Ecotoxicology and Environmental Safety 209 (2021) 111805

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

The association between perfluoroalkyl substances and lipid profile in exposed pregnant women in the Veneto region, Italy

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ARTICLE INFO

Edited by: Dr Fernando Barbosa

Keywords:
Perfluoroalkyl substances
Pregnancy
Serum lipids
Italy

ABSTRACT

Background: Residents of a large area of North-Eastern Italy were exposed for decades to high concentrations of perfluoroalkyl and polyfluoroalkyl substances (PFAS) via drinking water. Serum PFAS levels have been consistently associated with elevated serum lipids, but few studies have been conducted among pregnant women, and none has stratified analyses by trimester of gestation. Elevated serum lipid levels during pregnancy can have both immediate and long-lasting effects on pregnant women and the developing fetus. We evaluated the association between perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and perfluoro-hexanesulfonate (PFHxS) levels in relation to lipid profiles in highly-exposed pregnant women.

Methods: A cross-sectional analysis was conducted in 319 pregnant women (age 14–48 years) enrolled in the Regional health surveillance program. Non-fasting blood samples were obtained in any trimester of pregnancy and analyzed for PFOA, PFOS and PFHxS, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) was calculated. The associations between ln-transformed PFAS (and categorized into quartiles) and lipids were assessed using generalized additive models. Analyses were adjusted for potential confounders and stratified according to pregnancy trimester.

Results: The geometric means of PFOA, PFOS and PFHxS were 14.78 ng/mL, 2.67 ng/mL and 1.89 ng/mL, respectively. The plasma levels of TC, HDL-C and LDL-C increased steadily throughout the trimesters. In the 1st trimester, PFOS was positively associated with TC and PFHxS with HDL-C. In the 3rd trimester, instead, an inverse relationship was seen between PFOA and PFHxS and both TC and LDL-C.

Conclusions: Results suggest the associations between PFAS concentrations and lipid profiles in pregnant women might differ by trimesters of pregnancy. In the first trimester, patterns are similar to those of non-pregnant women, while they differ late in pregnancy. Different independent behavior of PFAS and lipid levels throughout the pregnancy might explain our observations. These findings support the ubiquitous exposure to PFAS and possible influence on lipid metabolisms during pregnancy and suggest a careful evaluation of the timing of PFAS measurement, when examining effects of PFAS during pregnancy on gestational outcomes related to serum lipids amounts.

Abbreviations: ALT, Alanine aminotransferase; BMI, Body mass index; CI, Confidence interval; GAM, Generalized additive models; GM, Geometric mean; HDC, Highly developed countries; HMPC, High migratory pressure countries; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; LOQ, Limit of quantification; LOD, Limit of detection; MET, Metabolic equivalent of task; PFAS, Perfluoroalkyl and polyfluoroalkyl substances; PFHxS, Perfluoro-hexanesulfonate; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctane sulfonate; SD, Standard deviation; TC, Total cholesterol.

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https://doi.org/10.1016/j.ecoenv.2020.111805
Received 14 September 2020; Received in revised form 30 November 2020; Accepted 10 December 2020
Available online 24 December 2020

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) comprise a large group of anthropogenic organic chemicals that have been used since the late 1940s in a wide variety of commercial products and industrial applications due to their unique surfactant and repellant properties (Fujii et al., 2015; Harada et al., 2007). PFAS are persistent environmental contaminants, resistant to biodegradation, photooxidation, direct photolysis, and hydrolysis (Organisation for Economic Co-operation and Development (OECD), 2018). Sources of exposure to PFAS for humans may include food, drinking water, house dust, air, and breast milk for infants (Fromme et al., 2010; Haug et al., 2011; Poothong et al., 2020).

Due to the ubiquitous presence of PFAS, persistency in the environment, tendency for bioaccumulation and biomagnification and a long half-life in humans (Bergman et al., 2013), exposure to PFAS will persist for many years, thereby making them a potential hazard to humans. PFAS have been associated with a variety of adverse health outcomes including hepatotoxicity, tumorigenesis, immunotoxicity, and developmental toxicity (Lau et al., 2007). Metabolic effects including changes in lipid profiles and possibly obesity, and diabetes, are some of the phenotypic alterations from PFAS exposures (ATSDR, 2018; EFSA Panel on Contaminants in the Food Chain (CONTAM) et al., 2018). Both in epidemiological studies of populations with background levels of exposure and highly exposed populations, levels of PFAS (mainly perfluorooctanoic acid-PFOA and perfluorooctane sulfonate-PFOS) have been associated with elevated plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) (Canova et al., 2020; Fitz-Simon et al., 2013; Frisbee et al., 2010; Li et al., 2020; Lin et al., 2019; Maisonet et al., 2015; Nelson et al., 2010; Steenland et al., 2009; Winquist and Steenland, 2014). Few of these studies performed gender-specific analyses (Canova et al., 2020; Frisbee et al., 2010; Winquist and Steenland, 2014).

While detectable blood levels of PFAS have been reported in pregnant women in several epidemiological studies (Manzano-Salgado et al., 2015; Mehta et al., 2020; Spratlen et al., 2019; Yang et al., 2019), only few studies investigated the association between PFAS concentrations and lipid profiles among the pregnant women (Gardener et al., 2021; Matilla-Santander et al., 2017; Skuladottir et al., 2015; Starling et al., 2014; Yang et al., 2020). Each of the five published studies took blood samples for PFAS and lipids measurements in a specific trimester of pregnancy. All of them found a positive association of one or more of the analyzed PFAS with TC. Only two studies (Starling et al., 2014; Yang et al., 2020), examined the association with HDL-C and LDL-C.

None of these studies of pregnant women was focused on highly exposed population. Furthermore, none of them analysed the differences in the association between PFAS levels and plasma lipid concentration across the three trimesters of pregnancy, nor stratified by trimester of pregnancy. Stratification by trimester is of great interest, within a study, because it has been demonstrated that serum cholesterol concentrations increase markedly over the course of pregnancy (Brizzi et al., 1999; Piechota and Staszewski, 1992; Wiznitzer et al., 2009), and PFAS levels in maternal serum are known to decrease during pregnancy (Fisher et al., 2016; Jain, 2013; Javins et al., 2013).

Exposure of susceptible populations, including pregnant women and developing foetuses to PFAS is a concern due to the vulnerability of early life stages to toxic effects and that can also influence health outcomes later in life (Rager et al., 2020). Epidemiological studies on pregnant women have revealed associations between exposure to specific PFAS and a variety of health effects, including altered immune and thyroid function, lipid and insulin dysregulation, pregnancy-induced hypertension or pre-eclampsia, adverse reproductive and developmental outcomes (Fenton et al., 2020). The association of PFAS levels and alteration of lipid profiles in pregnant woman might partially explain the pathological mechanisms beyond these associations, because altered plasma lipids during pregnancy, are associated with a number of adverse outcomes, including preeclampsia (Spracklen et al., 2014).

