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## Associations between prenatal exposure to PFAS and cardiometabolic health in preadolescents

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### A B S T R A C T

**Introduction:** While a number of studies have examined the effects of prenatal exposure to per- and polyfluoroalkyl substances (PFAS) on childhood obesity, the results reported have been inconsistent and few studies have integrated biological markers. The aim of this study was to investigate the associations between prenatal exposure to PFAS and cardiometabolic health parameters at age 12, taking pubertal stage into consideration.

**Method:** This study included 394 mother-child pairs enrolled in the PELAGIE mother-child cohort (France). Nine PFAS were measured in umbilical cord blood, and the children attended a clinical examination at age 12. Anthropometry, blood metabolic markers, and blood pressure were measured and used to build an internal cardiometabolic score. Linear regression and Quantile G-computation models were used to evaluate individual and mixture PFAS effects, adjusting for confounders and stratifying by sex and pubertal stage.

**Results:** No statistically significant association was observed between prenatal exposure to PFAS and cardiometabolic score at age 12. In post-menarche girls, perfluorohexane sulfonate (PFHxS) and perfluorodecanoic acid (PFDA) were statistically significantly associated with a decrease in a number of adiposity parameters (e.g., Body mass index z-score: beta [95%CI] = -0.37 [-0.67; -0.07]), as well as a decrease in low-density lipoproteins (LDL) and leptin levels. Similar results were observed with PFAS mixture, with statistically significantly decreased tricipital skinfolds (beta [95%CI] = -1.30 [-2.54; -0.06]). Isolated associations, including higher systolic blood pressure, changes in cholesterol levels, and lower adiponectin levels were observed in specific subgroups.

**Conclusion:** There is no clear evidence of an association between prenatal exposure to PFAS and the cardiometabolic health at earlier stage of pubertal development. However, inverse associations between PFAS and anthropometric measures have been observed in post-menarche girls. While the literature on this topic is scarce in pre-adolescents, these results suggest the importance of considering sex and pubertal stage in these associations.

### 1. Introduction

The world is witnessing a concerning rise in cardiometabolic issues, including obesity, hypertension, and type 2 diabetes (Malik et al., 2013). The growing prevalence of these diseases in children and adolescents underscores the importance of identifying and treating risk factors for cardiometabolic disorders as early as possible (Han et al., 2010; Ng et al., 2014). The Developmental Origins of Health and Disease (DOHaD) paradigm has highlighted the influence of early exposures on lifelong health (Barker, 2007; Charles et al., 2016). Pregnant women and children are exposed to a large number of chemicals that are suspected of having the potential to affect the cardiometabolic and endocrine

systems (Braun, 2017). Per- and polyfluoroalkyl substances (PFAS) have a wide range of uses, including greaseproof paper, fast-food containers/packaging, resistant coatings, cleaning products and personal hygiene products; the general population is exposed to PFAS through ingestion of contaminated food and water (Tittlemier et al., 2007; Vestergren et al., 2008; Schaidler et al., 2017). These compounds exhibit remarkable persistence in both the environment and the human body, which makes them a matter of great concern (De Silva et al., 2021; Ahrens, 2011).

Various studies have explored the link between prenatal exposure to PFAS and the cardiometabolic health of children. The Stratakis et al. (2022) (Stratakis et al., 2022) review concluded that there was insufficient evidence to support the notion that prenatal exposure to certain

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PFAS (such as perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)) has obesogenic effects in children. Similarly, the Frangione et al. (2024) (Frangione et al., 2024) review found no evidence of a positive association between prenatal PFAS exposure and pediatric obesity. The Frigerio et al. (2023) (Frigerio et al., 2023) review did report heterogeneous findings across studies, but suggested possible positive associations. Collectively, these reviews highlight the complexity and variability of the relationship between prenatal PFAS exposure and childhood obesity, indicating the necessity for further investigation (Stratakis et al., 2022; Frangione et al., 2024; Frigerio et al., 2023). Furthermore, most existing studies focus on specific cardiometabolic health indicators, and anthropometric factors in particular, even though a cardiometabolic health profile is best characterized using both clinical and biological markers (Frigerio et al., 2023). The few studies that do include cardiometabolic biomarkers in children also show heterogeneous results: some find that early exposure to PFAS was associated with an unfavorable cardiometabolic profile, indicating in particular a positive association with adiponectin (Ding et al., 2023) or low-density lipoproteins (LDL) (Blomberg et al., 2021), while other show a positive association with high density lipoproteins (HDL) and a negative association with triglycerides (Papadopoulou et al., 2021) or Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) levels (Fleisch et al., 2017).

According to this existing literature, the majority of studies examining prenatal PFAS exposure analyze children's health at a young age, meaning that there is a lack of results for preadolescents, even though this is a key developmental period of metabolic and anthropometric changes during pubertal development (Loomba-Albrecht and Styne, 2009; Perng et al., 2019). Pubertal stage significantly impacts body fat proportion, especially in girls, as multiple studies have shown (Loomba-Albrecht and Styne, 2009; Zheng et al., 2022). Moreover, puberty may also impact certain biological markers. For instance, in 12-year-old boys, increasing pubertal maturity is associated with a significant decrease in HDL cholesterol, while among girls, the most mature individuals exhibit lower total cholesterol levels than less mature preadolescents (Tell et al., 1985).

The objective of this study is to investigate the associations between prenatal PFAS exposure and the cardiometabolic health of preadolescents, taking sex and pubertal development into consideration.

## 2. Method

### 2.1. Study population

The study population is based on the French PELAGIE mother-child cohort, which included 3421 pregnant women in Brittany (north-western France), between 2002 and 2006 (Warembourg et al., 2024). The women were recruited at the start of their pregnancies (before 19 weeks of gestation) by gynecologists, midwives and sonographers. Information on newborn health (99%) and cord blood samples (62%) were collected at the maternity hospital. To collect data on their children's development, health and lifestyle at ages 2, 6 and 12, self-administered questionnaires were completed by the mothers.

Of the 2138 mothers for whom cord blood samples were available, 1181 were eligible for the 12-year follow-up of the PELAGIE cohort: 933 families were contacted by phone and 559 (60%) consented to their child attending the clinical examination held within a hospital setting (CHU de Rennes, France). Mother-child pairs where there was no remaining cord blood aliquot (17%), blood sampling refusal (7%), no remaining blood aliquot (5%) or missing bioimpedance or blood pressure data (<1%) were excluded, leaving a final study population of 394 mother-child pairs (Supplemental Fig. S1).

This study has been approved by the national ethical committees (CCTIRS, 2015; no. 15.326bis; CPP, 2015; no. 15/23-985) and data protection committee (CNIL, 2002, 2015, no. 915420/2015-456). Adults participating in this study gave written informed consent.

Participants under 18 years of age gave assent and written informed consent was obtained from their parents or legal guardians.

### 2.2. Cardiometabolic health assessment

The cardiometabolic health of the children was assessed by a clinical examination (anthropometry and blood pressure) and using biological assays in serum samples collected at age 12. The clinical examination was conducted by trained healthcare professionals in a standardized way.

#### 2.2.1. Anthropometry and blood pressure

Bioimpedance was used to ascertain percentages of body fat mass (%), lean body mass (%), and total body mass (kg). Standing height (cm) was assessed using a height gauge. Waist circumference (WC) was measured using a horizontal tape at the umbilicus with the child standing upright, their weight evenly distributed between the two feet, 25–30 cm apart, and in underwear. Skinfolds were measured using a Holtain compass: 1) the tricipital fold was measured on the posterior surface of the upper arm, midway between the acromion and the olecranon, and pinched vertically, and 2) the subscapular crease was measured 1 cm below the lower tip of the scapula. The fold was pinched following the natural fold of the skin at a 45° angle to the horizontal. Child height, WC, and skinfold measurements were taken at least twice (a third measurement was taken in the event of a difference between the two first measurements in excess of 0.5 cm, 0.5 cm and 0.1 cm, respectively), with the average value of the two or three measurement being computed and utilized for this study. Body mass index (BMI, kg/m<sup>2</sup>) was calculated by dividing total body mass by the square of height. The BMI z-score (z-BMI), which was standardized based on age and sex according to World Health Organization (WHO) references, was computed (de Onis, 2007). Children with a z-BMI equal to or greater than one were classified as overweight or obese.

