tint et al., 2016; Chen et al., 2016). Briefly, non-sedated, fed, and swaddled neonates who were 5–10 min into their sleep were placed supine in an immobilization bag within an adult head coil and had their abdomen scanned. Subsequently, T1-weighted water-suppressed axial fast spin echo sequences were acquired (GE Signa HDxt 1.5 TMR scanner, Wisconsin, USA). The water-suppressed images were processed using an in-house semi-automated quantitative analysis software (MATLAB 7.13; The MathWorks Inc., Massachusetts, USA) based on morphological image analysis operations. From these operations, the volumes of total subcutaneous adipose tissues (SAT) (i.e., sum of superficial subcutaneous adipose tissue [SSAT] and deep subcutaneous adipose tissue [DSAT]), SSAT, DSAT, and internal adipose tissue (IAT) were determined (Tint et al., 2016; Chen et al., 2016). Since neonates have hardly any visceral adipose tissue, we have combined volumes of visceral (intraperitoneal and retroperitoneal), intermuscular, as well as paravertebral and intra-spinal fat, into a single variable labeled internal adipose tissue (Tint et al., 2016). MRI in non-sedated neonates is challenging as image quality is sensitive to movement, and difficulty in obtaining parental consent poses further logistical constraint. Thus, MRI data was only available for a subset (about one third of live births).

2.3.4. Childhood adiposity

At age 6 years, the children underwent MRI of the abdomen without sedation using the Siemens Skyra 3T MR scanner (Sadananthan et al., 2019). Sixty axial slices were acquired using a water-suppressed HASTE sequence (repetition time [TR] = 1000 ms, echo time [TE] = 95 ms) and a body matrix coil for anatomical localization. The SAT and visceral adipose tissue (VAT) depots were segmented from the abdominal MR images using a fully automated graph-theoretic segmentation algorithm (Sadananthan et al., 2015). The SAT compartment was sub-classified into DSAT and SSAT by manually drawing a boundary along the fascial plane by a trained MR reader who was blinded to all participants' information.

Using magnetic resonance spectroscopy (MRS), liver fat was estimated from two $1 \times 1 \times 1$ cm^3 voxels placed within the left and right lobes of the liver using a point resolved spectroscopy (PRESS) sequence (TR = 2000 ms, TE = 33 ms) with respiratory gating. The spectra were quantified using LCModel (Provencher, 1993; Chabanova et al., 2012) and the liver fat percentage was determined from T_2 corrected lipid and water peaks and averaged (Michael et al., 2020). Intramyocellular lipids (IMCL) were estimated from $1 \times 1 \times 1$ cm^3 voxel placed within the soleus muscle using a PRESS sequence (Michael et al., 2020). The spectrum was quantified using LCModel and the amount of IMCL was expressed as a percentage of the water signal after correcting for T2 losses (Kautzky-Willer et al., 2003).

The whole-body composition (fat mass [FM] and lean mass) of the children at 6 years old was measured using quantitative magnetic resonance (QMR) with the EchoMRI-Adolescent Humans Body Composition Analyzer (EchoMRI Corporation, Singapore) (Chen et al., 2018). The equipment was calibrated daily, and a routine system test was conducted each day. The participants were measured while wearing light clothing and lying in a supine position.

2.3.5. Childhood anthropometry and metabolic syndrome scores

Offspring weight (measured using SECA model 813) and head-to-heel standing height (measured using SECA model 213) were obtained through duplicate measurements and averaged at the age of 6. Offspring BMI was calculated as the weight divided by height squared. An age- and sex- specific BMI z-score was then derived using a Singapore reference (National Healthcare Group Polyclinics, 2010). Childhood overweight and obesity (OWOB) were defined as a BMI z-score > 85th percentile (Barlow and Committee, 2007).

We generated a metabolic syndrome score for each child based on the sum of cohort-specific sex-standardized component z-score evaluated at the age 6 visit using components described in literature (Ahrens et al., 2014): waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides (TG), and high-density lipoprotein cholesterol (HDL). HDL z-score was multiplied by −1, due to the inverse association between HDL and metabolic risk. The following formula was then applied, as we have previously described, to derive the metabolic syndrome score for each child: $WC_{z\text{-score}} + (SBP_{z\text{-score}} + DBP_{z\text{-score}})/2 + HOMA\text{-}IR_{z\text{-score}} + (TG_{z\text{-score}} + [-1 * HDL_{z\text{-score}}])/2$. A higher metabolic syndrome score reflects higher risk of metabolic syndrome.

2.4. Covariates

Analyses were adjusted for the following *a priori* determined covariates based on previous literature: maternal ethnicity, educational attainment, maternal age at delivery, parity, pre-pregnancy BMI, maternal tobacco smoke exposure during pregnancy, and infant sex. Ethnicity and educational attainment were self-reported at study enrolment. Maternal age at delivery was calculated by subtracting the date of maternal birth retrieved from national registration from the date of offspring delivery. Parity and infant sex were extracted from medical records. Pre-pregnancy BMI was calculated using measured height in the first trimester and self-reported pre-pregnancy weight. Tobacco smoke

exposure during pregnancy was categorized into 4 groups with increasing exposure based on both interviewer-administered questionnaires and circulating cotinine levels at 26–28 weeks' gestation (Ng et al., 2019): 1) No self-reported environmental tobacco smoke (ETS) exposure and cotinine level < 0.17 ng/mL, 2) Self-reported ETS and cotinine level < 0.17 ng/mL, 3) ETS or light smoking (cotinine level between 0.17 and 13.99 ng/mL), and 4) Active smoking (cotinine level ≥ 14 ng/mL).

2.5. Statistical analyses

Since PFPeA and PFHxA had low detection rates (26.4 % and 1.0 %, respectively), they were not considered further in analyses. All other PFAS had high detection rates – 82.3 % for PFHpA and PFDoDA, and ≥99 % for the remaining PFAS. PFAS levels below the limit of quantification (LOQ; signal to noise [S/N] ratio < 10) and the limit of detection (LOD; S/N ratio < 3) were imputed with LOQ/2 and LOD/2, respectively.

PFAS levels were first described according to sociodemographic factors. Since most PFAS distributions were skewed, they were log-transformed (base 2) to achieve approximate Normal distributions before further analyses. Multivariable linear regressions with adjustment for covariates were used to examine associations between PFAS and studied outcomes. To ensure comparability of regression coefficients, all exposure variables were standardized and modeled as z-scores.

