A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP11840.

Associations between Per- and Polyfluoroalkyl Substances Exposures and Blood Lipid Levels among Adults—A Meta-Analysis

Binkai Liu,[1,2] Lu Zhu,[2*] Molin Wang,[1,3,4] and Qi Sun[1,2,4]*

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[2]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[3]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[4]Channing Division of Network Medicine, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, USA

Background: Associations between per- and polyfluoroalkyl substances (PFAS) and blood lipid levels in humans were mixed.

Objectives: The objective of this meta-analysis was to summarize associations between PFAS and blood lipids in adults.

Methods: A literature search was conducted on PubMed and Web of Science for articles published through 13 May 2022 that examined associations between PFAS and blood lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triacylglycerols (TGs). Inclusion criteria included the presence of associations between five PFAS (PFOA, PFOS, PFHxS, PFDA, and PFNA) and four blood lipid measures (TC, HDL-C, LDL-C, and TGs) in adults. Data on study characteristics and PFAS–lipid associations were extracted. Assessments of individual study quality were performed. Associations of changes of blood lipid levels corresponding to 1 interquartile range (IQR)-unit increase of blood PFAS levels were pooled using random effects models. Dose–response relationships were examined.

Results: Twenty-nine publications were included in the present analyses. Every IQR increase of PFOA was significantly associated with a 2.1-mg/dL increase in TC (95% CI: 1.2, 3.0), a 1.3-mg/dL increase in TGs (95% CI: 0.1, 2.4), and a 1.4-mg/dL increase in LDL-C (95% CI: 0.6, 2.2). PFOS was also significantly associated with TC and LDL-C levels, and the corresponding values were 2.6 (95% CI: 1.5, 3.6) and 1.9 (95% CI: 0.9, 3.0), respectively. Associations of PFOS and PFOA with HDL-C levels were largely null. For minor PFAS species, PFHxS was significantly associated with higher levels of HDL-C [0.8 (95% CI: 0.5, 1.2)]. Inverse associations were observed between PFDA and TGs [−5.0 (95% CI: −8.1, −1.9)] and between PFNA and TGs [−1.7 (95% CI: −3.5, −0.02)], whereas a positive association was observed between PFDA and HDL-C [1.4 (95% CI: 0.1, 2.7)]. Nonsignificant nonlinear dose–response relationships were identified for associations of PFOA and PFOS with certain blood lipids.

Discussion: PFOA and PFOS were significantly associated with TC and LDL-C levels in adults. Whether these findings may translate into an elevated cardiovascular disease risk associated with PFAS exposure warrants further investigation. https://doi.org/10.1289/EHP11840

Introduction

Per- and polyfluoroalkyl substances (PFAS) are chemicals that are widely used in numerous consumer and industrial products and are highly persistent in the environment and human bodies.[1] Since the early 2000s, many countries have implemented laws and regulations to reduce the production of PFAS, although production continues in other countries.[2] PFAS are now ubiquitous in the environment through transportation in the hydrologic cycle, causing deleterious effects in the environment and on human health at a global scale.[3] Of potential adverse health effects, it is well understood that PFAS, owing to their structural resemblance of lipid molecules, may disrupt human lipid metabolism by activating nuclear receptors, such as peroxisome proliferator-activating receptor alpha (PPARα).[4–6] Blood lipids are potential causal risk factors for cardiovascular disease (CVD).[7,8] Many epidemiological studies have been conducted to examine potential associations between PFAS exposure and blood lipid levels, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triacylglycerols (TGs) in human populations, although the findings were noticeably mixed.[9–12] Previous reviews on this topic were largely qualitative narratives and thus were not able to provide a quantitative overview and summary of associations between PFAS and blood lipid levels.[13–16]

To fill this knowledge gap, we conducted a meta-analysis to summarize associations between PFAS exposure and human blood lipid levels in adults. In light of the dramatic variations in PFAS exposure levels across different studies, we also specifically examined associations by baseline PFAS levels and conducted a dose–response meta-analysis to examine whether the associations of interest may depend on PFAS exposure levels.