After 5 min of rest, systolic and diastolic blood pressure measurements were acquired twice, in the lying position, using an automatic oscillometric professional device. The resulting average of 2 measurements, reported in mmHg, was calculated and utilized to calculate the Mean Arterial Pressure (MAP) according to the following formula: (Systolic Arterial Pressure + 2 \* Diastolic Arterial Pressure)/3 (DeMers and Wachs, 2023).

#### 2.2.2. Biological assays

Several of the biological markers involved in processes leading to lipid dysregulation and/or insulin resistance were assessed in non-fasting blood serum collected during the clinical examination at age 12.

Blood levels were measured for total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and triglycerides (TG) using a C501 Cobas Roche analyzer. Low-density lipoprotein cholesterol (LDL) was estimated using the Friedewald Formula (LDL = TC - (TG/2.2) - HDL) (Knopfholz et al., 2014). In consideration of the non-fasting state of the children at the time of blood sampling, fructosamine concentration was assessed to evaluate insulin resistance, instead of the fasting blood glucose that is traditionally measured. Fructosamine refers to all the glycated proteins present in serum, is proportional to blood glucose levels, and reflects glycemic status in the 2–3 weeks preceding the assay (Shohat et al., 2017, 2021). Blood fructosamine levels were measured on a C501 Cobas Roche analyzer. In addition, leptin and adiponectin, two adipokines secreted by adipose tissue and involved in insulin resistance, were measured. Leptin was measured by enzyme-linked immunosorbent assay (BioVendor Human Leptin ELISA, catalog number RD191001100, Brno, Czech Republic) and concentrations are expressed in ng per milliliter. The intra-assay CV was <7.6% and the inter-assay CV <6.7%. Total adiponectin was measured by enzyme-linked immunosorbent assay (ALPCO, HMW & Total Adiponectin ELISA, catalog number 80-ADPHU-E01, Salem, NH, USA) and concentrations are expressed in µg per milliliter. The intra-assay CV was <5.7% and the inter-assay CV <

6.4%.

### 2.2.3. Cardiometabolic score

In adults, the metabolic score usually includes markers of adiposity (e.g., waist circumference, BMI), dyslipidemia/lipid accumulation (e.g., TG, HDL, LDL), insulin resistance (HOMA-IR, glycemia), and blood pressure (e.g., systolic and diastolic blood pressure) (Pérez-Castro et al., 2022; Honarvar et al., 2023). In children, a cardiometabolic score was developed in the IDEFICS study, though this was only for children aged under 11 (Ahrens and Moreno, 2014). As a result, due to the absence of any validated external reference in the literature for a preadolescent population (at age 12) and the non-fasting condition of the children, an internal cardiometabolic score was constructed. This internal score included: proportion of body fat as anthropometric indicator, mean arterial pressure because it gives a good indication of systole and diastole, fructosamine as an indicator of glucose homeostasis, and triglycerides and cholesterol (LDL, HDL) as indicators of lipid homeostasis. Because these indicators are influenced by child sex and pubertal status, each was standardized by sex and pubertal status prior to application of the following formula, to calculate the cardiometabolic score:

$$\text{Cardiometabolic score} = z\text{-Proportion of Fat Mass} + z\text{-MAP} + z\text{-Fructosamine} + z\text{-TG} + z\text{-LDL} - z\text{-HDL}$$

Pubertal status was defined by menarche for girls, using the self-reported questionnaire completed at home and returned for the clinical examination, and by testicular volume ( $<$  or  $\geq$  6 mL) for boys, measured using an orchidometer during the clinical examination.

### 2.3. Exposure assessment

Nine PFAS were analyzed in cord blood samples by the Centre de Toxicologie du Québec (CTQ) at the Institut national de santé publique du Québec (INSPQ): perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUDA), Perfluorohexanoic acid (PFHxA), Perfluorobutanesulfonic acid (PFBS), Perfluorobutanoic acid (PFBA), perfluorohexane sulfonate (PFHxS), and perfluorooctanesulfonic acid (PFOS).

The analytical methods used to measure PFAS were described in more detail in Tillaut et al. (2023). In short, PFAS were extracted from cord serum samples (100  $\mu$ L) using the solid phase extraction technique with a weak anion exchange resin. The extracts were evaporated to dryness and dissolved in a mixture of 5 mM ammonium acetate with a proportion of methanol or acetonitrile. Samples were then subjected to analysis using Ultra Performance Liquid Chromatography with tandem mass spectrometry (UPLC-MS/MS). The limit of detection (LOD) ranged from 0.05 to 0.2  $\mu$ g/L, depending on the analytes. The LOD was determined by employing 3 times the standard deviation across 30 replicates (analyzed in separate analytical runs) of a serum sample at a concentration approximately 5–7 times higher than the estimated concentration, resulting in a signal to noise ratio of 3:1. Intra-day precision ranged from 2.6% to 8.1%, while inter-day precision varied between 5.4% and 7.4%, depending on the analytes.

The internal reference materials used to control the quality of the analyses were the certified reference material SRM-1958 from the National Institute of Standards and Technology (NIST; Gaithersburg, MD) alongside some in-house quality controls (QCs Low, Med and High) for PFAS. Overall quality and accuracy of the analytical method is monitored via participation in, for example, the interlaboratory program at the AMAP External Quality Assessment Scheme (Centre de Toxicologie du Québec (CTQ), Institut national de santé publique du Québec (INSPQ), Québec, Canada) and the German External Quality Assessment Scheme (G-EQUAS; Erlangen, Germany).

Of the 559 children who underwent clinical examination at age 12, 464 had their cord-blood samples analyzed for PFAS measurements. Concentrations were reported in micrograms per liter ( $\mu$ g/L) of wet

weight. Missing data stemmed from analytical interferences in certain samples for the PFNA ( $n = 11$ ), PFDA ( $n = 38$ ), and PFUDA ( $n = 22$ ) analytes, confirmed by qualifying ion ratio deviations exceeding the expected criterion of  $\pm 20\%$ .

### 2.4. Covariates

Information on the mothers' socio-demographic and lifestyle characteristics was collected at enrolment by self-administrated questionnaire. Covariates considered in this analysis include: age (continuous), urban area (towns  $< 20,000$  inhabitants and towns  $\geq 20,000$  inhabitants), education level (primary/secondary school, baccalaureate, postsecondary), parity status (primiparous; multiparous), pre-pregnancy BMI (continuous), fish consumption (less than once a month; less than once a week; more than twice a week), and shellfish consumption (less than twice a month; two to nine times a month; more than nine times a month).

### 2.5. Statistical analysis

#### 2.5.1. Data pre-processing

Three PFAS compounds (PFHxA, PFBS and PFBA) were excluded from consideration due to their exceedingly low detection frequencies ( $< 3\%$ ). To address concentrations falling below the LOD for the other compounds (all of which were detected in more than 74.9% of the samples), the values indicated by the instrument were used (Helsel, 1990); when no value was given, a value below the LOD was imputed by maximum likelihood method. Because of their skewed distribution, all concentrations were log-2 transformed (Helsel, 1990; Jain, 2016). Due to the very low level of missing data in covariates (specifically, a single observation each for parity and fish consumption), these were managed by replacing them with the mode of the respective covariate's distribution. The normality of the distribution of cardiometabolic indicators was verified graphically. The leptin and triglyceride distributions did not follow a trend towards normality, and were therefore log2-transformed for analysis. To estimate the correlations between cardiometabolic health indicators, Pearson correlation coefficients were calculated.