Because previous literature had identified sex as a potential effect modifier for the relationship between PFAS exposure and birth outcomes/childhood adiposity (Gui et al., 2022; Braun et al., 2016), we then *a priori* stratified our analyses by child sex (*P*-interactions for our main analyses provided in Supplemental Table S1). Since we later found that many PFAS were associated with higher birth size as well as with longer gestational duration, we postulated that PFAS exposure may be associated with higher birth size because of a longer gestational duration, i.e., gestational duration may act as a mediator on the causal pathway between PFAS exposure and birth size. To explore this hypothesis *a posteriori*, we additionally incorporated gestational duration into our statistical models to assess potential changes in the effect estimates; a substantial attenuation in these estimates would indicate that PFAS exposure impacts on gestational duration to explain its link with higher birth size. Additionally, we also examined the association of PFAS with birth weight z-score already intrinsically adjusted for sex and gestational age using local (Aris et al., 2014) and international (Mikolajczyk et al., 2011) standards. As preterm infants may have unique determinants of adiposity (Uthaya et al., 2005), we conducted sensitivity analysis excluding them from the analyses. For year 6 outcomes, we performed sensitivity analyses additionally adjusting for childhood variables (breastfeeding duration, energy intake at age 5 years, and average daily duration of outdoor play and screen time). For a set of measures that are mostly comparable at birth and at age 6 years (weight, length/height, head circumference, and MRI-based SAT, DSAT, and SSAT), we further utilized generalized estimating equations (GEE) to examine the overall PFAS-outcome-associations between birth and 6 years, and whether the associations change across time by including a PFAS * time interaction term.

2.5.1. Utilizing PCA along with predetermined criteria for characterizing PFAS

In addition to investigation involving individual PFAS, the PFAS were also categorized based on predetermined and data-driven methods. For predetermined criteria, we categorized all perfluorocarboxylic acids (PFCAs) with ≥8 carbon chain length and perfluoroalkane sulfonic acids (PFSAs) with ≥6 carbon chain length as "long-chain PFAS" (About PFASs - OECD Portal on Per and Poly Fluorinated Chemicals n.d. https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/aboutpfass/ (accessed January 20, 2023), and PFCAs with ≤7 carbon chain length and PFSAs with ≤5 carbon chain length as "short-chain PFAS". In the real world, individuals are simultaneously exposed to clusters of PFAS, hence the need for a data-driven method which identifies relevant patterns of PFAS exposure. These were derived by principal component analysis (PCA) with varimax rotation on the 10 PFAS. Three principal components (PC) of PFAS (i.e., PFAS patterns) which cumulatively explained 65.4 % of variance in PFAS were retained based on the inflexion point of the Scree plot (Supplementary Fig. S1), eigenvalues > 1, and factor interpretability. The PFAS PC1, PC2, PC3 were labelled as "very long PFAS pattern", "long PFAS pattern", and "short PFAS pattern", respectively based on the factor loadings (Supplemental Table S2). There is no official categorization for "very long PFAS", but this PC pattern in our study is characterized by high loadings of PFCAs with ≥10 carbon chain length (PFDA, PFUnDA, and PFDoDA) and also PFOS. PFAS PC scores for each participant were then calculated by summing the concentrations of the individual PFAS weighted by their factor loadings (correlation coefficients between each PFAS and the PFAS principal component). A higher PC score indicates higher exposure to the PFAS patterns.

All analyses were conducted using the statistical software Stata version 15.1 (StataCorp., College Station, Texas, USA). Statistical significance was defined as a two-sided *P*-value < 0.05.

3. Results

A total of 1098 eligible live births were delivered in the GUSTO study. Among them, 783 cord blood plasma samples were available for PFAS analysis. The detailed participant flow chart is presented in Supplemental Fig. S2. The study population comprised 49 % Chinese, 21 % Indian, and 31 % Malay participants. Indian participants had significantly lower levels of long-chain PFAS (specifically PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFHxS, and PFOS levels) and lower scores on PC1 and PC2 compared to the other ethnic groups (all $P \leq 0.001$) (Table 1 and Supplemental Table S3). Parous women had lower levels of long-chain PFAS (specifically PFOA and PFOS) compared to nulliparous women (all $P < 0.05$) (Table 1 and Supplemental Table S3). Although only 4.3 % of the pregnant women reported active smoking during pregnancy, another 47 % reported exposure to environmental tobacco smoke (ETS) or had detectable levels of plasma cotinine at 26–28 weeks' gestation. Non-smoking women without ETS exposure had significantly lower PC1 scores ($P = 0.016$) and a trend of lower cord plasma levels of short-chain PFAS ($P = 0.050$) (Table 1). For individual PFAS, they also had the lowest levels of short-chained PFBS and long-chained PFDoDA, PFHxS, and PFOS (all $P < 0.05$) (Supplemental Table S3). Women who completed tertiary education accounted for 27 % of the total population and had significantly lower cord plasma levels of short-chain PFAS and lower scores on PC1 (both $P < 0.05$) compared to women without a degree (Table 1). For individual PFAS, they also had lower levels of short-chained PFBS and long-chained PFHxS and PFOS (all $P < 0.05$) (Supplemental Table S3). The majority of women had a normal pre-pregnancy BMI (62 %), while 19 % and 8 % were classified as having overweight and obesity, respectively. Cord plasma PFAS levels did not differ across pre-pregnancy BMI categories or by infant sex (47 % female).

3.1. Associations of cord plasma PFAS levels with anthropometry at birth

Fig. 1 panel A and Supplemental Table S4A depict the associations of cord plasma PFAS levels with anthropometric outcomes at birth. Most cord plasma PFAS generally showed trends of positive associations with birth size, with the sum of long-chain PFAS demonstrating a significant association with birth size while the sum of short-chain PFAS showed no association (Fig. 1 panel A; Supplemental Table S4A).

Birth weight: Higher cord plasma levels of the PFHpA, PFOA, PFDA, PFOS, and sum of long-chain PFAS and higher scores on PC1 and PC2 were associated with a higher birth weight (β range 37.5–50.2 g per 1 SD

Table 1
Concentrations of PFAS group and scores of PFAS principal components according to participants' characteristics.