PFAS have been demonstrated to have strong binding affinity to serum proteins (Gao et al., 2019). In particular, PFAS are structurally similar to fatty acids, which leads to a strong binding affinity of PFAS to liver-fatty acid binding protein (L-FABP) and an accumulation of PFAS in the liver. LFABP is also one of the major proteins in serum (Pelsers et al., 2003). The binding between L-FABP and PFAS is suggested to potentially influence the uptake and transport of fatty acids and might further interfere with glycolipid metabolism (Ng and Hungerbühler, 2014). The structural similarity of PFAS to fatty acids and their binding to L-FABP reinforces the hypothesis of possible lipid regulation disruption by PFAS (Gao et al., 2019). Human serum albumin (HSA) which is the main protein in the blood (Jones et al., 2003; Luo et al., 2012) is involved in the transport and distribution of endogenous and exogenous ligands (Sleep, 2015). Therefore, the PFASs bound to HSA may also be transported to target organs that regulate serum lipid levels. A recent study (Fan et al., 2020) showed that HSA mediated the interaction between PFAS mixtures and serum lipid profiles (HDL, LDL and TC).

Residents in a large area of the Veneto Region (North-Eastern Italy) were exposed to high concentrations of PFAS, particularly PFOA, via contaminated drinking water from a manufacturing plant active since the late 1960s, until autumn 2013 when water treatment plants were equipped with granular activated carbon filters (Pitter et al., 2020). In 2015–16, a study was conducted to compare the serum PFAS levels of the exposed population with those of a control population group living in neighbouring areas at background exposure (Ingelido et al., 2018). Median concentrations of serum PFOA, PFOS and PFHxS were higher in exposed subjects than in non-exposed due to this historical exposure. The largest difference was observed for PFOA: median value of the exposed group was 13.77 ng/g, eight times higher than the median value of the non-exposed group (1.64 ng/g). A publicly funded health surveillance program has been established to aid in the prevention, early diagnosis, and treatment of chronic disorders possibly associated with PFAS exposure (Pitter et al., 2020).

Thus, the objective of this study was to evaluate the association between PFOA, PFOS, and perfluoro-hexanesulfonate (PFHxS) levels and serum TC, HDL-C, LDL-C in highly exposed pregnant women. In order to analyze the differences in the association between PFAS levels and lipid concentration throughout the gestational weeks, we stratified the results by trimester of gestation.

2. Material and methods

2.1. Study population

The cross-sectional study included 33,273 individuals (17,271 women, 51.9%) recruited from January 2017 to February 2020 in the health surveillance program offered to the community of Veneto Region that was exposed to elevated levels of PFAS via drinking water since the late 1960s. Only women who were pregnant at the time of enrolment (n = 394) are included in the analysis. Participants ranged in age from 14 to 48.

The health surveillance program has been described in more detail elsewhere (Pitter et al., 2020). Surveillance involved the active calling of the eligible population and the free offer of health examinations including: i) a questionnaire on socio-demographic characteristics, personal health history, diet and lifestyle characteristics, self-reported height and weight; ii) measurement of blood pressure; and iii) non-fasting blood and urine samples. All participants provided written informed consent.

Out of 394 pregnant women at enrolment, 72 with missing information on gestational weeks and three with missing information on the selected covariates were excluded from the analysis, leaving 319 pregnant women with complete information on covariates and outcomes of interest. There was no missing data on exposure or outcome variables (eFig. 1).

2.2. PFAS exposure

Serum concentrations of twelve PFAS were measured by high performance liquid chromatography–isotope dilution tandem mass spectrometry (HPLC–MS/MS) (Shimadzu UFLC XR 20 Prominence coupled to Sciex API 4000). Further details on the analytical method have been described elsewhere (Pitter et al., 2020). The limit of detection (LOD) of the method was estimated by injecting consecutive dilutions of calibration standards, and was 0.1 ng/mL for all PFAS. The limit of quantification (LOQ) has been chosen to warrant the same methodological performances for all analytes in the measuring range, which was 0.5–500 ng/mL, and it was experimentally estimated at 0.5 ng/mL through repeated tests.

Only three PFAS were quantifiable in at least 50% of samples and these were included in the analyses: PFOA (100%), PFOS (98.8%) and PFHxS (92.8%). Samples with a concentration below the LOQ were assigned a value equal to the LOQ divided by the square root of 2.

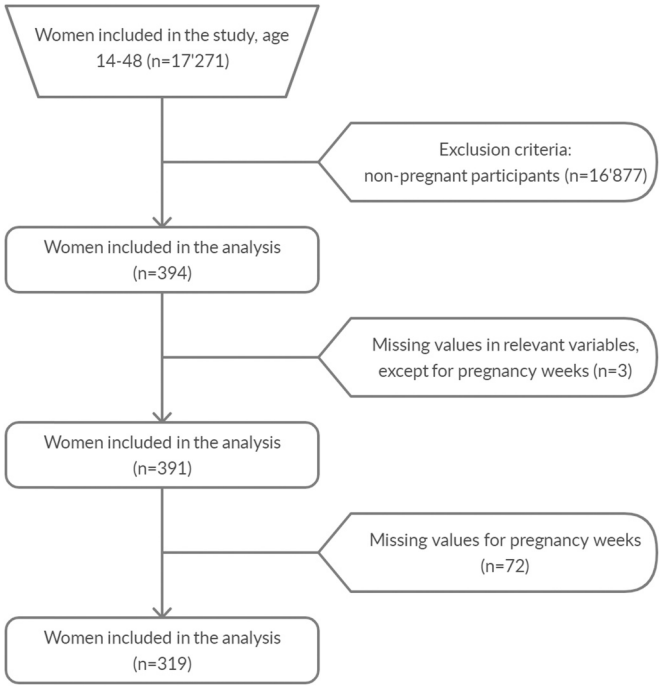
2.3. Outcome assessment

Plasma lipid parameters (TC, HDL-C, LDL-C) were measured in non-fasting plasma samples, analysed in three laboratories (Arzignano, San Bonifacio, Legnago). TC and HDL-C were measured by a direct enzymatic colorimetric assay using cholesterol esterase and cholesterol oxidase. The measurement of serum lipids was performed in a Cobas automated clinical chemistry analyser (Roche Diagnostics GmbH, Mannheim, Germany) in two laboratories and in an AU automated clinical chemistry analyser (Beckman-Coulter, CA, USA) in the third laboratory. LDL-C was calculated by the Friedewald equation when triglycerides were less than 400 mg/dL.