#### 2.5.2. Associations between PFAS prenatal exposure and cardiometabolic health

First, a single-exposure approach was used to evaluate the association between each PFAS and each outcome parameter: cardiometabolic score, z-BMI, WC, percentage of fat mass, tricipital skinfold, scapular skinfold, MAP, systolic blood pressure, diastolic blood pressure, LDL, HDL, TG, fructosamine, leptin, and adiponectin. Multivariable linear regressions were used for all continuous outcomes. The linearity of the associations was explored using cubic regression splines with third-degree polynomials. A non-linear association was considered if the effective degrees of freedom (edf) was greater than 1.5 and the p-value of the dose-response association was  $< 0.05$ . In that case, the exposure variable was then categorized into tertiles and introduced to the regression model. Due to limited sample size, categorization in tertiles was tested for total population and stratified by sex population only.

In a second approach, Quantile G-computation models were used to evaluate potential PFAS mixture effects. Quantile G-computation converts all exposure variables into quantile, then builds a generalized linear regression that estimates the joint effect of the mixture in reference to the lowest quantile (Keil et al., 2020). In addition to the joint mixture effect, the contributions made by each individual PFAS to this mixture effect are also reported.

All models were performed across the whole population, stratified by sex, as well as stratified by sex and pubertal stage. A directed acyclic graph was used to identify potential confounders (Supplemental Fig. S2) and all models were therefore adjusted for maternal BMI, maternal age, parity, mother's level of education, urbanization, fish and shellfish



consumption, as well as for child sex and pubertal status for the non-stratified analyses.

### 2.5.3. Sensitivity analyses

To explore the stability of the regression models, all models among the total population were performed over again after excluding the five most influential observations. These observations were identified using Cook's distance, which measures their impact on the overall model. The aim of excluding these observations was to examine both the consistency of the results and the potential influence of some individuals on the findings.

All analyses were performed using R version 4.2.

## 3. Results

### 3.1. Characteristics of the study population

The study population includes 394 mother-child pairs. At enrollment, women were 30.8 years old on average, most were multiparous (62%) and had a university degree (73%). The average birth weight of the children was 3477 g, and most (98%) were born at term (Table 1). At the time of the clinical examination, the children were 12.8 years old on average, and the vast majority were of normal weight (86%). Among boys, 35% and 65% were classified as peripubertal and postpubertal respectively while among girls, 57% were pre-menarche and 43% were post-menarche. Comparing this study population (n = 394) with the eligible population (n = 1181), we observed that women are a bit older, with higher educational level, less smoker, and higher fish consumption (data not shown). A descriptive table of the cardiometabolic indicators by sex and pubertal stage is provided in Supplementary Table S1. Some differences can be observed between pubertal stages in girls with higher leptin levels, tricipital, and scapular skinfolds in post-menarche girls. For skinfolds, these differences are more or less reversed between pre-pubertal and post-pubertal boys. The correlation coefficients between the cardiometabolic outcomes are presented in Supplemental Fig. S3. Strong positive correlations (>0.70) were observed between anthropometric indicators (scapular and tricipital skinfolds, proportion of body fat, abdominal circumference, BMI z-score). In addition, strong positive correlations between cholesterol indicators (LDL, HDL and total cholesterol) were confirmed. Finally, leptin levels were positively correlated with anthropometric indicators.

### 3.2. Levels of PFAS exposure during pregnancy

The PFAS concentrations measured in cord blood are described in Table 2. The compounds included in the study were detected in 75%–100% of the samples. PFOS and PFOA were the compounds with the highest medians (4.63 µg/L and 2.25 µg/L, respectively). Correlation coefficients between PFAS are presented in Supplemental Fig. S3 and shows positive correlations between all PFAS, with the strongest correlation between PFNA and PFDA (0.80).

### 3.3. Association between prenatal exposure to PFAS and cardiometabolic health

#### 3.3.1. Cardiometabolic score

No statistically significant association was found between any PFAS and cardiometabolic score (Fig. 1). In peripubertal boys, prenatal exposure to PFHxS and PFOS shows a trend toward increased cardiometabolic score (beta [95 % CI] = 1.06 [−0.17; 2.28] and beta [95 % CI] = 0.90 [−0.26; 2.05], respectively). In menarche girls, the trend is the opposite, with prenatal exposure to PFDA and a decrease in cardiometabolic score (beta [95 % CI] = −0.76 [−1.73; 0; 18]).

**3.3.1.1. Anthropometric measures.** In the overall population, no

**Table 1**  
Characteristics of the study population (n = 394).

	MEAN ± SD/N (%)	Q1	MEDIAN	Q3
<b>Maternal age (years)</b>	30.8 ± 3.8	28.1	30.6	33.1
<b>Maternal education level</b>				
<i>primary/secondary school</i>	43 (10.9)			
<i>Baccalaureate</i>	65 (16.5)			
<i>Postsecondary</i>	286 (72.6)			
<b>Place of residence</b>				
<i>Rural</i>	324 (82.2)			
<i>Urban</i>	70 (17.8)			
<b>Parity</b>				
<i>No children</i>	150 (38.1)			
<i>At least 1 child</i>	244 (61.9)			
<b>Maternal BMI (kg/m<sup>2</sup>)</b>	22.2 ± 3.9	19.9	21.3	23.2
<b>Maternal fish consumption</b>				
<i>Less than once a month</i>	47 (11.9)			
<i>Less than once a week</i>	228 (57.9)			
<i>More than twice a week</i>	119 (30.2)			
<b>Maternal shellfish consumption</b>				
<i>Less than twice a month</i>	267 (67.8)			
<i>Two to nine times a month</i>	96 (24.4)			
<i>More than nine times a month</i>	31 (7.9)			
<b>Maternal smoking</b>				
<i>Non-smoker</i>	302 (76.4)			
<i>Smoker at conception</i>	55 (13.7)			
<i>Smoker during the first trimester</i>	37 (9.1)			
<b>Sex of the child</b>				
<i>Boys</i>	193 (49.0)			
<i>Girls</i>	201 (51.0)			
<b>Birth weight (g)</b>	3477 ± 462	3180	3448	3770
<b>Preterm birth (&lt;37 weeks)</b>	8 (2)			
<b>Pubertal stage<sup>a</sup></b>				
<i>Peripubertal boys</i>	67 (17.0)			
<i>Postpubertal boys</i>	126 (32.0)			
<i>Pre-menarche girls</i>	114 (28.9)			
<i>Post-menarche girls</i>	87 (22.1)			
<b>cardiometabolic score<sup>b</sup></b>	−0.109 ± 2.3	−1.7	−0.3	1.1
<b>Child BMI z-score (WHO references)</b>	−0.2 ± 1.0	−0.9	−0.2	0.4
<i>Underweight</i>	17 (4.3)			
<i>Normal</i>	340 (86.3)			
<i>Overweight</i>	28 (7.1)			
<i>Obese</i>	9 (2.3)			
<b>Waist circumference (cm)</b>	67.5 ± 7.7	62.0	66.0	70.9
<b>Percentage of fat mass</b>	17.4 ± 6.9	11.8	16.0	22.2
<b>Tricipital skin fold (mm)</b>	12.7 ± 5.0	9.1	11.8	15.0
<b>Scapular skin fold (mm)</b>	8.2 ± 3.8	6.0	7.0	9.3
<b>Mean arterial blood pressure (mmHg)</b>	81.9 ± 6.5	77.0	81.7	86.0
<b>Systolic blood pressure (mmHg)</b>	115.7 ± 9.0	110.0	114.5	121.0
<b>Diastolic blood pressure (mmHg)</b>	65.0 ± 6.8	59.5	65.0	69.5
<b>Total Cholesterol (mmol/L)</b>	2.7 ± 1.0	2.1	2.6	3.2
<b>Low-density lipoproteins (LDL, mmol/L)</b>	1.7 ± 0.7	1.3	1.6	2.1
<b>High-density lipoproteins (HDL, mmol/L)</b>	0.9 ± 0.3	0.7	0.8	1.0
<b>Triglycerides (mmol/L)</b>	0.8 ± 0.4	0.5	0.7	1.0
<b>Fructosamine (µmol/L)</b>	243 ± 15.9	232	243	254
<b>Adiponectin (µg/mL)</b>	7.5 ± 2.7	5.6	7.2	8.9
<b>Leptin (µg/mL)</b>	6.3 ± 7.9	1.9	3.7	7.2

BMI: Body mass index; Q1: First quartile 1; Q3: Third quartile; SD: Standard deviation; WHO: World Health Organization.