Methods

Data Sources and Searches

This meta-analysis was conducted under a predefined protocol, and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guideline was followed.[17] Studies published before 13 May 2022 were examined, with language restricted to English. Two researchers (B.L. and L.Z.) independently searched PubMed and Web of Science using search terms for titles and abstracts. The search terms were built based on the terms used in review by Bull et al. on PFAS,[18] which included a combination of relevant subject headings and text words of blood lipid types (such as "cholesterol," "HDL," "LDL"), lipid disorders (such as "dyslipidemia") and PFAS (such as "PFAS," "PFOS," "perfluoro-"). In PubMed, the literature was searched using "((perfluoro* OR pfos OR pfas OR pfoa OR fluorotelomer alcohol [Title/Abstract])) AND (lipid* OR cholesterol OR triglyceride OR hdl OR ldl OR hdl to total cholesterol ratio OR hdl/total cholesterol ratio OR high-density lipoprotein OR low-density lipoprotein OR lipoprotein OR dyslipidemia OR hypercholesterolemia [Title/Abstract])." In Web of Science, the literature was searched using "Topic = (perfluoro * OR pfos OR pfas OR pfoa OR fluorotelomer alcohol)" AND "Topic = (lipid * OR cholesterol OR triglyceride OR hdl OR ldl OR "hdl to total cholesterol ratio" OR "hdl/total cholesterol ratio" OR "high density lipoprotein" OR "low density lipoprotein" OR lipoprotein OR dyslipidemia OR hypercholesterolemia)".

*These authors contributed equally to this work.
Address correspondence to Qi Sun. Email: qisun@hsph.harvard.edu
Supplemental Material is available online (https://doi.org/10.1289/EHP11840).
The authors declare no competing interests associated with the manuscript.
Received 8 July 2022; Revised 15 March 2023; Accepted 30 March 2023; Published 4 May 2023.

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to 508 standards due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehpsubmissions@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

Study Selection

The search results from PubMed and Web of Science entered a primary round of screening using a key word search on titles to exclude animal studies and studies solely focused on toxicology and biological pathways and to include studies mentioning lipids and lipid-related disorders. The abstracts of the studies that remained were reviewed by two researchers (B.L. and L.Z.), independently, to identify studies that provided valid data of associations of interest. Any disagreements between the two researchers about study selection were resolved through discussions with the senior author if needed. Inclusion criteria included the presence of original results of associations between at least one of five subtypes of PFAS [perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA)], and at least one of four blood lipid measures (TC, HDL-C, LDL-C, and TGs). There was no restriction on the calendar time or background PFAS exposure route/levels (e.g., professional exposure or not).

Data Extraction

Two researchers (B.L. and L.Z.) extracted the data on study characteristics to Microsoft Excel, including publication year, study location, study population, study design, funding sources, age, sex, body mass index (BMI), distribution of blood PFAS and blood lipids, study estimates (e.g., β coefficients) of associations of interest, and variables adjusted.

Data Synthesis and Analysis

The measure of associations in this meta-analysis was differences of blood lipid level corresponding to 1 interquartile range (IQR)-unit increase of blood PFAS exposures. For studies that examined the associations of interest using linear regressions on the untransformed original scales of PFAS and blood lipids, we derived the regression coefficient and standard error (SE) corresponding to the IQR increment of PFAS. Changes of lipid per IQR increase in PFAS level (Δ) was calculated as $\Delta = \beta \times IQR_{PFAS}$, where β is the reported mean change in lipid level per 1-unit increase in PFAS, holding all other covariates in the model constant, and IQR_{PFAS} is the IQR of PFAS level in the study population. For studies that examined log-transformed exposures or outcomes, we derived a formula to approximate the estimates of associations that would be calculated based on the original scales of PFAS and blood lipids. Specifically, when only PFAS was log-transformed and lipid was in original scale in the model, $\Delta = \beta \times IQR_{\log(PFAS)}$, where β is the reported mean lipid changes per 1-unit increase in log(PFAS), holding all other covariates in the model constant, and $IQR_{\log(PFAS)}$ is the IQR of log (PFAS) level in the study population. When only lipid was log-transformed and PFAS was in original scale, we approximated $\Delta = \bar{Y} \times \beta \times IQR_{PFAS}$, where $\bar{Y}$ is the mean level of original-scaled lipid in the study population, β is the reported mean changes in log (lipid) per 1-unit increase in PFAS, holding all other covariates in the model constant, and IQR_{PFAS} is the IQR of PFAS level in the study population. When both lipid and PFAS were log-transformed, we approximated $\Delta = \bar{Y} \times \beta \times IQR_{\log(PFAS)}$, where $\bar{Y}$ is the mean level of original-scaled lipid in the study population, β is the reported mean changes in log(lipid) per 1-unit increase in PFAS, holding all other covariates in the model constant, and $IQR_{\log(PFAS)}$ is the IQR of log(PFAS) level in the study population. IQR of log-transformed lipids or PFAS, if not reported, were calculated based on the reparameterization formula published elsewhere.[19] Full formula derivation processes are listed in the Supplemental Material, "Supplemental 2. Risk conversion methodology." To facilitate comparisons across different studies, we also standardized the units for both PFAS (in nanograms per milliliter) and blood lipids (in milligrams per deciliter) so that estimates from different studies had the same interpretation. Studies that reported incomplete or nontransformable data, or only reported logistic regression coefficients, were further excluded owing to difficulties in transformation.