Factor	N (%)	Short PFAS, ng/mL[a]	Long PFAS, ng/mL[b]	PC1 score[c]	PC2 score[c]	PC3 score[c]
Total	783	20.57 (14.90, 31.03)	4.72 (3.51, 6.33)	0.15 (−0.71, 0.97)	−0.05 (−0.98, 0.94)	−0.05 (−0.78, 0.72)
Ethnicity						
Chinese	379 (48.5 %)	19.89 (14.68, 31.20)	4.69 (3.39, 6.26)	0.14 (−0.55, 0.91)	0.01 (−0.94, 0.87)	−0.07 (−0.83, 0.78)
Indian	162 (20.7 %)	20.91 (14.79, 29.15)	4.05 (2.86, 5.69)	−0.52 (−2.63, 0.36)	−0.41 (−1.37, 0.76)	0.03 (−0.78, 0.70)
Malay	241 (30.8 %)	21.84 (15.11, 32.05)	5.28 (4.08, 6.95)	0.45 (−0.23, 1.37)	0.15 (−0.86, 1.29)	−0.09 (−0.78, 0.66)
P-value		0.57	<0.001	<0.001	0.001	0.87
Parity at recruitment						
Nulliparous	324 (41.4 %)	20.30 (14.54, 30.85)	5.02 (3.70, 6.46)	0.21 (−0.61, 1.02)	0.03 (−0.88, 1.04)	−0.09 (−0.93, 0.74)
Primiparous	285 (36.5 %)	20.50 (15.13, 31.13)	4.38 (3.29, 5.95)	−0.00 (−1.00, 0.91)	−0.16 (−0.99, 0.93)	0.01 (−0.75, 0.75)
Multiparous	173 (22.1 %)	20.90 (15.13, 30.63)	4.84 (3.43, 6.54)	0.15 (−0.55, 0.99)	−0.03 (−1.23, 0.93)	−0.07 (−0.72, 0.65)
P-value		0.80	0.024	0.13	0.37	0.46
Pre-pregnancy BMI[d]						
Underweight	77 (10.9 %)	18.25 (14.73, 27.76)	4.37 (3.51, 6.35)	0.32 (−0.40, 1.07)	−0.21 (−1.18, 1.16)	−0.14 (−0.84, 0.58)
Normal Weight	436 (61.9 %)	20.51 (14.83, 30.44)	4.74 (3.48, 6.34)	0.19 (−0.70, 1.04)	−0.03 (−0.99, 0.92)	−0.05 (−0.85, 0.74)
Overweight	135 (19.2 %)	22.00 (15.14, 32.37)	4.72 (3.58, 6.32)	0.08 (−1.04, 0.90)	−0.05 (−0.82, 1.20)	−0.09 (−0.75, 0.65)
Obese	56 (8.0 %)	22.66 (15.12, 33.02)	4.99 (3.29, 7.05)	0.14 (−0.58, 1.00)	−0.03 (−0.95, 1.47)	0.12 (−0.73, 0.91)
P-value		0.31	0.84	0.57	0.68	0.60
Cigarette smoking						
No ETS exposure	345 (49.0 %)	19.67 (14.39, 29.79)	4.37 (3.28, 6.25)	−0.00 (−1.00, 0.87)	−0.18 (−0.99, 0.90)	−0.09 (−0.93, 0.71)
Self-reported ETS	215 (30.5 %)	20.25 (14.83, 31.59)	4.91 (3.63, 6.51)	0.20 (−0.51, 0.97)	0.15 (−0.81, 1.04)	−0.04 (−0.72, 0.74)
ETS or light smoking	114 (16.2 %)	25.72 (15.60, 33.31)	4.94 (3.90, 6.46)	0.34 (−0.24, 1.13)	0.06 (−0.92, 0.89)	0.16 (−0.59, 0.79)
Active smoking	30 (4.3 %)	21.83 (16.28, 28.57)	4.96 (3.55, 7.50)	−0.08 (−1.08, 1.01)	0.38 (−1.57, 1.53)	−0.02 (−0.62, 0.68)
P-value		0.050	0.071	0.016	0.33	0.31
Education						
Degree	208 (27.0 %)	18.44 (13.98, 28.69)	4.55 (3.26, 6.25)	0.03 (−0.97, 0.79)	−0.14 (−1.08, 0.84)	−0.14 (−0.95, 0.69)
No degree	563 (73.0 %)	21.87 (15.06, 31.59)	4.84 (3.57, 6.42)	0.20 (−0.63, 1.02)	−0.02 (−0.93, 0.97)	−0.03 (−0.77, 0.74)
P-value		0.003	0.054	0.031	0.27	0.15
Child sex						
Female	368 (47.1 %)	20.13 (14.85, 31.12)	4.76 (3.42, 6.49)	0.15 (−0.99, 1.00)	0.05 (−0.93, 1.00)	−0.14 (−0.81, 0.68)
Male	413 (52.9 %)	21.45 (15.00, 30.81)	4.71 (3.53, 6.11)	0.15 (−0.62, 0.92)	−0.16 (−0.98, 0.93)	0.02 (−0.77, 0.79)
P-value		0.61	0.63	0.57	0.20	0.41

Estimates presented are median (interquartile range) unless otherwise specified. *P*-values were derived from Wilcoxon rank-sum (2 groups) or Kruskal-Wallis (>2 groups) test.
Per- and poly- fluoroalkyl substances (PFAS); principal component (PC); environmental tobacco smoke (ETS).
[a] Short PFAS include sum of perfluorobutanoic acid (PFBA), perfluoroheptanoic acid (PFHpA), and perfluorobutanesulfonic acid (PFBS) concentrations.
[b] Long PFAS include sum of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorohexanesulphonic acid (PFHxS), and perfluorooctanesulfonic acid (PFOS) concentrations.
[c] PC scores for each participant were calculated by summing the concentrations of the individual PFAS weighted by their factor loadings (correlation coefficients between each PFAS and the PFAS principal component) in each principal component derived from principal component analysis.
[d] BMI categories were defined using the following cutoffs: Underweight: <18.5 kg/m^2; Normal weight: 18.5–24.9 kg/m^2; Overweight: 25.0–29.9 kg/m^2; and Obese: >30 kg/m^2.

increase in the exposure variables, all $P < 0.05$), with most of these associations being more apparent in boys, except for the sum of long-chain PFAS-birth weight association, which was more prominent in girls.

Birth length: Higher cord blood plasma levels of PFBA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFOS, and sum of long-chain PFAS levels, and higher scores on PC1 and PC2 were associated with a longer birth length (β range 0.21–0.39 cm, all $P < 0.05$), with these associations being more prominent in girls.

Head circumference: Higher cord plasma levels of the long-chained PFOA, PFNA, PFDA, PFOS, and sum of long-chain PFAS, and higher PC1 and PC2 scores were associated with a larger head circumference (β range 0.11–0.21 cm, all $P < 0.05$), also more apparent in girls.

Gestational duration: Long-chain PFAS (individual, sum, and PC2 and PC3), but not short-chain PFAS except for PFHpA, were associated with a longer gestational duration (β range 0.15–0.24 week, all $P < 0.01$) (Supplemental Table S4A). Most of the associations between cord plasma PFAS levels and birth anthropometry could be partly explained by a longer gestational duration (Supplementary Fig. S3A). Of note, none of the observed associations between PFAS and birth weight remained statistically significant after further adjustment for gestational duration. Furthermore, cord PFAS was not associated with birth weight z-score already intrinsically adjusted for sex and gestational age (Supplemental Fig. S3B), consistent with the suggestion that the association between cord PFAS and birth size could be attributed to longer gestational duration.