<sup>a</sup> Pubertal stage was defined as pre-menarche or post-menarche for girls, and testicular volume below or above 6 mL for boys.

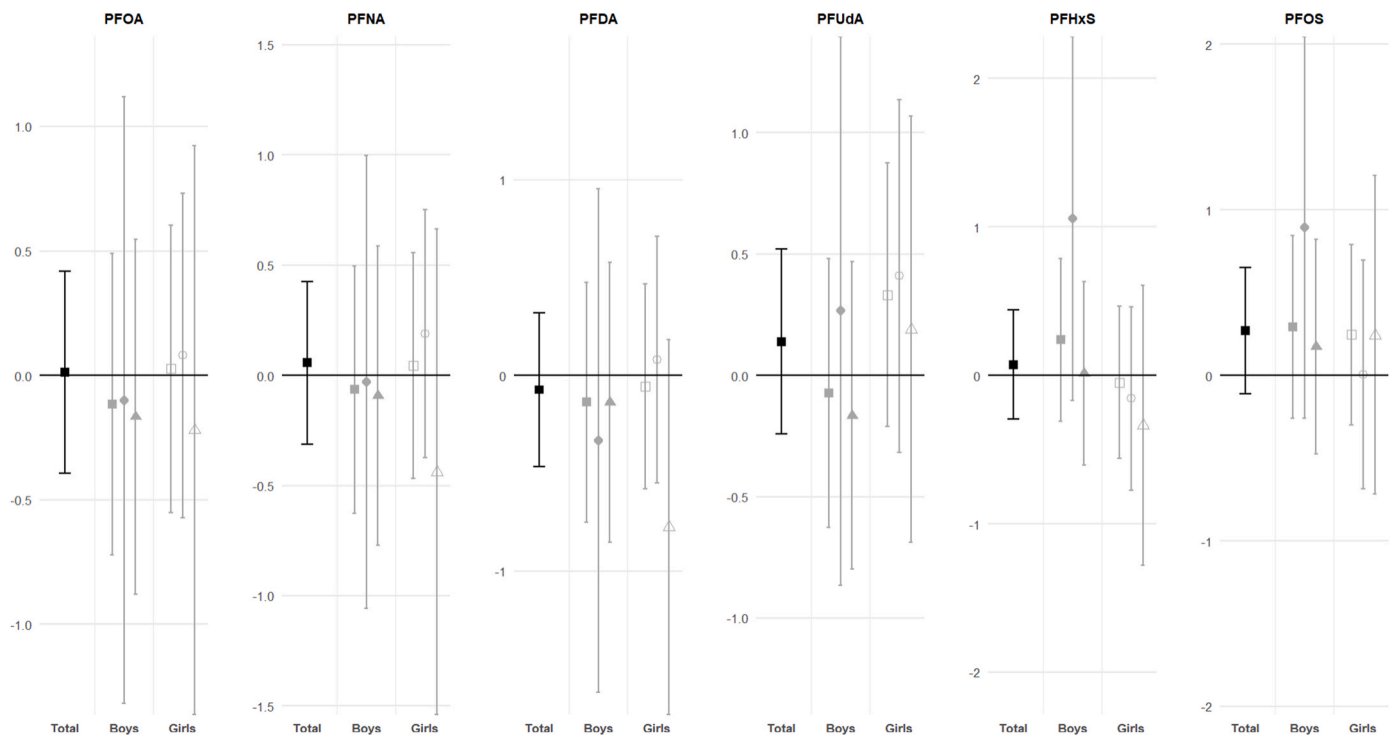
<sup>b</sup> The cardiometabolic score is defined as the sum of proportion of fat mass, mean arterial blood pressure, fructosamine, triglycerides, low-density lipoproteins and high-density lipoproteins, after standardization of each indicators by sex and pubertal stage.

**Table 2**  
Distribution of PFAS exposure levels assessed in cord blood (n = 394).

PFAS compounds <sup>a</sup>	N	LOD	% >LOD	Q1	Median	Q3	Maximum
PFOA, perfluorooctanoic acid	394	0.066	100.0	1.71	2.25	2.83	7.36
PFNA, perfluorononanoic acid	386	0.085	99.7	0.26	0.35	0.46	1.55
PFDA, perfluorodecanoic acid	361	0.058	89.5	0.08	0.10	0.13	0.51
PFUdA, perfluoroundecanoic acid	371	0.048	74.9	0.05	0.07	0.09	0.30
PFHxS, perfluorohexane sulfonate	394	0.063	98.7	0.42	0.56	0.70	1.78
PFOS, perfluorooctanesulfonic acid	394	0.160	100.0	3.53	4.63	6.08	27.17

LOD: Limit of detection; PFAS: per- and polyfluoroalkyl substances; Q1: First quartile 1; Q3: Third quartile.

<sup>a</sup> Ordered by carbon chain length.



**Fig. 1.** Association between prenatal exposure to PFAS and the cardiometabolic score in the overall study population and after stratification by sex and pubertal stage (n = 394).

**Fig. 1** legend: The black lines represent the total population (both sexes and all pubertal stages) and the grey lines represent boys and girls across all pubertal stages. The shapes denote pubertal stages: squares for all stages combined, circles for peripubertal/premenarchal stages, and triangles for postpubertal/postmenarche stages. Filled black shapes represent the total population, filled grey shapes for boys, and unfilled shapes for girls. All models were adjusted for maternal body mass index, maternal age, parity, mother's level of education, urbanization, fish and shellfish consumption. PFDA: perfluorodecanoic acid; PFHxS: perfluorohexane sulfonate; PFNA: perfluorononanoic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonic acid; PFUdA: perfluoroundecanoic acid.

statistically significant associations were observed between prenatal exposure to PFAS and anthropometric measures. However, exposure to PFUdA was associated with a tendency toward a higher z-BMI (beta [95 % CI] = 0.13 [-0.03; 0.28]), especially among boys (beta [95 % CI] = 0.21 [-0.006; 0.43]) (Fig. 2).