2.4. Covariates

Socio-demographic, lifestyle characteristics and medical history information were collected using structured computer-assisted questionnaire directly from participants during an in-person interview at the time of enrolment. In order to maximize data quality by minimizing errors and missing values, standard data checks and cleaning procedures (e.g., range and consistency checks) were performed.

The following range of potential confounders were considered based on prior literature and through the construction of a directed acyclic graph (DAG): laboratory in charge of blood sampling, smoking status (current smokers, previous smokers, non-smokers), education (Elementary/Middle school, High school, University), country of birth (Italy plus other Highly Developed Countries - HDC, High Migratory Pressure Countries- HMPC), degree of physical activity (Light, Moderate, or Heavy based on metabolic equivalents of task (METs) per hour per day), number of previous deliveries (0, 1, 2+), gestational weeks, age (years), pre-pregnancy body mass index (BMI (kg/m^2) at baseline survey), food intake (tertiles of fruit/vegetables, milk/yogurt, cheese, meat, sweet/snacks/sweet beverage, eggs, fish, bread/pasta/cereals servings per week). Pregnancy trimesters were classified according to the reported gestational week: 1st trimester 0–13 weeks, 2nd trimester 14–26 weeks, and 3rd trimester 27+ weeks.



eFig. 1. Flowchart of the exclusions.

2.5. Statistical analysis

Since the distributions of PFAS were right-skewed, exposures were natural log transformed for statistical analyses. Spearman correlation coefficients among PFAS concentrations were calculated. The relationship between PFAS, serum lipids and pregnancy trimester was evaluated using a Kruskal-Wallis non-parametric test.

We fitted generalized additive models (GAMs) with thin plate spline smooth terms (Duchon, 1977) to determine linearity of exposure–outcome associations for each PFAS. Degree of smoothing was selected by generalized cross validation as implemented in the R package mgcv (Wood and Simon, 2012) . Since the spline analysis showed associations compatible with a linear relationship on the natural-log transformed PFAS, linear regression coefficient (β) and 95% confidence intervals (CI) were reported. Exposure levels were also treated as quartiles, in order to limit the influence of extreme values.

All analyses were fully adjusted for the established set of covariates. Serum PFAS concentrations were also categorized into quartiles for all the analyses. All the continuous variables in the models (age, pregnancy BMI at baseline survey, gestational weeks) were modelled using thin plate spline. All the analyses were also stratified according to pregnancy trimester.

A sensitivity analysis of the dose-response relationship between PFOA and TC was performed adjusted by different subsets of covariates, to select the best combination of variables. We fitted a model excluding the BMI and a model considering the covariate “pregnancy trimester” instead of “gestational weeks”. We also investigated the role of liver metabolism as a possible confounder in the relationship between PFAS levels and serum lipids. In fact, PFOA activates the lipid anabolism related genes which are largely expressed in liver and suppressed lipid transport gene, potentially causing elevated lipid synthesis and fat deposits in liver cells (Wen et al., 2020). Therefore, we fitted a model including alanine aminotransferase (ALT) as continuous variable as covariate. ALT was chosen because of its correlation with both abdominal fat (Stranges et al., 2004) and with PFAS serum levels (Darrow et al., 2016; Gallo et al., 2012; Gleason et al., 2015).

The level of statistical significance was set at 0.05. All statistical analyses were performed with STATA/SE version 13.0 and R version 4.0.2 were used for statistical analyses.

3. Results

The population of 319 pregnant women included in the analysis had a mean age of 32.7 years (SD = 4.8). 101 of them (31.66%) were in the 1st trimester of gestation, 88 (27.59%) in the 2nd trimester and 130 (40.75%) in the 3rd trimester at the time of enrolment in the study. Population characteristics are shown in Table 1.

PFOA was detected at the highest level (GM 14.78 ng/mL), followed

by PFOS (GM 2.67 ng/mL) and PFHxS (GM 1.89 ng/mL) (Table 1). PFAS concentrations showed high to moderate pairwise correlations, with the stronger correlation seen between PFOA and PFHxS ($\rho = 0.89$). The correlations between PFOS with PFOA ($\rho = 0.54$) and PFHxS ($\rho = 0.56$) were moderate.

Table 2 depicts the exposure levels of PFAS and lipid levels in study population throughout all three trimesters of pregnancy. There was some variability between trimesters and weak evidence of a trend but only for PFOA. (Table 2).

The median plasma concentrations for TC, HDL-C and LDL-C were 197, 68, and 101 mg/dL, respectively (Table 1). The plasma levels of TC, HDL-C and LDL-C increased steadily throughout the trimesters ($p < 0.01$ for all outcomes) (Table 2).

The results on GAM models assessing the relationship between each PFAS, considered as ln-linear predictors or categorical (quartiles of exposure), and cholesterol levels after adjustment for confounding factors are presented in Table 3. There was generally a positive association for HDL in relation to all three PFAS and inverse associations for LDL. For cholesterol, only PFOA showed an association, with a decrease of −4.3 mg/dL (95% CI: −8.3,−0.2) for each ln-increase of PFOA, and an increasing effect across quartiles. Each ln-increase in PFOA was associated with an increase in HDL-C of 2.0 mg/dL (95% CI: 0.5,3.5), 4.8 mg/dL for PFOS (95% CI: 2.1,7.5), and 2.6 mg/dL (95% CI: 0.7,4.5) for PFHxS. Subjects in the highest PFOS quartile had 9.2 mg/dL (95% CI: 4.7,13.8) higher HDL-C levels than those in the lowest quartile. Slightly lower increments were seen for the other PFAS.

In the other direction, negative associations between PFOA and PFHxS and LDL-C were found. A 1-unit increase in ln-PFOA and ln-PFHxS was associated with −6.7 mg/dL, (95% CI: −10.2,−3.3) and −8.2 mg/dL (95% CI: −12.5,−3.8) decrease in LDL-C, respectively. Subjects in the highest PFOA quartile had −21.2 mg/dL (95% CI: −32.2,−10.1) lower HDL-C levels than those in the lower quartile. For subjects in the highest PFHxS quartile the decrease was −18.5 mg/dL (95% CI: −29.3,−7.7) relative to the first quartile. The association between PFOS and LDL-C was slightly negative but not significant. As a sensitivity analysis, adjusting for pregnancy trimesters instead of gestational weeks did not modify the effect estimates in models.