3.2. Associations of cord plasma PFAS levels with anthropometry at age 6 years

In contrast, cord plasma PFAS were not generally associated with anthropometric measures when the children reached 6 years of age (Fig. 1 panel B; Supplemental Table S4B), with some exceptions of inverse associations mainly observed in girls.

BMI: Specifically, a higher cord plasma level of the long-chained PFDA was associated with a lower BMI at 6 years (β: −0.21 kg/m^2), mainly observed in girls, and higher PC1 score was additionally associated with a lower BMI at this age in girls only (β: −0.35 kg/m^2) (all $P < 0.01$). For BMI z-score at 6 years of age, the long-chained PFOS levels showed an inverse association in the overall population (β: −0.09; $P < 0.05$), while higher levels of long-chained PFDA, PFHxS, and higher PC1 score were associated with a lower BMI z-score only in girls (β range: −0.13 to −0.15; all $P < 0.05$). Similarly, higher levels of long-chained PFDA, PFDoDA, and PC1 score were associated with a lower odds of being overweight and obese at 6 years old only in girls (OR range: 0.64–0.65; all $P < 0.05$).

3.3. Associations of cord plasma PFAS levels with body composition and abdominal adiposity at birth

Fig. 2 panel A and Supplemental Table S5A show the associations of PFAS with whole body and abdominal adiposity measures at birth.

Whole body adiposity: At birth, whether individually or in groups,

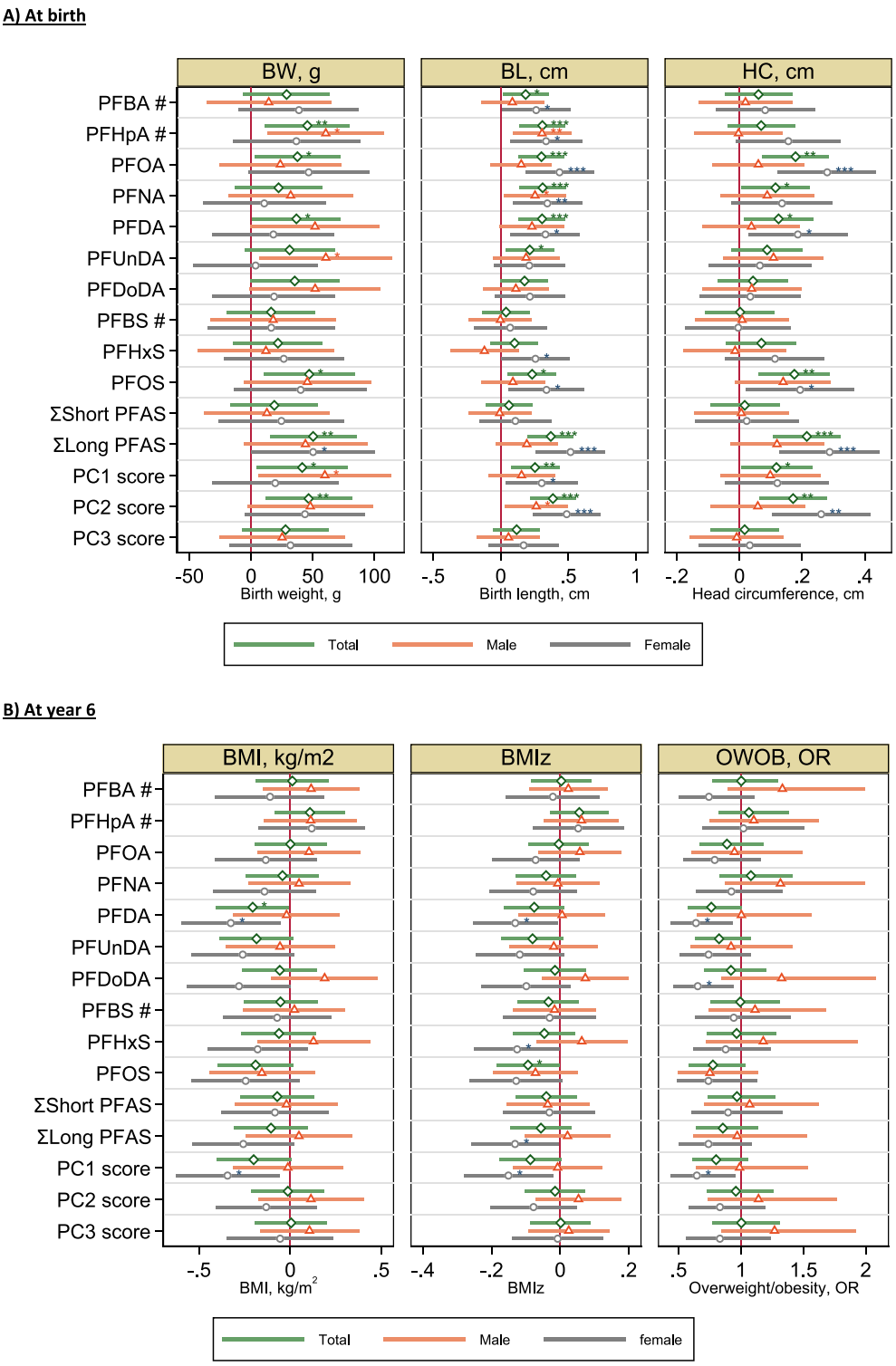

Fig. 1. Associations of cord PFAS levels with anthropometric outcomes at birth and at year 6. A) At birth; B) At year 6. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Estimates shown are beta coefficient (β) (diamonds) with the corresponding 95 % confidence interval (horizontal lines extending from the diamonds). Associations at birth were adjusted for maternal ethnicity, highest educational attainment, age at delivery, parity, pre-pregnancy BMI, cigarette smoking during pregnancy, and offspring sex. Associations at year 6 were additionally adjusted for child's exact age for year 6 measurements. # indicates short-chained PFAS (long-chained otherwise). Outcome abbreviations: Birth weight (BW); birth length (BL); head circumference (HC); body mass index (BMI); body mass index z-score (BMIz); overweight and obesity (OWOB); odds ratio (OR) Exposure abbreviations: Per- and poly- fluoroalkyl substances (PFAS); perfluorobutanoic acid (PFBA); perfluoroheptanoic acid (PFHpA); perfluorooctanoic acid (PFOA); perfluorononanoic acid (PFNA); perfluorodecanoic acid (PFDA); perfluoroundecanoic acid (PFUnDA); perfluorododecanoic acid (PFDoDA); perfluorobutanesulfonic acid (PFBS); perfluorohexanesulphonic acid (PFHxS); perfluorooctanesulfonic acid (PFOS); principal components (PC).