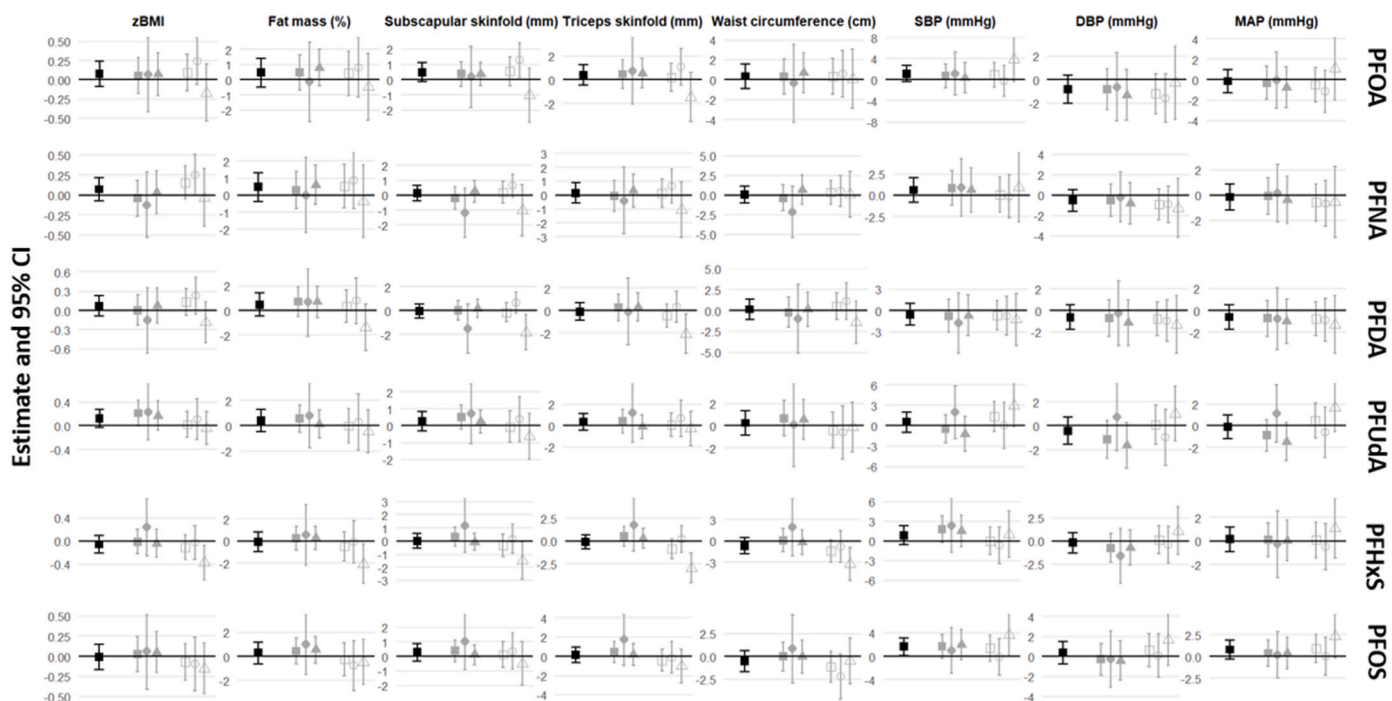
In pre-menarche girls, PFOA was statistically significantly associated with higher scapular skinfold levels (beta [95 % CI] = 1.3 [0.16; 2.4]) (Fig. 2).

In post-menarche girls, PFHxS was statistically significantly associated with lower z-BMI (beta [95 % CI] = -0.37 [-0.66; -0.07]), WC (beta [95 % CI] = -3.2 [-5.6; -0.9]), fat mass proportion (beta [95 % CI] = -2.05 [-3.8; -0.3]), tricipital skinfold (beta [95 % CI] = -2.9 [-4.5; -1.3]) and scapular skinfold (beta [95 % CI] = -1.5 [-2.9; -0.05]). Lower tricipital and scapular skinfolds were also observed with PFDA (beta [95 % CI] = -2.1 [-3.8; -0.3] and beta [95 % CI] = -1.8 [-3.3; -0.35], respectively) (Fig. 2).

No association was observed in the other population subgroups, or with other PFAS.

**3.3.1.2. Blood pressure.** In the total population, PFOS was statistically significantly associated with an increase in systolic blood pressure (beta [95 % CI] = 1.64 [0.164; 3.12]), especially among post-menarche girls (beta [95 % CI] = 3.7 [0.17; 7.25]) (Fig. 2). No significant association was found with MAP and diastolic blood pressure.

**3.3.1.3. Metabolic blood markers.** In the total study population, no statistically significant association was observed between prenatal PFAS exposure and blood lipid levels. However, a non-linear dose-response association has been observed between PFUdA and leptin levels, which suggests an inverse U-shape relation (Supplemental Fig. S4). After categorization, intermediate level of PFUdA was associated with a non-significant increase in leptin levels (beta [95 % CI] 2nd tertile = 0.22 [-0.003; 0.46]; 3rd tertile = 0.1 [-0.14; 0.34]) (Fig. 3). A statistically significant association was found between PFDA exposure and lower HDL concentrations in girls (beta [95 % CI] = -0.08 [-0.15; -0.004]) (Fig. 3). In pre-menarche girls, statistically significant associations were found between PFOS and PFUdA with increased LDL levels (beta [95 %



**Fig. 2.** Association between prenatal exposure to each PFAS and anthropometric and blood pressure measurements ( $n = 394$ ).

**Fig. 2 legend:** The black lines represent the total population (both sexes and all pubertal stages), and the grey lines represent boys and girls across all pubertal stages. The shapes denote pubertal stages: squares for peripubertal/premenarchal stages, and triangles for postpubertal/postmenarche stages. Filled black shapes represent the total population, filled grey shapes for boys, and unfilled shapes for girls. All models were adjusted for maternal body mass index, maternal age, parity, mother's level of education, urbanization, fish and shellfish consumption, as well as for child sex and pubertal status for the non-stratified analyses. BMI: Body mass index; CI: Confidence interval; DBP: Diastolic blood pressure; MAP: Mean arterial blood pressure; PFDA: perfluorodecanoic acid; PFHxS: perfluorohexane sulfonate; PFNA: perfluorononanoic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonic acid; PFUdA: perfluoroundecanoic acid; SBP: Systolic blood pressure.

CI] = 0.25 [0.019; 0.49] and beta [95 % CI] = 0.34 [0.09; 0.6] respectively) (Fig. 3). PFUdA was also statistically significantly associated with higher total cholesterol levels (beta [95 % CI] = 0.4 [0.07; 0.8]) and lower fructosamine concentrations (beta [95 % CI] =  $-4.7$  [ $-9.45$ ;  $-0.004$ ]) (Fig. 3).

In post-menarche girls, a statistically significant association was found between PFDA with lower LDL levels (beta [95 % CI] =  $-0.3$  [ $-0.6$ ;  $-0.02$ ]) and total cholesterol levels (beta [95 % CI] =  $-0.4$  [ $-0.8$ ;  $-0.03$ ]). A statistically significant association was also found between PFHxS prenatal exposure and low leptin concentration (beta [95 % CI] =  $-0.3$  [ $-0.6$ ;  $-0.09$ ]) (Fig. 3). Nonlinear U-shape relations were found between PFDA and PFNA and HDL levels (Supplemental Fig. S4).

In boys, increased levels of prenatal PFOA exposure are statistically significantly associated with lower levels of adiponectin concentration (beta [95 % CI] =  $-0.8$  [ $-1.57$ ;  $-0.096$ ]), with this association primarily driven by peripubertal boys (beta [95 % CI] =  $-2.04$  [ $-3.67$ ;  $-0.4$ ]) (Fig. 3). Also, in peripubertal boys, statistically significant prenatal exposure to PFHxS was associated with increased LDL concentrations (beta [95 % CI] = 0.41 [0.02; 0.8]) (Fig. 3). PFUdA was also statistically significantly associated with higher leptin levels in peripubertal boys (beta [95 % CI] = 0.66 [0.03; 1.3]) (Fig. 3). In addition, U-shape nonlinear associations were observed in peripubertal boys with PFUdA and LDL and total cholesterol levels (Supplemental Fig. S4). In postpubertal boys, U-shape non-linear associations were found with PFDA and PFNA and leptin levels (Supplemental Fig. S4).

Detailed beta estimates and CI are available in Supplemental Table S3.

Sensitivity analyses, which involved excluding the five most influential values, revealed no difference in results compared with the principal analysis (Supplemental Table S4).