Table 4 shows the relationship of PFAS and cholesterol levels stratified by trimester of gestation. During the 1st trimester, HDL-C tended to be associated positively with the clearest association with PFOS (8.31 mg/dL per ln-PFOS increase, 95% CI: 1.07,15.55) and PFHxS (5.27 mg/dL per ln-PFHxS increase, 95% CI: 0.62,9.92). In the 2nd trimester no associations were evident. In the 3rd trimester, rather strong inverse relationships were seen for TC and LDL-C and PFOA and PFHxS and less clearly for PFOS. Foreach ln-increase in PFOA a drop of −11.02 mg/dL (95% CI: −18.07,−3.96) and −13.92 mg/dL (95% CI: −20.31,−7.52) for TC and LDL-C, respectively. Similarly, a decrease of −14.27 mg/dL (95% CI: −23.51,−5.03) was seen for TC and − 17.36 mg/dL (−25.78,−8.94) for LDL-C for each ln-increase in PFHxS.

A sensitivity analysis was performed to examine the potential for confounding by the time-lag between the interview and the beginning of the study. Adjustment for this variable did not materially change the observed association between PFAS and TC levels. Additionally, the analysis without the adjustment for BMI did not change the results of the associations between PFAS and cholesterol levels. Finally, the analysis with the results adjusted for ALT are presented in Supplementary Tables 1 and 2; ALT did not modify the associations between PFAS and cholesterol levels observed.

Table 1
Characteristics of the study population (n = 319).

		TOTAL (n = 319)		
Exposure variables	GM	Mean (SD)	Min-max	Median (Q1-Q3)
PFOA	14.8	26.2 (28.8)	0.5–181	16 (6.7–35.5)
PFOS	2.7	3.2 (2.0)	0.35–15.8	2.7 (1.9–3.8)
PFHxS	1.9	2.8 (2.5)	0.35–16	1.9 (1–3.7)
Outcomes		Mean (SD)	Min-max	Median (Q1-Q3)
Total Cholesterol		202.7 (52.8)	109–370	197 (163–234)
HDL Cholesterol		69.8 (15.2)	35–114	68 (59–79)
LDL Cholesterol		107.5 (38.8)	0–275	101 (82–128)
Continuous covariates		Mean (SD)	Min-max	Median (Q1-Q3)
Age		32.7 (4.8)	18–44	33 (29–36)
Gestation weeks		21.5 (10.8)	0–41	22 (12–31)
BMI		24.8 (4.3)	16.6–41.5	24.0 (21.6–27.2)
Categorical covariates		Frequency (%)		
Laboratory				
Arzignano		153 (48.0)		
Legnago		78 (24.5)		
San Bonifacio		88 (27.6)		
Number of previous deliveries				
0		164 (51.4)		
1		116 (36.4)		
2 +		39 (12.2)		
Education				
Elementary/Middle school		41 (12.9)		
High school		163 (51.1)		
University		115 (36.1)		
Physical activity[a]				
Light		271 (85.0)		
Moderate		27 (8.5)		
Heavy		21 (6.6)		
Country of birth				
HDC		279 (87.5)		
HMPC		40 (12.5)		
Smoking habit				
Non-smokers		215 (67.4)		
Current smokers		20 (6.3)		
Previous smokers		84 (26.3)		

[a] defined based on an algorithm that combined information reported by each subject to intensity, duration and frequency of all types of physical activity practiced during the week.

4. Discussion

To our knowledge, this is the first study that provides data on the associations of PFAS and lipids in a population of highly exposed pregnant women, and the first study that stratified the results by trimester of pregnancy.

Overall, in this relatively small population of highly exposed pregnant women there was no clear positive association between TC and PFOA, PFOS and PFHxS. In contrast to a number of previous studies, the pattern even suggested a modest inverse relationship. Consistent with previous studies, we found a positive association between HDL-C and all three analysed PFAS. Contrary to previous findings conducted in both pregnant and non-pregnant women, though, we found a negative association between PFOA and PFHxS and LDL-C. Most importantly, the associations between PFAS concentrations and cholesterol profile seemed to differ by trimester of pregnancy. In particular, the inverse association between PFAS and LDL-C was seen only in the third trimester of pregnancy.

Previous studies which examined the associations between PFAS and lipid profiles in pregnant women only included a homogeneous population by gestational week, precluding the examination of patterns across trimester. Matilla-Santander et al. (2017) considered 2150 women in the first trimester of pregnancy. The population of 891 women included in the study by Starling et al. (2014), was overwhelmingly in the 2nd trimester of gestation., The study by Skuladottir et al. (2015), examined 854 women in the 30th gestational week, and the study by Gardener et al. considered 433 women in the third trimester of pregnancy (Gardener et al., 2021). Finally, the study by Yang et al. included 436 women and analysed PFAS from a blood draw during the first trimester of pregnancy, and lipids levels from a blood draw in the late term of pregnancy (Yang et al., 2020). The range of gestational weeks of our population was from 0 to 41, with 32%, 28% and 41% in the 1st, 2nd and 3rd trimester, respectively.

The association of PFOA with TC was investigated by all- studies, and

Table 2
Characteristics of the study population (n = 319), stratified by pregnancy trimester.

Variable	I° TRIMESTER (n = 101)			II° TRIMESTER (n = 88)			III° TRIMESTER (n = 130)			p-value[a]
	Mean (SD)	min-max	Median (Q1-Q3)	Mean (SD)	min-max	Median (Q1-Q3)	Mean (SD)	min-max	Median (Q1-Q3)	
Exposure variables										
PFOA	29.9 (32.5)	1.5–181	17.7 (8.9–35.9)	25.3 (27.8)	0.6–163	15.4 (4.7–35.5)	23.99 (26.15)	0.5–144.7	14.5 (6.5–34.4)	0.204
PFOS	3. 5 (2.0)	0.8–11.1	2.9 (2.2–3.9)	2.7 (1.3)	0.35–8.4	2.5 (1.8–3.5)	3.26 (2.25)	0.35–15.8	2.9 (1.8–4.2)	0.026
PFHxS	2.9 (2. 7)	0.35–16	2.1 (1.1–4.1)	2.6 (2.5)	0.35–14.8	1.7 (0.8–3.4)	2.7 (2.44)	0.35–14	1.9 (1–3.7)	0.549
Outcomes										
Total Cholesterol	166.2 (34.0)	111–316	164 (139–189)	183.1 (34.1)	109–269	182.5 (159.5–206.5)	244.3 (46.2)	127–370	236 (213–271)	0.0001
HDL Cholesterol	63.2 (14.0)	35–108	62 (54–71)	67.3 (14.6)	39–106	65.5 (57–75)	76.7 (13.7)	44–114	75 (67–87)	0.0001
LDL Cholesterol	88.4 (26.3)	35–184	88 (70–103)	94.3 (24.6)	42–160	94 (76–115)	131.5 (42.3)	0–275	127 (107–160)	0.0001
Age	32.7 (4.1)	19–44	32 (30–35)	32.5 (4.8)	22–43	33 (29–36)	32.9 (5.2)	18–44	34 (29–37)	0.6726
Gestational weeks	8.9 (3.0)	0–13	9 (7–11)	19.5 (3.8)	14–26	19 (16–23.5)	32.8 (3.6)	27–41	32 (30–36)	–
BMI	23.1 (4.5)	16.56–41.5	22.2 (20.2–24.9)	24.4 (3.6)	18.96–35.57	23.9 (21.4–26.7)	26.4 (3.9)	18.07–40.4	25.5 (23.7–28.7)	0.0001