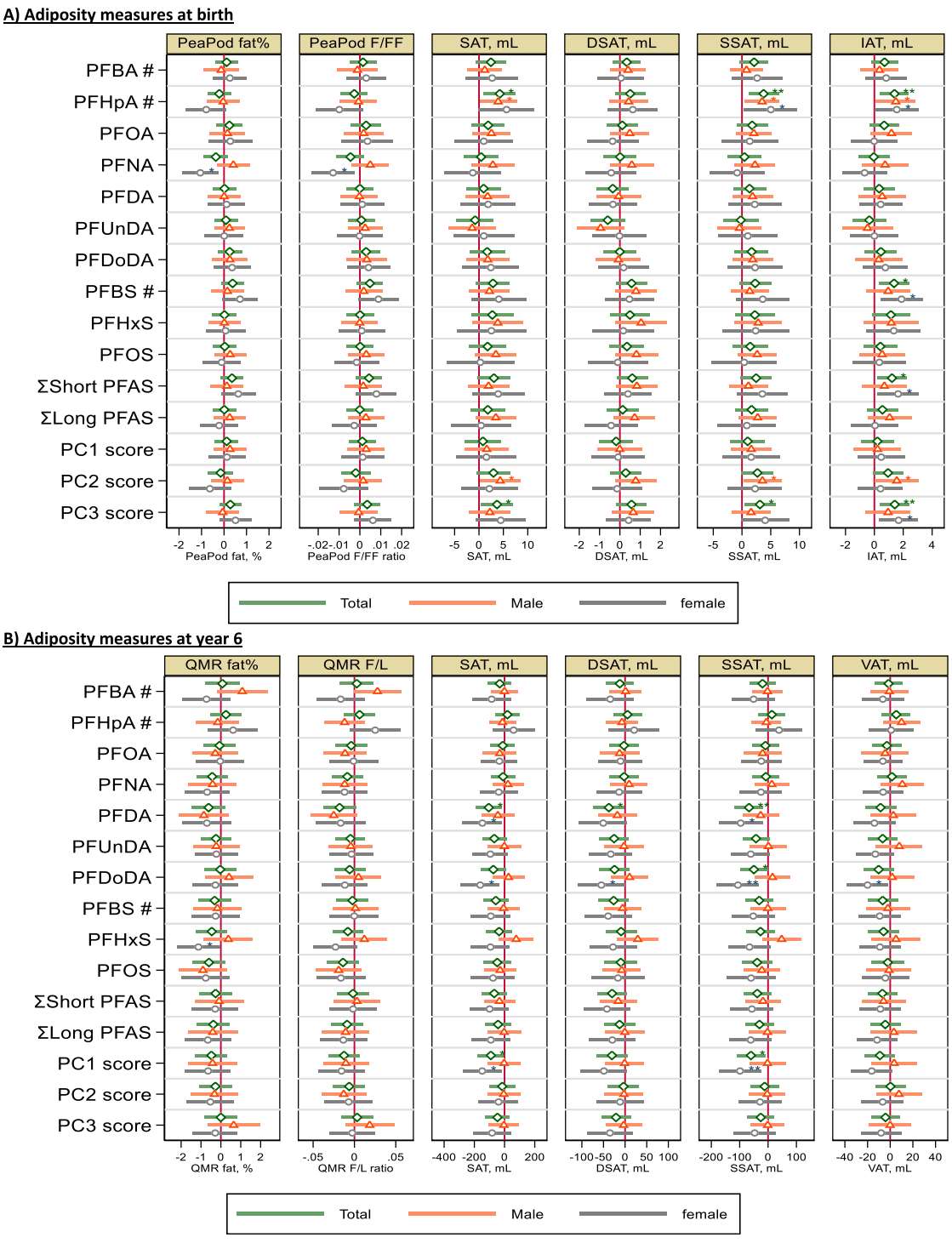

Fig. 2. Associations of cord PFAS levels with adiposity outcomes at birth and at year 6. A) Adiposity measures at birth; B) Adiposity measures at year 6; C) Other measures at year 6. *$P < 0.05$; **$P < 0.01$. Estimates shown are beta coefficient (β) (diamonds) with the corresponding 95 % confidence interval (horizontal lines extending from the diamonds). Associations were adjusted for maternal ethnicity, highest educational attainment, age at delivery, parity, pre-pregnancy BMI, cigarette smoking during pregnancy, and offspring sex and exact age at adiposity measurements. # indicates short-chained PFAS (long-chained otherwise). Outcome abbreviations: Fat/fat free mass ratio (F/FF); Subcutaneous adipose tissues (SAT); deep subcutaneous adipose tissues (DSAT); superficial subcutaneous adipose tissue (SSAT); internal adipose tissues (IAT); quantitative magnetic resonance (QMR); visceral adipose tissues (VAT); intramyocellular lipids (IMCL); metabolic syndrome score (Met score) Exposure abbreviations: Per- and poly- fluoroalkyl substances (PFAS); perfluorobutanoic acid (PFBA); perfluoroheptanoic acid (PFHpA); perfluorooctanoic acid (PFOA); perfluorononanoic acid (PFNA); perfluorodecanoic acid (PFDA); perfluoroundecanoic acid (PFUnDA); perfluorododecanoic acid (PFDoDA); perfluorobutanesulfonic acid (PFBS); perfluorohexanesulphonic acid (PFHxS); perfluorooctanesulfonic acid (PFOS); principal components (PC).

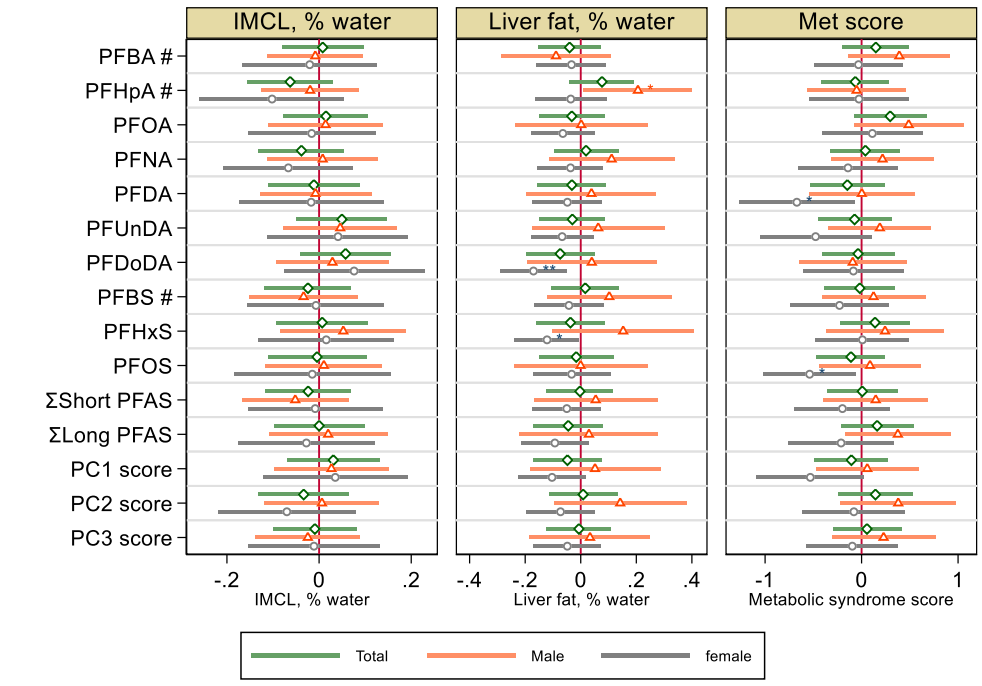

Fig. 2. (*continued*).