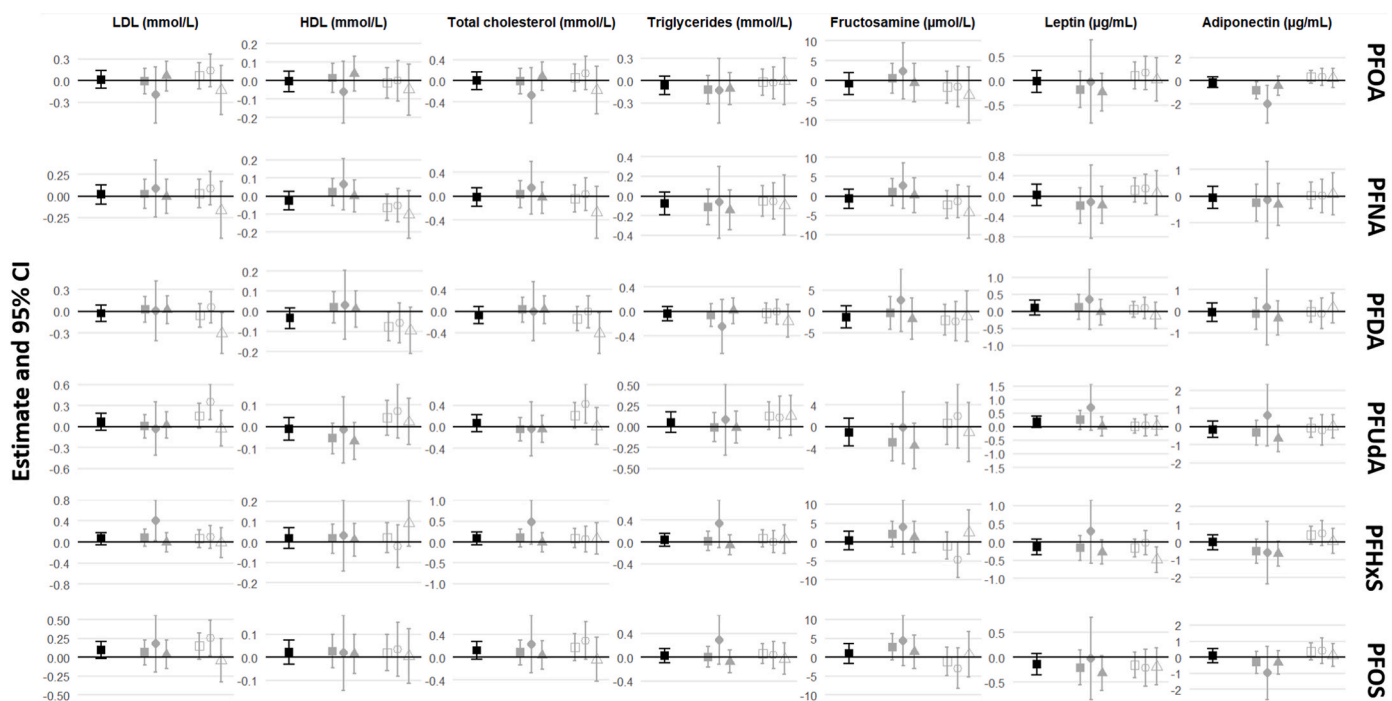
### 3.4. Study of the mixture effects of pollutants

No associations were observed in the overall study population, nor after stratification by sex (Table 3). However, in peripubertal boys, PFAS mixture was statistically significantly associated with increased leptin levels (beta [95% CI] = 0.5 [0.01; 1]), PFDA, PFUdA, and PFHxS being the main contributors to the mixture effect (Supplemental Fig. S5). In post-menarche girls, the PFAS mixture was associated with a statistically significant decrease in triceps skinfold (beta [95% CI] =  $-1.3$  [ $-2.5$ ;  $-0.06$ ]), PFHxS and PFDA being the main contributors to the mixture effect (Supplemental Fig. S5).

## 4. Discussion

This study looked at the association between prenatal exposure levels to PFAS and the cardiometabolic health of 12-year-old children from the PELAGIE cohort. The results revealed no significant associations between maternal exposure to PFAS and the cardiometabolic score of their children. Statistically significant associations were however identified for certain cardiometabolic indicators studied independently, in a specific subgroup of the study population. In particular, in post-menarche girls, prenatal exposure to PFHxS and PFDA was significantly associated with a decrease in several anthropometric parameters as well as lower LDL and leptin levels. Some PFAS show consistent associations with cardiometabolic health indicators. Indeed, PFOS tends to increase several biological indicators (LDL, total cholesterol and fructosamine) both in the total population and other subgroups. On the other hand, PFDA tends to decrease lipids (LDL, HDL, triglycerides) in some subgroups.

Median cord blood PFAS exposure levels in this study seem comparable to those of other studies in the literature (mainly set up after the



**Fig. 3.** Association between prenatal exposure to each PFAS and metabolic blood markers ( $n = 394$ ).

**Fig. 3 legend:** The black lines represent the total population (both sexes and all pubertal stages), and the grey lines represent boys and girls across all pubertal stages. The shapes denote pubertal stages: squares for all stages combined, circles for peripubertal/premenarchal stages, and triangles for postpubertal/postmenarche stages. Filled black shapes represent the total population, filled grey shapes for boys, and unfilled shapes for girls. All models were therefore adjusted for maternal body mass index, maternal age, parity, mother's level of education, urbanization, fish and shellfish consumption, as well as for child sex and pubertal status for the non-stratified analyses. CI: Confidence interval; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; PFDA: perfluorodecanoic acid; PFHxS: perfluorohexane sulfonate; PFNA: perfluorononanoic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonic acid; PFUDA: perfluoroundecanoic acid.

2010s in Europe and USA, and to a lesser extent in Asia) for PFOA (from 1.6  $\mu\text{g/L}$  to 5.7  $\mu\text{g/L}$  and 2.25  $\mu\text{g/L}$  in this study) and PFOS (from 0.38  $\mu\text{g/L}$  to 1.51  $\mu\text{g/L}$  and 0.35  $\mu\text{g/L}$  in this study) but lower for PFDA (from 0.36 to 0.39  $\mu\text{g/L}$  and 0.1  $\mu\text{g/L}$  in this study) and PFUDA (from 0.40 to 0.43  $\mu\text{g/L}$  and 0.07  $\mu\text{g/L}$  in this study) (Stratakis et al., 2022; Chen et al., 2019; de Cock et al., 2014; Kim et al., 2011). For this study, the measurement of PFAS levels have been performed in cord blood which appears to accurately represent the exposure reaching the fetus (Liu et al., 2024; Gützkow et al., 2012). Indeed, studies on PFAS concentrations assessed longitudinally during pregnancy have indicated a decline in maternal blood circulating level over gestation, possibly due to factors like expanded plasma volume and placental/fetal absorption (Chen et al., 2019). Furthermore, a meta-analysis has shown varying transplacental transfer efficiencies of PFAS, influenced by factors such as chain length and functional groups (Appel et al., 2022). Nonetheless, humans exhibit prolonged half-lives for PFOS, PFHxS, and PFOA, suggesting ongoing exposure from prenatal exposure and transfer across the placental barrier to early childhood (Olsen et al., 2007). Therefore, it is plausible that what is measured in cord blood may also reflect exposure during the early months of life.