[a] Kruskal-Wallis test

Table 3
Association between PFAS (ln ng/mL) and lipid profile from GAM models (n = 319), adjusted β coefficients[a] and 95% Confidence Intervals (CI).

PFAS	Total Cholesterol β (CI 95%)	HDL Cholesterol β (CI 95%)	LDL Cholesterol β (CI 95%)
PFOA			
per ln-ng/mL	**−4.25 (−8.26,−0.23)**	**2.01 (0.53,3.48)**	**–6.74 (−10.15,−3.34)**
1Q (0.5–6.7)	*213.37*	*68.37*	*122.81*
2Q (7–16)	–1.12 (−13.24,11.0)	**4.56 (0.13,9.00)**	–4.70 (−15.02,5.62)
3Q (16.2–35.5)	**–12.65 (−**(Liew et al., 2014)**25.25,−0.06)**	3.74 (−0.88,8.37)	**–15.81 (−26.55,−5.07)**
4Q (35.6–181)	**–13.76 (−26.68,−0.83)**	**6.88 (2.14,11.62)**	**–21.17 (−32.22,−10.12)**
PFOS			
per ln-ng/mL	3.01 (−4.51,10.53)	**4.84 (2.15,7.54)**	–2.50 (−8.99,3.98)
(0.35–1.9)	*199.06*	*68.67*	*108.24*
(2–2.7)	4.42 (−8.21,17.05)	**8.60 (4.07,13.14)**	–2.76 (−13.73,8.21)
(2.8–3.8)	–1.65 (−13.80,10.50)	**4.81 (0.49,9.14)**	–5.10 (−15.63,5.43)
(3.9–15.8)	9.89 (−2.82,22.59)	**9.20 (4.65,13.76)**	0.01 (−11.04,11.06)
PFHxS			
per ln-ng/mL	–4.91 (−10.06,0.24)	**2.58 (0.69,4.46)**	**–8.17 (−12.54,−3.81)**
(0.35–1)	*209.83*	*68.42*	*119.31*
(1.1–1.9)	1.86 (−10.30,14.02)	4.34 (−0.11,8.78)	–1.29 (−11.69,9.11)
(2–3.7)	–4.61 (−17.07,7.85)	**6.63 (2.07,11.19)**	**–11.15 (−21.71,−0.60)**
(3.8–16)	–11.60 (−24.36,1.16)	**6.13 (1.49,10.77)**	**–18.46 (−29.27,−7.66)**

Figures in bold are statistically significant results (p-value < 0.05)
[a] adjusted by age, number of previous deliveries, BMI, physical activity, smoking habits, country of birth, education level, laboratory in charge of the analyses of serum lipids, gestation weeks and reported fish consumption (in tertiles)

a positive relationship was found only in two of them Matilla-Santander et al. (2017) and Skuladottir et al. (2015). Three out of five studies also found a positive association between PFOS and TC (Gardener et al., 2021; Skuladottir et al., 2015; Starling et al., 2014). These results were not confirmed in our study. In particular our results on a negative association in the third trimester were opposite to the positive associations reported for the third trimester measurements in Skuladottir et al. (2015) and Gardener et al. (2021). Only one out of four studies that analysed PFHxS association with TC found a positive relationship (Yang et al., 2020).

Starling et al. and Yang et al. investigated the HDL-C and LDL-C associations with PFAS (Starling et al., 2014; Yang et al., 2020). Similar to the results of our study, Starling et al. found that PFOS, PFOA and PFHxS (together with all other analysed PFAS) had higher HDL-C levels associated with the highest quartile of exposure, compared to the lowest quartile. Yang et al., too, found that serum PFHxS was positively associated with serum HDL-C levels. As for LDL-C, in Starling et al., the beta-coefficient for an ln-unit change in PFOS was elevated, but it was not significant and none of the other six PFAS were associated with LDL-C. In the paper by Yang et al., although the association of PFOA with HDL-C and LDL-C was non-significant, PFOA was negatively associated with the LDL/HDL ratio. Whereas, in the present study we found a negative association between PFOA and PFHxS and LDL-C.

The discrepancies in results between our study and other studies may be explained in part by higher PFAS concentrations measured in our population and a dominant environmental source, with values of PFOA 6 times or more and PFHxS 3 times higher than concentrations reported in previous studies with a background exposure. These differences in concentration were not seen for PFOS, though. Therefore, since we found the same patterns of association for both PFOA and PFOS and cholesterol levels, there might be other factors influencing the results.

Our results indicated in the 1st trimester a positive association between PFOS and TC and between PFHxS and HDL-C. Non-pregnant women recruited in the Veneto health surveillance plan (age range

Table 4
Association between PFAS (ln ng/mL) and lipid profile from GAM models (n = 319), adjusted β coefficients[a] and 95% Confidence Intervals (CI), stratified by pregnancy trimester.