PFAS were generally not associated with whole body PEA POD-measured fat% and fat/fat-free mass (F/FF) ratio; the only exceptions were the inverse associations between long-chained PFNA and fat% (β: −1.06 %) and F/FF ratio (β: −0.013) (both $P < 0.05$) in girls (Fig. 2 panel A; Supplemental Table S5A).

Abdominal adiposity: In contrast, PFAS were generally associated with higher abdominal adiposity, driven mostly by short-chain PFAS. For example, PFHpA (7 carbon chain length) was associated with higher volumes of SAT (β: 4.26 mL), SSAT (β: 3.75 mL), and IAT (β: 1.39 mL) (all $P < 0.05$), with no obvious differences in these associations between the sexes. Higher levels of short-chained PFBS, sum of short-chain PFAS, and PC3 were associated with higher IAT volume (β range 1.22–1.39 mL; all $P < 0.05$), and these associations were more prominent in girls. Meanwhile, a positive association between PC2 score and IAT (β: 1.55 mL; $P < 0.05$) was only observed in boys. Higher scores on PC2 (in the male infants) and PC3 (in overall population) were additionally associated with higher SAT and SSAT volumes.

In contrast to the associations observed with birth anthropometry, the relationships between PFAS and birth adiposity measures remained largely unchanged even after further adjustment for gestational duration (Supplemental Fig. S4).

3.4. Associations of cord plasma PFAS levels with body composition and abdominal adiposity at age 6 years

By 6 years of age, most of the observed associations at birth did not persist, but some new associations emerged, in that the PFAS were generally associated with lower adiposity, mainly observed in girls (Fig. 2 panel B; Supplemental Table S5B).

Whole body adiposity: An inverse association between the long-chained PFHxS level and total fat% (β: −1.13 %; $P < 0.05$) measured using QMR was observed in girls only.

Abdominal adiposity: In the overall population, the long-chained PFDA, PFDoDA and PC1 were inversely associated with SAT (β range: −74.5 to −104.5 mL) and SSAT volumes (β range: −50.0 to −66.9 mL; all $P < 0.05$), and in stratified analyses, these associations were all statistically significant in girls but not in boys. In addition, an inverse association between the long-chained PFDoDa level and DSAT (β: −55.1 mL; $P < 0.05$) was also observed in girls only.

3.5. Associations of cord plasma PFAS levels with other measures at age 6 years

Regional adiposity: There were no consistent associations between cord plasma PFAS levels and intramyocellular lipids (IMCL) at age 6 years. For liver fat, inverse associations were noted for the long-chained PFDoDA (β: −0.17 %) and PFHxS (β: −0.12 %) in girls, whereas a positive association with PFHpA (β: 0.21 %) was observed in boys (all $P < 0.05$). (Fig. 2 panel C; Supplemental Table S5C).

Metabolic syndrome score: The long-chained PFDA (β: −0.67) and PFOS (β: −0.54) (both $P < 0.05$) were inversely associated with metabolic syndrome scores among girls only (Fig. 2 panel C; Supplemental Table S5C).

3.6. Sensitivity and other analyses

In sensitivity analyses, when all preterm birth cases were excluded, the associations remained very similar and did not influence the conclusions and interpretation (Supplemental Fig. S5). In sensitivity analyses adjusting for childhood variables, some slight attenuation in PFAS-associations were noted for year 6 outcomes, especially the anthropometric measures, but association patterns remained largely similar (Supplemental Fig. S6) and do not alter conclusions.

In GEE analyses, higher long-chain PFAS concentrations (PFOA, PFNA, PFDA, PFOS, the sum of long PFAS, and PC1 and PC2) were associated with an overall larger head circumference over time from birth to age 6 years (β range: 0.12–0.21 cm; all $P < 0.05$) (Supplemental Table S6). Similarly, higher concentrations of the same set of PFAS, with

the addition of PFHpA, PFUnDA, and PFDoDA, were associated with a longer length/height from birth to age 6 years (β range: 0.31–0.48 cm; all $P < 0.05$). However, the negative PFAS*time interaction term (*P*-interaction < 0.1 except for PFOA*time and PFHpA*time for length/height) suggests that these associations weaken over time. Many of the main PFAS-outcome associations found at birth concerning weight, and MRI-based SAT, DSAT, and SSAT were not demonstrated over the first 6 years in the GEE model, with negative PFAS*time interactions observed for PFUnDA, PFDoDa, and PC1, indicative of weakening associations over time. Such PFAS*time interaction findings align with our general observations of a greater influence of PFAS at birth than at age 6 years. Results in female infants closely mirror those of the overall population (see Supplemental Table S6). For male infants, generally no main PFAS-outcome-associations were observed, but there were some positive PFAS*time interactions for PFBA, PFHxS, and PC3 detected. For example, positive PFHxS*time interactions were noted for weight, head circumference, SSAT, DSAT, and SAT outcomes, indicative of strengthening associations with time. The sex-specific variations in PFAS-outcome associations over time further emphasize the complexity of the impact of PFAS on offspring outcomes.

4. Discussion

In this prospective Asian mother–child cohort study located in the relatively developed setting of Singapore, we observed that a higher level of short-chain PFAS in cord plasma was associated with higher neonatal abdominal adiposity measured using MRI, but these associations in general did not persist over a follow-up period of 6 years. Levels of PFAS in umbilical cord plasma reflect maternal exposure during pregnancy (Kingsley et al., 2018; Cariou et al., 2015) and even prior to conception, given the known accumulation of PFAS in the body with their long half-lives. These results reinforce the need for ongoing monitoring of PFAS exposure, particularly for newer replacement PFAS of shorter chain lengths, where there remains scarce data on the impact on human development, and call for additional research with longer follow-up periods to fully understand the impact of PFAS exposure on the offspring.