In our statistical analyses, we pooled study-specific estimates using random effects models. To reduce the impact by extremely diverse PFAS exposures in different studies, the analyses were stratified by mean PFOA (≥100 ng/mL, <100 ng/mL) and by mean PFOS (≥20 ng/mL, <20 ng/mL) levels. We produced forest plots to visualize estimates and corresponding 95% confidence intervals (CIs) across studies. Heterogeneity between studies was assessed using Cochrane Q statistics and the I^2 statistic, and $p < 0.05$ indicated statistical significance. Cumulative meta-analysis and leave-one-out analyses were conducted to examine any studies with significant influence on the overall results. Secondary analyses excluding industrially funded studies or longitudinal studies were performed. We also conducted meta-regression analyses to explore factors that might potentially account for the observed heterogeneity, including sex (percentage of males), mean age (years), study design (longitudinal vs. cross-sectional), region (U.S. vs. others), year of blood collection (after 2010 vs. before 2010), number of variables adjusted, funding source of the study (industry vs. others), and mean PFAS level (in nanograms per milliliter). In addition, we created Begg's funnel plots to investigate potential publication bias for each association, and used Egger's test to obtain p-values for significance. Trim-and-fill analysis was further conducted if publication bias was detected. Furthermore, to evaluate potential nonlinear dose–response relations between PFOS, PFOA, and lipid changes, we used meta-regression with study effect size as the outcome and restricted cubic spline terms of mean PFAS levels as the independent variable (number of knots = 3).[20] We used Wald tests to obtain p-values for nonlinearity as the significance of restricted cubic spline terms, and p-values for linearity as the significance of linear term.

All statistical tests in our analyses were two-sided and used a significance level of $p < 0.05$. All analyses were conducted using Stata (version 16; StataCorp) and R (version 4.0.3; R Development Core Team).

Results

Included Studies and Baseline Characteristics

A detailed flow chart of literature selection process with number of publications at each step is shown in Figure S1. Through key word searching and abstract review of potentially eligible studies, 105 publications of longitudinal or cross-sectional studies that assessed the association between blood PFAS exposure and human blood lipid level were retained for further review. Studies that were not original ($n = 10$) or did not provide values of PFAS or lipid measurements ($n = 28$) were excluded. Studies among children (<18 years of age) were also excluded ($n = 24$). During data extraction stage, studies that only reported logistic regression coefficients were further excluded owing to difficulties in transformation ($n = 3$),[21–23] along with studies that reported incomplete or nontransformable data ($n = 11$).[24–34] After thorough screening, 29 publications, which gave rise to 360 data points from an estimated >80,500 participants, were identified and included in this meta-analysis. Of the 29 studies, 4 were longitudinal investigations, and others were cross-sectional studies.

Table 1 summarizes the characteristics of each study included in the meta-analysis. Blood PFOA levels were measured in 28 studies, and only 21 studies measured blood PFOS levels. Fewer studies examined PFHxS ($n = 15$), PFDA ($n = 7$), and PFNA ($n = 12$). High levels of mean PFOA (≥100 ng/mL) were observed in 9 studies and high levels of mean PFOS (≥20 ng/mL) were

Table 1. Baseline characteristics of studies of blood serum PFAS level in relation to blood lipids: participants, exposures, outcomes, and covariates.