	TOTAL CHOLESTEROL		HDL CHOLESTEROL		LDL CHOLESTEROL	
	Gestation trimesters	β (CI 95%)	Gestation trimesters	β (CI 95%)	Gestation trimesters	β (CI 95%)
PFOA						
I Trimester	Per ln-ng/mL	7.62 (−1.33,16.57)	Per ln-ng/mL	2.88 (−1.03,6.8)	Per ln-ng/mL	3.45 (−3.30,10.22)
	1Q (1.5–8.9)	*145.44*	1Q (1.5–8.9)	*56.14*	1Q (1.5–8.9)	*81.17*
	2Q (9.1–17.7)	18.7 (−4.65,42.07)	2Q (9.1–17.7)	7.49 (−2.08,17.07)	2Q (9.1–17.7)	8.48 (−9.91,26.88)
	3Q (18.2–35.9)	7.85 (−15.63,31.34)	3Q (18.2–35.9)	3.91 (−5.68,13.52)	3Q (18.2–35.9)	0.49 (−17.95,18.93)
	4Q (37.2–181)	18.85 (−5.49,43.2)	4Q (37.2–181)	**12.32 (2.36,22.28)**	4Q (37.2–181)	5.05 (−14.07,24.18)
II Trimester	Per ln-ng/mL	–0.55 (−7.20,6.08)	Per ln-ng/mL	1.34 (−1.85,4.54)	Per ln-ng/mL	–1.8 (−6.93,3.31)
	1Q (0.6–4.6)	*206.28*	1Q (0.6–4.6)	*55.51*	1Q (0.6–4.6)	*125.32*
	2Q (4.8–14.7)	–4.78 (−25.62,16.05)	2Q (4.8–14.7)	4.61 (−4.60,13.84)	2Q (4.8–14.7)	–10.61 (−26.9,5.67)
	3Q (16–35.4)	–5.67 (−28.46,17.11)	3Q (16–35.4)	6.03 (−4.05,16.12)	3Q (16–35.4)	–12.53 (−30.03,4.95)
	4Q (35.6–163)	–8.5 (−31.64,14.62)	4Q (35.6–163)	6.71 (−3.53,16.95)	4Q (35.6–163)	–15.67 (−33.46,2.12)
III Trimester	Per ln-ng/mL	**–11.02 (−18.07,−3.96)**	Per ln-ng/mL	1.98 (−0.15,4.13)	Per ln-ng/mL	**–13.92 (−20.31,−7.52)**
	1Q (0.5–6.5)	*300.17*	1Q (0.5–6.5)	*76.52*	1Q (0.5–6.5)	*187.63*
	2Q (6.6–14.3)	–6.95 (−30.65,16.74)	2Q (6.6–14.3)	5.93 (−1.02,12.89)	2Q (6.6–14.3)	–8.57 (−30.11,12.96)
	3Q (14.6–34.4)	**–29.62 (−53.12,−6.13)**	3Q (14.6–34.4)	**7.24 (0.39,14.09)**	3Q (14.6–34.4)	**–27.79 (−49.15,−6.43)**
	4Q (35.2–144.7)	**–40.48 (−65.15,−15.81)**	4Q (35.2–144.7)	**9.53 (2.30,16.75)**	4Q (35.2–144.7)	**–48.6 (−71.21,−25.99)**
PFOS						
I Trimester	Per ln-ng/mL	15.34 (−1.08,31.78)	Per ln-ng/mL	**8.31 (1.07,15.55)**	Per ln-ng/mL	6.65 (−5.9,19.2)
	1Q (0.8–2.2)	*140.76*	1Q (0.8–2.2)	*58.68*	1Q (0.8–2.2)	*69.56*
	2Q (2.3–2.9)	2.53 (−20.66,25.73)	2Q (2.3–2.9)	7.94 (−1.68,17.57)	2Q (2.3–2.9)	–3.5 (−21.15,14.13)
	3Q (3–3.9)	21.00 (−3.65,45.65)	3Q (3–3.9)	5.96 (−4.25,16.18)	3Q (3–3.9)	16.63 (−2.13,5.36)
	4Q (4.2–11.1)	8.86 (−14.42,32.14)	4Q (4.2–11.1)	9.39 (−0.24,19.04)	4Q (4.2–11.1)	–0.64 (−18.33,17.03)
II Trimester	Per ln-ng/mL	–2.86 (−17.86,12.13)	Per ln-ng/mL	3.76 (−3.35,10.87)	Per ln-ng/mL	–3.51 (−14.72,7.69)
	1Q (0.35–1.8)	*198.26*	1Q (0.35–1.8)	*52.82*	1Q (0.35–1.8)	*116.47*
	2Q (1.9–2.4)	3.01 (−20.08,26.1)	2Q (1.9–2.4)	9.71 (−0.13,19.57)	2Q (1.9–2.4)	–4.04 (−22.23,14.14)
	3Q (2.5–3.4)	–1.32 (−23.86,21.2)	3Q (2.5–3.4)	1.23 (−8.37,10.84)	3Q (2.5–3.4)	0.59 (−17.22,18.4)
	4Q (3.5–8.4)	3.06 (−20.52,26.66)	4Q (3.5–8.4)	**10.07 (0.01,20.13)**	4Q (3.5–8.4)	–4.56 (−23.81,14.68)
III Trimester	Per ln-ng/mL	–4.51 (−18.13,9.09)	Per ln-ng/mL	**4.25 (0.26,8.24)**	Per ln-ng/mL	–10.05 (−22.71,2.61)
	1Q (0.35–1.8)	*284.64*	1Q (0.35–1.8)	*76.62*	1Q (0.35–1.8)	*174.85*
	2Q (1.9–2.8)	**–31.64 (−56.9,−6.38)**	2Q (1.9–2.8)	**7.57 (0.31,14.83)**	2Q (1.9–2.8)	**–32.16 (−55.9,−8.42)**
	3Q (2.9–4.2)	**–28.75 (−52.59,−4.9)**	3Q (2.9–4.2)	**10.70 (3.85,17.56)**	3Q (2.9–4.2)	**–31.94 (−54.39,−9.5)**
	4Q (4.3–15.8)	–3.18 (−28.23,21.86)	4Q (4.3–15.8)	6.11 (−1.08,13.31)	4Q (4.3–15.8)	–10.74 (−34.3,12.8)
PFHxS						
I Trimester	Per ln-ng/mL	10.08 (−0.58,20.75)	Per ln-ng/mL	**5.27 (0.62,9.92)**	Per ln-ng/mL	3.43 (−4.68,11.56)
	1Q (0.35–1.1)	*142.55*	1Q (0.35–1.1)	*54.06*	1Q (0.35–1.1)	*78.5*
	2Q (1.2–2.1)	16.31 (−6.91,39.54)	2Q (1.2–2.1)	4.83 (−4.56,14.23)	2Q (1.2–2.1)	11.49 (−6.53,29.53)
	3Q (2.2–4.1)	5.66 (−17.79,29.11)	3Q (2.2–4.1)	3.79 (−5.73,13.31)	3Q (2.2–4.1)	-0.01 (−18.27,18.24)
	4Q (4.2–16)	16.22 (−8.15,40.6)	4Q (4.2–16)	**13.08 (3.18,22.98)**	4Q (4.2–16)	2.28 (−16.68,21.25)
II Trimester	Per ln-ng/mL	-1.13 (−10.18,7.92)	Per ln-ng/mL	0.4 (−3.94,4.76)	Per ln-ng/mL	-1.1 (−8.02,5.82)
	1Q (0.35–0.8)	*207.65*	1Q (0.35–0.8)	*57.3*	1Q (0.35–0.8)	*125.9*
	2Q (0.9–1.7)	-8.05 (−30.21,14.09)	2Q (0.9–1.7)	7.47 (−2.31,17.26)	2Q (0.9–1.7)	-12.04 (−29.16,5.08)
	3Q (1.9–3.3)	-6.48 (−30.93,17.97)	3Q (1.9–3.3)	6.46 (−4.34,17.27)	3Q (1.9–3.3)	-9.52 (−28.33,9.29)
	4Q (3.4–14.8)	-8.35 (−32.13,15.42)	4Q (3.4–14.8)	3.37 (−7.13,13.88)	4Q (3.4–14.8)	-12.69 (−31.19,5.8)
III Trimester	Per ln-ng/mL	**-14.27 (−23.51,−5.03)**	Per ln-ng/mL	**2.88 (0.05,5.71)**	Per ln-ng/mL	**-17.36 (−25.78,−8.94)**
	1Q (0.35–1)	*286.97*	1Q (0.35–1)	*79.48*	1Q (0.35–1)	*173.07*
	2Q (1.1–1.9)	-10.86 (−36.43,14.7)	2Q (1.1–1.9)	3.97 (−3.38,11.34)	2Q (1.1–1.9)	-8.82 (−32.43,14.78)
	3Q (2–3.7)	**-26.27 (−50.3,−2.24)**	3Q (2–3.7)	**8.67 (1.74,15.6)**	3Q (2–3.7)	**-26.18 (−48.15,−4.21)**
	4Q (3.8–14)	**-30.68 (−55.44,−5.92)**	4Q (3.8–14)	6.99 (−0.15,14.14)	4Q (3.8–14)	**-35.88 (−58.52,−13.24)**