PFAS exposure adversely impact on multiple health outcomes and are ubiquitous in various environmental matrices (Qi et al., 2022) and consumer products such as food contact materials (Schaider et al., 2017) and waterproof clothing (Xia et al., 2022), leading to high levels of human exposure. Longer-chain PFAS, like PFOS and PFOA with long half-lives have been increasingly replaced with shorter-chain PFAS like PFBS and PFBA, which still provide oil- and water- repellent properties. Nonetheless, although some studies show that short-chain PFAS have shorter serum half-lives (e.g., ~1.5 month for PFBS) than their long-chain counterparts (e.g., ~2.9 years for PFOS) (Xu et al., 2020), other studies have shown that short-chain PFAS are more mobile in the environment (Li et al., 2020) and more readily translocated to edible crops than long-chain PFAS (Costello and Lee, 2020). In addition, although bioaccumulation potential increases with increasing PFAS chain length, shorter half-life in blood does not mean short-chain PFAS are readily excreted. A Spanish study measured 21 PFAS from 99 samples of autopsy tissues and found that the short-chained PFBA was the most frequently found compound (and also at the highest concentrations) in the kidneys and lungs; PFBS was also found to accumulate in lung, liver, kidney and bone tissues (Pérez et al., 2013). Thus, the safety of short-chain PFAS as alternatives to their long-chain counterparts is still a highly debatable topic that warrants further research.

Although the negative effects of legacy long-chain PFAS exposure on human health have been studied for decades, regulation and legislation to restrict their use have been progressing slowly. Early efforts to phase out the legacy PFAS have been primarily driven by voluntary measures undertaken by major manufacturers of PFAS. For example, between 2000 and 2002, the 3 M Company in the United States voluntarily stopped producing PFOA, PFOS, and other legacy long-chain PFAS (Land et al., 2018). The Stockholm Convention, an international treaty created by the United Nations Environment Programme, only recently (in 2019) included PFOA in its Annex A (Convention, 2023), which includes a list of chemicals that should be eliminated from production and use. Following that, the National Environment Agency (NEA) in Singapore imposed a ban on the manufacture, import, and export of PFOA, its salts, and related compounds in 2019 (National Environment Agency. Listing of Chemicals Under the Rotterdam and Stockholm Conventions, n.d.). In view of this timeline for phasing out PFAS, our study participants (first recruited in 2009) were likely exposed to substantial levels of both the legacy and newer replacement PFAS concurrently.

To the best of our knowledge, this is the first study to show that higher prenatal PFAS exposure is associated with higher neonatal abdominal adiposity measured using MRI. In contrast, we did not find consistent associations between cord plasma PFAS and neonatal whole-body fat mass measured using ADP (PEA POD), except for an inverse association between PFNA and fat mass% in female neonates. In the Odense Child Cohort, higher maternal pregnancy serum long-chained PFNA and PFDA concentrations were associated with higher skinfold based-body fat% of 3-month-old infants (but not at 18 months); no associations were observed for PFHxS, PFOS, and PFOA (Jensen et al., 2020). Mixed findings were reported in the Healthy Start Study, of higher maternal pregnancy serum PFOA, PFNA, PFHxS concentrations, but not PFOS and PFDA, being associated with lower neonatal body fat percentage measured using PEA POD (Starling et al., 2017). In the same study, PFOA and PFNA were additionally associated with higher body fat percentage of 5-month-old infants, but only among boys; no associations were observed for PFOS, PFDA, and PFHxS (Starling et al., 2019). Differences in ethnicity, geographical location, diet, and other environmental differences in addition to differences in PFAS and adiposity measurement and timepoints might explain differences in our results compared with these previous studies. Nonetheless, our study substantially extends the evidence base by investigating MRI-based neonatal abdominal adiposity and shorter-chain PFAS in an Asian population.

Our study found that various PFAS could have either a null or positive association with birth weight, which is somewhat different from previous findings that have mostly suggested that prenatal PFAS exposure, as assessed in maternal and cord blood, has either a null or an inverse association with birth weight. This discrepancy could be due to several factors, such as differences in the populations studied and variations in PFAS exposure levels and sources. Most of the positive associations with birth size in our study were observed for long-chain PFAS and were mediated through a longer gestational duration. While most previous studies reported an inverse or null association between prenatal PFAS exposure and gestational duration (Lee et al., 2021), a positive association has been noted in two studies for PFOA (Hjermitslev et al., 2020) and PFOS (Li et al., 2017), although the underlying mechanism remains unknown. Considering the efforts to phase out/limit the use of legacy long-chain PFAS with longer half-lives, and our study period (recruitment from 2009 to 2010), it is possible that the long-chain PFAS levels in our study primarily represent past exposure, possibly at levels that did not adversely affect offspring birth size. This is speculative and warrants replication in future studies.

We did not find consistent associations between cord plasma PFAS exposure and childhood anthropometric and adiposity outcomes at age 6 years. Existing evidence is equivocal, with studies reporting null, direct, or inverse associations between different PFAS and indicators of childhood adiposity, and between the same PFAS and adiposity outcomes at different life stages (birth to 2 years, 2–12 years, and 13–20 years) (Lee et al., 2021). Again, evidence related to short-chain PFAS is scarce when compared to long-chain PFAS. Child growth and adiposity gain are complex, with an initial adiposity peak before 1 year of age and an adiposity rebound typically around 5–7 years old. Adipocyte proliferation occurs extensively during infancy and just prior to adolescence typically occurring between the ages of 9–14 years; however, adipocyte

proliferation is limited in between these periods (Godfrey et al., 2011; Baum et al., 1986). It is possible that the inconsistent associations observed at 6 years of age in our study may be partially attributed to variability in the timing of such developmental events within the cohort as well as to possible catch-down growth patterns in children who had experienced greater growth *in utero*. Taken together, future research investigating PFAS influence on childhood adiposity may benefit from more frequent measurements of adiposity and longitudinal modeling of adiposity trajectory from birth until adolescence.

The mechanism underlying the association between short-chain PFAS and higher abdominal adiposity at birth is not fully understood. However, PFAS are known endocrine disruptors that disturb hormone homeostasis and metabolic processes (Mokra, 2021). *In vitro* evidence suggests that PFAS potently induce adipogenesis mainly by interfering with the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway (Watkins et al., 2015; Ma et al., 2018; Qi et al., 2018). In C57BL/6JxFVB mice, perinatal PFAS exposure elicited a sex-specific response, with more profound metabolic alterations observed in female offspring (van Esterik et al., 2016). This is consistent with our observation that short-chain PFAS are more strongly associated with abdominal adiposity in girls. The relatively high levels of short-chain PFAS concentrations (compared to long-chain PFAS) in our study may explain why we observed such associations mainly for short-chain congeners. Additionally, when compared to studies conducted in China (Shanghai) (Chen et al., 2021) and Korea (Seoul) (Lee et al., 2016) with a similar sampling period and biological matrix (cord blood) for PFAS measurement (Supplemental Table S7), we observed similar levels of most PFAS except for the short-chained PFBS, which was higher in our study, and the long-chained PFOA and PFOS, which were higher in the Shanghai study.