A number of systematic reviews have been published on prenatal exposure to PFAS and its associations with anthropometric indicators in children, such as BMI, body fat percentage and WC. The conclusions of these reviews are not uniform (Stratakis et al., 2022; Frangione et al., 2024; Frigerio et al., 2023). Overall, these 3 reviews included 36 articles: 16 focused on anthropometric indicators during the first 2 years of life, 20 during childhood (2–12 years old; i.e., closer to our peripubertal population), and only 4 in 12 years-old children or older (i.e., closer to our postpubertal population). All three meta-analyses reported no associations with BMI nor WC for PFOS and PFOA (Stratakis et al., 2022; Frangione et al., 2024; Frigerio et al., 2023). Only Frigerio's review has meta-analyzed this association for other PFAS and reported an increased

z-BMI and WC with prenatal exposure to PFNA (in both boys and girls), a decreased risk of overweight with prenatal exposure to PFHxS (both sexes combined), and no association for the other PFAS (Frigerio et al., 2023). When focusing more specifically on the few studies performed among a population close in age to that of the participants in this study (age 12), discordant results are also reported. Three studies came from the HOME study (Cincinnati,  $n = 212$  to 345 mother-child pairs, maternal and cord blood serum) and looked at different cardiometabolic outcomes at age 12 in association with prenatal exposure to PFOA, PFOS, PFNA, and PFHxS (Braun et al., 2021; Li et al., 2021; Liu et al., 2020). Braun et al. reported that children born to women with higher PFOA concentrations displayed higher BMI trajectory from birth to age 12, while those with higher PFOS concentrations exhibited lower BMI trajectory compared to lower tertiles (Braun et al., 2021). Similarly, the study by Liu et al. reported higher waist-to-hip ratio in association with prenatal exposure to PFOA and PFHxS (Liu et al., 2020). The third study by Li et al. showed that PFOA and PFHxS, as well as the PFAS mixture, were associated with an increased cardiometabolic risk score at age 12, and also reported increased mean blood pressure and insulin levels, as well as decreased glucose levels and adiponectin/leptin ratio with at least one out of the four PFAS of interest (Li et al., 2021). Finally, two studies evaluated the associations between prenatal exposure to PFAS and BMI in late adolescence (17–20 years old): from a Danish birth cohort ( $n = 422$  to 665), higher BMI and risk of overweight, higher leptin levels, and lower adiponectin levels were observed in girls prenatally exposed to the highest PFOA levels (no association in boys) (Halldorsson et al., 2012), while, from the project VIVA study (Boston,  $n = 545$ ), higher BMI trajectory were reported in association with prenatal exposure to a mixture of PFAS (PFOS being the main contributor) (Zhang et al., 2023). In summary, previous studies have reported heterogeneous results, with sometimes contradictory directions of effect depending on the compound, the child age and sex, and the outcome of



Table 3

Association between prenatal exposure to PFAS mixture and cardiometabolic health indicators (n = 394).

	Total Population	All boys	Boys peripubertal	Boys postpubertal	All Girls	Girls pre-menarche	Girls post-menarche
	beta [95 % CI]	beta [95 % CI]	beta [95 % CI]	beta [95 % CI]	beta [95 % CI]	beta [95 % CI]	beta [95 % CI]
<b>Cardiometabolic score</b>	0.10 (−0.23, 0.43)	0.10 (−0.4, 0.61)	0.50 (−0.55, 1.54)	0.07 (−0.52, 0.66)	0.10 (−0.36, 0.56)	0.18 (−0.45, 0.8)	−0.36 (−1.06, 0.33)
<b>zBMI</b>	0.04 (−0.09, 0.17)	0.05 (−0.15, 0.25)	0.18 (−0.24, 0.61)	0.04 (−0.18, 0.27)	0.02 (−0.16, 0.21)	0.14 (−0.14, 0.42)	−0.14 (−0.38, 0.1)
<b>Fat mass (%)</b>	0.07 (−0.69, 0.83)	0.36 (−0.63, 1.35)	1.09 (−1.11, 3.28)	0.26 (−0.77, 1.28)	−0.04 (−1.17, 1.1)	0.37 (−1.46, 2.21)	−0.90 (−2.32, 0.52)
<b>Subscapular skinfold (mm)</b>	−0.04 (−0.51, 0.43)	0.13 (−0.51, 0.78)	0.34 (−1.17, 1.84)	0.03 (−0.6, 0.65)	−0.14 (−0.84, 0.55)	0.44 (−0.42, 1.29)	−0.95 (−2.13, 0.23)
<b>Triceps skinfold (mm)</b>	−0.08 (−0.74, 0.58)	0.35 (−0.66, 1.36)	1.05 (−1.37, 3.46)	0.15 (−0.86, 1.16)	−0.39 (−1.27, 0.5)	0.66 (−0.64, 1.97)	−1.30 (−2.54, −0.06)
<b>Waist circumference (cm)</b>	−0.26 (−1.2, 0.69)	−0.21 (−1.71, 1.3)	0.96 (−2.27, 4.18)	−0.10 (−1.78, 1.57)	−0.38 (−1.66, 0.91)	−0.08 (−1.96, 1.79)	−1.09 (−2.91, 0.72)
<b>SBP (mmHg)</b>	0.83 (−0.41, 2.06)	0.66 (−1.18, 2.49)	2.00 (−1.37, 5.37)	0.11 (−2.14, 2.35)	1.04 (−0.74, 2.82)	0.33 (−2.38, 3.04)	1.06 (−1.27, 3.39)
<b>DBP (mmHg)</b>	−0.41 (−1.36, 0.53)	−0.98 (−2.37, 0.42)	−0.29 (−2.68, 2.1)	−1.37 (−3.05, 0.31)	0.01 (−1.35, 1.36)	−0.75 (−2.58, 1.09)	0.04 (−1.78, 1.85)
<b>MAP (mmHg)</b>	0.00 (−0.90, 0.90)	−0.43 (−1.75, 0.89)	0.48 (−1.81, 2.76)	−0.88 (−2.47, 0.71)	0.35 (−0.98, 1.68)	−0.39 (−2.29, 1.51)	0.38 (−1.32, 2.08)
<b>LDL (mmol/L)</b>	0.02 (−0.08, 0.12)	0.07 (−0.08, 0.22)	0.19 (−0.12, 0.51)	0.01 (−0.15, 0.17)	0.05 (−0.09, 0.19)	0.21 (−0.00, 0.41)	−0.13 (−0.34, 0.08)
<b>HDL (mmol/L)</b>	−0.01 (−0.06, 0.03)	0.00 (−0.06, 0.06)	0.04 (−0.09, 0.17)	−0.01 (−0.09, 0.06)	−0.01 (−0.07, 0.06)	0.02 (−0.07, 0.11)	−0.02 (−0.1, 0.07)
<b>Total Cholesterol (mmol/L)</b>	0.01 (−0.13, 0.14)	0.07 (−0.12, 0.26)	0.24 (−0.16, 0.65)	−0.01 (−0.22, 0.2)	0.04 (−0.15, 0.23)	0.22 (−0.06, 0.5)	−0.15 (−0.42, 0.13)
<b>Triglycerides<sup>a</sup> (mmol/L)</b>	0.01 (−0.09, 0.11)	−0.02 (−0.18, 0.14)	0.12 (−0.24, 0.47)	−0.04 (−0.21, 0.13)	0.03 (−0.11, 0.17)	0.01 (−0.19, 0.21)	0.02 (−0.18, 0.22)
<b>Fructosamine (μmol/L)</b>	−0.57 (−2.71, 1.57)	0.44 (−2.57, 3.46)	2.81 (−2.92, 8.53)	−0.53 (−4.13, 3.07)	−0.98 (−4.18, 2.22)	−0.58 (−5.18, 4.03)	−1.99 (−6.47, 2.48)
<b>Leptin<sup>a</sup> (μg/mL)</b>	−0.00 (−0.18, 0.18)	0.03 (−0.29, 0.34)	0.75 (0.04, 1.45)	−0.18 (−0.47, 0.11)	−0.03 (−0.24, 0.18)	0.06 (−0.26, 0.37)	−0.13 (−0.42, 0.15)
<b>Adiponectin (μg/mL)</b>	−0.07 (−0.44, 0.3)	−0.46 (−1.07, 0.15)	0.21 (−1.14, 1.54)	−0.60 (−1.23, 0.03)	0.24 (−0.2, 0.68)	0.39 (−0.3, 1.09)	0.08 (−0.47, 0.63)

BMI: Body mass index; CI: Confidence interval; DBP: Diastolic blood pressure; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; MAP: Mean arterial blood pressure; SBP: Systolic blood pressure.