[a] adjusted by age, number of previous deliveries, BMI, physical activity, smoking habits, country of birth, education level, laboratory in charge of the analyses of serum lipids, gestation weeks and reported fish consumption (in tertiles)

20–39 years) showed similar serum cholesterol levels (means 175.7 mg/dL for TC, 64.1 mg/dL for HDL-C and 94.2 mg/dL for LDL-C), and PFAS levels (means: 36.89 ng/mL for PFOA, 3.59 ng/mL for PFOS and 3.23 ng/mL for PFHxS) to that of women in the 1st trimester (Canova et al., 2020). Remarkably, non-pregnant women showed a positive relationship of PFAS with HDL-Cholesterol that was nonsignificant among males, and a lower magnitude of the effect on LDL-C compared to men (Canova et al., 2020). Few studies have published gender-specific results on lipids and PFAS associations (Canova et al., 2020; Frisbee et al., 2010; Winquist and Steenland, 2014), therefore limiting comparisons with non-pregnant women.

However, in the 3rd trimester a strong inverse relationship was seen between PFOA and PFHxS and both TC and LDL-C. This unexpected pattern, opposite in direction to what would have been expected, could potentially be explained by different behavior of PFAS and lipid levels among pregnancy trimesters influenced by maternal excretion and differential transfer and bioaccumulation of lipids and PFAS in the placenta and foetus across gestation.

In fact, in our study, the concentration of PFOA decreased during pregnancy from 17.7 ng/mL in the first trimester, to 14.5 ng/mL in the third trimester. The same pattern has been also found in previous studies with background exposure (Mamsen et al., 2019; Monroy et al., 2008). In a previous study where PFAS serum samples were collected at 24–28 weeks of gestation and at delivery, authors found that the concentrations of PFOS and PFOA were significantly higher at mid-pregnancy compared with delivery (median PFOA level of 2.13 ng/mL at 24/28 weeks and 1.58 ng/mL at delivery) (Monroy et al., 2008). Another study examining women in different trimesters of gestation found that the maternal serum PFAS concentrations were higher in the first trimester than the second and third trimesters, with PFOA levels of 1.51 ng/mL and 1.36 ng/mL in the first and third trimester, respectively (Mamsen et al., 2019). These changes throughout the gestation could be explained by the physiological increase in maternal blood volume, renal clearance during pregnancy or transfer of PFAS to the fetus (Loccisano et al.,

2013). The study by Monroy et al. found that PFOA and PFOS were also detectable, to a lesser extent, in 100% of samples of umbilical cord, concluding that PFOA and PFOS can cross the fetal–placental barrier during pregnancy resulting in exposure of the developing fetus (Monroy et al., 2008). Furthermore, there was a high correlation between maternal serum levels and cord blood at delivery. The study by Mamsen et al. analysed presence of PFAS in the placenta and fetal tissues and found that fetal age was positively associated with the placenta: maternal serum ratios of PFOS, PFOA and PFNA, suggesting that these substances accumulate in the placenta across gestation and give rise to an increased fetal burden (Mamsen et al., 2019). Prenatal exposure to PFOS and PFOA has been associated with low birth weight in humans (Fei et al., 2007; Lauritzen et al., 2017; Maisonet et al., 2012), although reports were inconsistent (Bach et al., 2015). In rodents, high exposure of PFOS and PFOA during pregnancy have been associated with reduced postnatal survival, lower birth weight, decreased growth of the pups, disturbed lactation (Lau et al., 2006, 2004, 2003; Olsen et al., 2009), and disrupted thyroid function (Yu et al., 2009). Also, concentrations of PFOS and PFOA in cord blood have been associated with an increased risk of congenital cerebral palsy in Danish boys (Liew et al., 2014) and PFOA in cord plasma has been suggested to increase the thyroxine hormone level in newborn girls (de Cock et al., 2014). It has been also demonstrated that lipid parameters are elevated in pregnancy. TC and LDL-C start to rise significantly in the second and third trimesters (Brizzi et al., 1999; Piechota and Staszewski, 1992), while for HDL-C the trend is less linear, with a maximum increase in the 2nd trimester and a decrease hereafter (Piechota and Staszewski, 1992). Also, some studies support the hypothesis that maternal cholesterol can cross the placenta, even if the fetus can produce endogenous cholesterol and has some ability to regulate its own cholesterol levels (Woollett, 2005). In fact, the correlation between maternal and fetal cholesterol seems to be strong up to the 28th week of gestation only, and not correlated at birth (Napoli et al., 1997). A recent study by Spratlen et al. on the correlation between PFAS and lipids in cord blood found that there were significant associations between higher levels of PFOS, PFOA, and PFHxS with higher total cord lipids (Spratlen et al., 2020). This association may also explain some health outcomes in the newborns. Higher cord lipid levels have been consistently reported in low birth weight and small-for-gestational-age newborns, both established risk factors for cardiovascular disease in adulthood (Crispi et al., 2018; Smith et al., 2016).