A major strength of our study is the relatively comprehensive panel of PFAS congeners measured, which provides an unprecedented opportunity to investigate the potential adverse influence of PFAS in an understudied region and population. Moreover, we employed cutting-edge body composition measurement techniques, including PEA POD, QMR, and MRI, which greatly improved the accuracy and resolution of adiposity outcomes (both whole-body adiposity and adiposity distribution). Our novel observation that PFAS is generally more strongly associated with abdominal adiposity at birth, particularly the metabolically active internal adipose tissue depot, highlights the need for further confirmation studies. In addition, we adjusted for a comprehensive list of covariates. Finally, we utilized a dual approach in our analysis, modeling individual PFAS to gain insight into their use in products, and grouping them based on *a priori* (chemical structures) and *a posteriori* (data-driven dimension reduction techniques) classifications to account for the inter-relatedness of individual PFAS. This provided complementary insights into PFAS exposure and its health impact from different dimensions.

Several limitations are worth noting. First, although we measured cord plasma PFAS which more closely reflects fetal exposure, multiple measurements of PFAS longitudinally across pregnancy may have disclosed trimester-specific influences of PFAS exposure. Nonetheless, since the half-lives of PFAS, even for short-chain congeners, are long (ranging from months to years) (Xu et al., 2020), we believe that our PFAS measurement in cord plasma at delivery is still a good reflection of overall fetal exposure. PFAS has been shown to cross the placenta, and there are strong correlations between cord and maternal PFAS levels (Kingsley et al., 2018; Cariou et al., 2015). However, the efficiency of transfer of specific PFAS vary depending on both chain length and functional group (Appel et al., 2022), leading to differences in their passage through the placenta to the fetus. This suggests that cord PFAS levels may more accurately reflect fetal exposure rather than maternal exposure profiles. Future studies should investigate the relationship between maternal PFAS exposure and child health outcomes concurrently to provide a more complete picture and suggest actionable strategies, including the identification of which PFAS, products, or behaviors to avoid, in order to optimize pregnancy and child outcomes. When using maternal levels of PFAS to reflect fetal exposure, it is important to consider the changing permeability of the placental barrier with advancing gestation (Al-Enazy et al., 2017) and the potential impact of PFAS on placental function (Szilagyi et al., 2020), which can affect fetal growth and development independently of fetal exposure. Second, missing outcome measurements due to logistical difficulties and the challenge of obtaining adiposity/metabolic measurements in infants/young children could give rise to selection bias, meaning there could be selective loss-to-follow-up that is related to both exposure and outcome. Nonetheless, since cord plasma PFAS levels in general did not differ significantly between offspring with and without MRI abdominal adiposity information in our study (Supplemental Table S8), it is unlikely that loss-to-follow-up is related to exposure, and thus selection bias appears unlikely. Additionally, we did not adjust for multiple testing since our analyses were considered exploratory in nature. Therefore, further confirmatory investigations are warranted to validate these findings. Finally, as with any observational study, the possibility of residual confounding such as route of exposure to PFAS, co-exposure to other pollutants, and childhood PFAS exposure cannot be excluded completely.

5. Conclusions

Our study found a link between fetal exposure to emerging short-chain PFAS and higher abdominal adiposity at birth, but further research is needed to determine if these effects persist into late childhood and adulthood. Our study highlights the importance of monitoring exposure to newer PFAS and the need for more research on their health effects. Moreover, evidence from a wider geographical area and long-term follow-up in other mother-offspring cohorts is needed to fill the knowledge gap in these understudied populations.

CRediT authorship contribution statement

Ling-Wei Chen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sharon Ng:** Conceptualization, Data curation, Methodology, Project administration, Resources, Writing – review & editing. **Mya-Thway Tint:** Data curation, Investigation, Methodology, Writing – review & editing. **Navin Michael:** Data curation, Investigation, Methodology, Writing – review & editing. **Suresh Anand Sadananthan:** Data curation, Investigation, Methodology, Writing – review & editing. **Yi Ying Ong:** Data curation, Investigation, Methodology, Writing – review & editing. **Wen Lun Yuan:** Data curation, Investigation, Methodology, Writing – review & editing. **Ze-Ying Chen:** Data curation, Investigation, Methodology, Writing – review & editing. **Chia-Yang Chen:** Data curation, Investigation, Methodology, Writing – review & editing. **Keith M. Godfrey:** Data curation, Investigation, Methodology, Resources, Writing – review & editing. **Kok Hian Tan:** Data curation, Investigation, Methodology, Resources. **Peter D. Gluckman:** Data curation, Investigation, Methodology, Resources, Writing – review & editing. **Yap-Seng Chong:** Data curation, Funding acquisition, Investigation, Methodology, Resources, Writing – review & editing. **Johan G. Eriksson:** Data curation, Investigation, Methodology, Resources, Writing – review & editing. **Fabian Yap:** Investigation, Methodology, Resources, Writing – review & editing. **Yung Seng Lee:** Investigation, Methodology, Resources, Writing – review & editing. **Marielle V. Fortier:** Data curation, Investigation, Methodology,

Resources, Writing – review & editing. **Sendhil S. Velan:** Data curation, Investigation, Methodology, Resources, Writing – review & editing. **Shiao-Yng Chan:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S. Y.C reports a relationship with Société Des Produits Nestlé S.A. that includes: funding grants, and speaking and lecture fees. K.M.G. reports a relationship with Société Des Produits Nestlé S.A. and BenevolentAI Bio Ltd that includes: funding grants and speaking and lecture fees. Y.S.C. reports a relationship with Société Des Produits Nestlé S.A. that includes: funding grants.

K.M.G., Y.S.C. and S.Y.C. are part of an academic consortium that has received research funding from Société Des Produits Nestlé S.A. and BenevolentAI Bio Ltd, and are co-inventors on patents filed on nutritional factors and metabolic risk outside the submitted work. K.M.G. and S.Y.C. have received reimbursement from nutritional companies for speaking at conferences. All other authors declare that they have nothing to disclose.

Data availability

Data are available upon request to the GUSTO team for researchers who meet the criteria for access to confidential data.

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Author contributions

L.W.C., S.N., and S.Y.C. conceptualized the current study. L.W.C. conducted formal statistical analysis and wrote the first draft of the manuscript. S.N, M.T.T., N.M., S.A.S., Y.Y.O., and W.L.Y. contributed to data acquisition and curation. Z.Y.C. and C.Y.C. performed PFAS analyses. K.M.G., K.H.T., P.D.G., Y.S.C, J.G.E., F.Y., Y.S.L., M.V.F., S.S.V., and S.Y.C. designed and led the GUSTO cohort study. All authors interpreted the findings and revised drafts of the manuscript. All authors read and approved the final version of the manuscript submitted for publication.

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Appendix A. Supplementary material

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