<sup>a</sup> log<sub>2</sub>-transformed.

interest.

A large number of experimental studies have shown that exposure to PFAS has an impact on cholesterol metabolism and glucose homeostasis (Fletcher et al., 2013; Guruge et al., 2006; Fenton et al., 2021; Zhang et al., 2020; Chiang and Ferrell, 2020; Qin et al., 2020). One potential biological mechanism that may explain how PFAS can affect cholesterol metabolism is through the disruption of bile acid synthesis. Indeed, PFAS exposure is associated with alterations in gene expression related to cholesterol metabolism. Bile acid synthesis, catalyzed by the key enzyme cholesterol 7 alpha-hydroxylase (CYP7A1), is an essential pathway in cholesterol metabolism (Guruge et al., 2006; Chiang and Ferrell, 2020). The literature confirms the importance of CYP7A1 in the conversion of cholesterol into bile acids, thus contributing to the elimination of cholesterol from the liver (Fletcher et al., 2013). However, exposure to PFAS may disrupt this process (Fletcher et al., 2013). Exposure to PFAS alters CYP7A1 activity, causing impairment of normal bile acid synthesis that may lead to an accumulation of cholesterol in the liver (Chiang and Ferrell, 2020). In addition, long-term exposure to PFAS can induce insulin resistance by activating G protein-coupled receptor 40 (GPR40) on islet β-cells, thereby stimulating insulin secretion (Zhang et al., 2020). The literature establishes an association between PFAS exposure and alterations in oxidative stress biomarkers (Wielsoe et al., 2015). Indeed, PFAS can induce oxidative stress in vitro, suggesting a plausible mechanism by which these substances could contribute to increased levels of oxidative stress in biological systems (Wielsoe et al., 2015). Oxidative stress plays a central role in the pathophysiology of hypertension, influencing endothelial dysfunction, inflammation and vascular remodeling – all of which are integral components in the onset and progression of hypertension (Rodrigo et al.,

2011). Adiponectin, a hormone secreted by adipocytes, plays a crucial role in regulating cardiometabolic metabolism. This bioactive protein exerts beneficial effects on several aspects of health, including insulin sensitivity, modulation of inflammation, and protection against atherosclerotic processes. In particular, adiponectin promotes glucose regulation, reduces vascular inflammation, and improves endothelial function, all of which are essential to the prevention of cardiovascular disease. Exposure to PFAS can modify adipogenicity (the formation and accumulation of fat cells). As potential endocrine disruptors, PFAS can disrupt adipocyte metabolism, leading to alterations in adiponectin secretion. This dysregulation of adipogenicity may contribute to the decrease in adiponectin levels observed under PFAS exposure conditions (Jeffery et al., 2008; Kraugerud et al., 2011).

This study revealed sex- and puberty-specific results, particularly in post-menarche girls. Puberty is characterized by a gradual process, marked by a complex sequence of transformations that lead to internal and external changes in primary and secondary sexual characteristics, and eventual reproductive competence (Dorn and Biro, 2011). At puberty onset, important physiological and anthropometric changes start, conducting to the growth of muscle and bone tissue that can also have an impact on blood lipid levels (Schoenau, 2006). These changes may explain why we have observed lower skinfolds and LDL levels in post-menarche girls only. In addition, puberty is characterized by significant hormonal changes, notably an increase in estrogens in girls and it is known that estrogen has a cardiovascular protective effect with lower LDL and higher HDL levels and increased vasodilatation (Mendelsohn et al., 1999; Guetta and Cannon, 1996). Therefore, another possible hypothesis to explain our sex- and puberty-specific findings might be related to estrogens, some studies reporting that exposure to

PFAS was associated with higher levels of female sex hormones (Ernst et al., 2019; Li et al., 2024).

One notable aspect of this study is its inclusion of a number of cardiometabolic indicators, enabling the analysis of both composite cardiometabolic score and individual parameters. However, it should be acknowledged that the cardiometabolic score used in this study raises questions as to the representativeness of the cardiometabolic health. Indeed, cardiometabolic profiles can be heterogeneous, with both favorable anthropometric indicators (e.g. low BMI) and unfavorable biological indicators (e.g. high LDL) within a single profile. This complexity of mixed profiles highlights the value of studying a wide range of clinical and biological indicators of cardiometabolic health. In addition, the present cardiometabolic score (which is built as the sum of individual indicators) does not rely on reference values limiting its reliability; even though the IDEFICS study developed a metabolic score for children under 11, it does not align well with our age group (Ahrens and Moreno, 2014). It should also be acknowledged that the measurement of blood pressure and biological parameters was conducted only once at the age of 12, and this single measurement may lead to misclassification error. The biological tests were not performed on an empty stomach, and this prevented obtaining fasting blood glycemia levels. As a way of circumventing this limitation, fructosamine was used as an indicator of glucose homeostasis. Fructosamine is an interesting and original indicator that reflects glycemic status over a longer period of time (around 3 weeks), but fructosamine is rarely used in studies, and even less so at a young age, so there are no solid protocols, standards or references for age 12.

Because this study used data from a longitudinal mother-child cohort, there was the advantage of being able to study preadolescent health while also measuring prenatal exposure. On the other hand, due to the voluntary nature of participation, this study population tends toward a high level of education, maternal non-smokers, normal pregnancy BMI, and normal weight (>80%) for the adolescents. This means that the conclusions of the present findings might be primarily relevant to a population with similar characteristics.

Another limitation of this study is the definition of the puberty; indeed, it is essential to consider puberty as an evolutionary process rather than a binary characteristic. This study's dichotomization of pubertal stage (by selecting only menarche status in girls and testicular volume in boys) may obscure the evolutionary nature of this process. In addition, our consideration of pubertal development stages via stratification of the analyses has resulted in small sample sizes, limiting both statistical power and our ability to draw firm conclusions. The statistically significant differences observed are mostly within the smallest groups ( $n = 67$  peripubertal boys and  $n = 87$  post-menarche girls). In addition, the p-values for multiple tests have not been corrected, as our study was exploratory. Therefore, we accepted the possibility of the risk of falsely identifying a statistical difference. As recommended, all statistical tests were specified in advance, and all results are reported accordingly. Finally, as any observational study, residual confounding cannot be excluded.

## 5. Conclusion

The results of this study do not reveal any significant association between prenatal exposure to PFAS and the cardiometabolic score. However, prenatal exposure to PFAS, considered individually or in mixture, was associated with decreased anthropometric factors and LDL and leptin concentrations in post-menarche girls. These results suggest the importance of considering the intricate relationship between sex and pubertal stage in these associations.

## CRediT authorship contribution statement

**Naomi Lejeune:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Elke**

**Rouxel:** Writing – review & editing, Methodology, Data curation. **Christine Monfort:** Writing – review & editing, Methodology, Investigation, Data curation. **Hélène Tillaut:** Writing – review & editing, Methodology, Data curation. **Florence Rouget:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Nathalie Costet:** Writing – review & editing, Methodology, Investigation. **Frank Giton:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Éric Gaudreau:** Writing – review & editing, Formal analysis, Data curation. **Fabrice Lainé:** Writing – review & editing, Supervision, Investigation. **Ronan Garlantézec:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Sylvaine Cordier:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Cécile Chevrier:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Charline Warembourg:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2024.120607>.

## Data availability

The authors do not have permission to share data.

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