To explain our observations, it is also possible to hypothesize a role for placental transfer of PFAS. It has been demonstrated that PFAS may bind to albumin (Fan et al., 2020) and, although albumin levels are positively associated with PFASs also in pregnant women (Jiang et al., 2014), passive diffusion of PFAS is more likely involved for the placental transport of free fraction, as albumin can hardly transfer across the placental barrier (Lambot et al., 2006). During pregnancy, and particularly during the 3rd trimester, albumin concentration is reduced in the mother circulation due to plasma volume expansion, increased extravascular volume and increase in urinary excretion (Higby et al., 1994; Kristensen et al., 2007). This process may contribute to an altered equilibrium between free and albumin-bound fraction of PFAS in favor of an increase in the free fraction, readily available for placental transfer. Fan et al. (2020) demonstrated that albumin mediates the toxic effect of PFAS exposure on the levels of serum lipids. Therefore, the decrease in circulating levels of albumin-bound PFAS may be associated to a reduction of PFAS-induced lipid changes in pregnant women. One can therefore hypothesize that the lower availability of albumin-bound PFAS in maternal serum caused by placental transfer of free fraction of PFAS can, in some way, disrupts the positive association of PFAS with lipids observed in early phases of pregnancy. It should be noted that these explanations are speculative and that this and other mechanisms should be explored. Moreover, whatever the relative contribution of the proposed mechanism to the inversion of associations found at the 3rd semester, it is probably overcome by the high increase in lipids levels observed in maternal serum in this period.

Given all these differences, in both lipids and PFAS during pregnancy, it is plausible that whatever causal or non-causal mechanism leads to observed associations between PFAS and lipids, the associations differ in pregnant women compared to non-pregnant women, and throughout the trimesters of pregnancy. Also, given the independent effect of pregnancy on PFAS and lipids, isolating the direct effect of PFAS on lipids over the course of pregnancy is a complex challenge as reflected in our findings. All of these aspects can lead to exposure misclassification when PFAS levels are measured at different pregnancy time-points.

The strengths of our study are the adjustment for a large set of possible confounders and the robust statistical methods. The limitations are the small sample size, and the cross-sectional design which does not allow causal interpretation of the finding. Another limitation is that we did not retrieve any data about previous breastfeeding of our subjects. Breastfeeding is one of the major determinants of PFAS excretion and serum levels of adult women (Herrick et al., 2017; Liu et al., 2011). Nevertheless, we adjusted our models for parity that could reflect, although not precisely, number of previous breastfed children. We also did not retrieve information on the pre-pregnancy BMI and changes in BMI (weight gain) in different gestational weeks during the pregnancy. To avoid possible bias related to the changes in pregnancy BMI, a sensitivity analysis was conducted excluding information on the pregnancy BMI at baseline survey as covariate and found a similar association between PFOA and TC.

Another possible limitation is that PFAS have been suggested to impair fertility (Bach et al., 2016) and to increase risk of miscarriages (Darrow et al., 2014). All these mechanisms could result in a selection bias, for which those most highly exposed might possibly have a lower chance of being enrolled in a pregnancy cohort.

In this study, serum lipids were analysed in 3 different labs, using different analytical platforms. Although not identical, these methods have been shown to be correlated (Kim et al., 2014). With adjusting for laboratory in charge of blood sampling, we accounted for any effects of the different analytical analyses. Finally, no adjustment was possible for fasting because the information of time since the last meal was lacking. Fasting status may affect serum lipid levels, however, circulating levels of plasma lipids are modestly influenced by food consumption. Studies comparing fasting with non-fasting lipid levels stated that there was no relevant change in TC, LDL-C, and HDL-C. (Dipankar and Pawar, 2019; Langsted et al., 2014; Langsted and Nordestgaard, 2019; Mora et al., 2008). Therefore, we believe it's unlikely that the variability of fasting time significantly affected serum cholesterol levels.

5. Conclusion

Altogether, despite the small sample size, this study makes an innovative contribution, that should be confirmed by further studies with a bigger sample size. For the first time it has been found that the associations between PFAS and cholesterol profiles change throughout all three trimesters of pregnancy. While in the first trimester the patterns of associations between PFAS and LDL-C were similar to those of non-pregnant women, the associations were inverted during the third trimester of gestation, with a negative relationship. Prospective studies that evaluated effects of prenatal exposure to PFAS have utilized different pregnancy time-points, varying from the 1st trimester to delivery (Liew et al., 2018). These results, if confirmed, indicate that the timing of PFAS measurement during pregnancy should be carefully evaluated, when planning longitudinal studies examining effects of PFAS during pregnancy on gestational outcomes or children related to serum lipids amounts.

Funding

CORIS/REGIONE VENETO (Italy) supported this research with a

grant to Cristina Canova. Award Number: CANO_ALFREVE18_01 (CONVENZIONE CORIS PER REALIZZAZIONE PROGETTI DI RICERCA INNOVATIVI SUI PFAS 2017–18).

CRediT authorship contribution statement

Teresa Dalla Zuanna: Investigation, Conceptualization, Methodology, Writing - original draft preparation. **David A. Savitz:** Conceptualization, Methodology, Writing - review & editing. **Giulia Barbieri:** Data curation, Formal analysis, Software. **Gisella Pitter:** Conceptualization, Writing - review & editing. **Maryam Zare Jeddi:** Conceptualization, Writing - review & editing. **Francesca Daprà:** Funding acquisition, Writing - review & editing. **Aline S.C. Fabricio:** Conceptualization, Writing - review & editing. **Francesca Russo:** Funding acquisition, Investigation, Writing - review & editing. **Tony Fletcher:** Conceptualization, Methodology, Writing - review & editing. **Cristina Canova:** Conceptualization, Methodology, Resource, Roles/Writing - original draft, Supervision.

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.

Acknowledgements

The authors gratefully acknowledge the contributions of Filippo Da Re (Regional Directorate of Prevention, Food Safety, Veterinary Public Health - Regione del Veneto), Elena Narne (Screening and Health Impact Assessment Unit - Azienda Zero), Rinaldo Zolin (Local Health Unit 8 Berica), Annamaria Bettega (Local Health Unit 8 Berica), Lorena Zambelli (Local Health Unit 9 Scaligera), Katia Grego (Local Health Unit 9 Scaligera), Daniele Bottigliengo, Ileana Baldi Dario Gregori (University of Padova).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2020.111805.

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