Author(s) and year of publication	Study design	Country	*N*	Percentage male (%)	Age [y (mean)]	Study population	Exposure(s) and reported serum mean levels	Outcome(s)	Variables adjusted
Gilliland and Mandel, 1996[35]	Cross-sectional	USA	115	100	39.2	Employees at a PFOA production plant (3M) during 1985–1989, and they were considered highly exposed.	PFOA (mean = 3,300 ng/mL)	HDL-C	Age, BMI, smoking, and testosterone
Olsen et al., 2000[36]	Cross-sectional	USA	115	100	41.1	Production workers at 3M company's fluorochemical factory in 1993, 1995 and 1997.	PFOA (mean = 5,000, 6,800, 6,400 ng/mL for 1993, 1995, 1997, respectively)	HDL-C	Age, BMI, cigarette use, nonrespondents to alcohol question, and testosterone level
Emmett et al., 2006[37]	Cross-sectional	USA	371	46.6	50	Residents in the Little Hocking water district (PFOA polluted) in southeastern Ohio.	PFOA (mean = 354 ng/mL)	TC	NA
Olsen and Zobel, 2007[38]	Cross-sectional	USA	*N* = 196 (Antwerp), *N* = 188 (Decatur), *N* = 122 (Cottage Grove)	100	40	Employees from three sites of chemical plants.	PFOA (mean = 1,020, 1,890, 4,630 ng/mL for Antwerp, Decatur, and Cottage Grove sites, respectively)	TC, HDL-C, LDL-C	Age, BMI, and alcohol
Sakr et al., 2007[39]	Longitudinal	USA	454	73.6	43	Employees from a chemical company (DuPont) that has been producing fluoropolymers since 1951. These participants have completed two or more measurements of serum PFOA and were under medical surveillance.	PFOA (mean = 1,130 ng/mL)	TC, HDL-C, LDL-C	Age, age-squared, BMI, sex, and decade of hire
Sakr et al., 2007[40]	Cross-sectional	USA	1,019	76.4	45.9	Nonpregnant employees from the DuPont company.	PFOA (mean = 428 ng/mL)	TC, HDL-C, LDL-C	Age, sex, BMI, alcohol, family history of heart attack in a parent, and use of lipid-lowering medications
Costa et al., 2009[41]	Longitudinal	Italy	56	100	43.7	Workers who are current, previously exposed, or nonexposed at a chemical plant in Miteni, Trissino, Italy, where PFOA has been produced since 1968.	PFOA (mean = 10,126 ng/mL)	TC, HDL-C, TGs	Age, job, seniority, BMI, alcohol consumption, and year of observation
Steenland et al., 2009[42]	Cross-sectional	USA	46,294	46.1	36.4	Participants were from the C8 Health Project who were >18 years of age and were not taking cholesterol-lowering medication.	PFOA (mean = 80.3 ng/mL), PFOS (mean = 22.4 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, BMI, sex, smoking, education, regular exerciser, and alcohol
Nelson et al., 2010[43]	Cross-sectional	USA	860	52	20–80	Participants were from the NHANES conducted by the U.S. CDC, representing the civilian noninstitutionalized U.S. population.	PFOA (mean = 4.6 ng/mL), PFOS (mean = 25.3 ng/mL), PFHxS (mean = 2.6 ng/mL), PFNA (mean = 1.3 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, sex, race/ethnicity, SES, saturated fat intake, exercise, time in front of a TV or computer, BMI, alcohol consumption, and smoking
Olsen et al., 2012[44]	Longitudinal	USA	179	95	40.2	Fourteen 3M employees and 165 contract workers.	PFOA (mean = 95.5 ng/mL), PFOS (mean = 65.3 ng/mL)	TC, HDL-C	Sex, age, BMI, and alcohol
Wang et al., 2012[11]	Cross-sectional	China	*N* = 55 (workers), *N* = 132 (residents)	100 (workers), 56.8 (residents)	27.8 (workers), 46.9 (residents)	Participants included 55 occupational males at fluorochemical plants in Jiangsu, China, and 132 residents in the nearby community.	PFOA (mean = 2,157.7, 378.3 ng/mL for workers and residents, respectively)	TC, TGs, HDL-C, LDL-C	Age and BMI

Table 1. (*Continued.*)

Author(s) and year of publication	Study design	Country	*N*	Percentage male (%)	Age [y (mean)]	Study population	Exposure(s) and reported serum mean levels	Outcome(s)	Variables adjusted
Eriksen et al., 2013[12]	Cross-sectional	Denmark	753	88	50–65	Participants were from the prospective Danish Diet, Cancer and Health (DCH) cohort, which enrolled individuals without cancer history during 1993 and 1997.	PFOA (mean = 7.1 ng/mL), PFOS (mean = 36.1 ng/mL)	TC	Sex; education; age; BMI; smoking status; intake of alcohol, egg, and animal fat; and physical activity
Jain and Ducatman, 2019[45]	Cross-sectional	USA	*N* = 1,237 (nonobese males), *N* = 640 (obese males), *N* = 1,053 (nonobese, females), *N* = 699 (obese females)	NA	50	Participants' data were from individuals >20 years of age and had fasted for >8 h in the NHANES 2005–2014.	PFOA (male mean = 3.4 ng/mL, female mean = 2.5 ng/mL), PFOS (male mean = 11.5 ng/mL, female mean = 7.4 ng/mL), PFHxS (male mean = 2 ng/mL, female mean = 1.2 ng/mL), PFNA (male mean = 1.1 ng/mL, female mean = 0.9 ng/mL), PFDA (male mean = 0.26 ng/mL, female mean = 0.23 ng/mL)	TC, TGs, HDL-C, LDL-C	Race/ethnicity, smoking, age, age-squared, poverty/income ratio, fasting time in hours, use of lipid-lowering medicine, physical exercise, survey year, daily dietary intake of TC, total saturated fat, calories, caffeine, alcohol, protein, and menopausal status (female)
Donat-Vargas et al., 2019[9]	Cross-sectional	Sweden	358	50	46	Participants' data were from the Västerbotten Intervention Program (VIP), a subcohort in the Northern Sweden Health and Disease Study initiated in 1985. The association between repeated measurements at baseline and at follow-up were reported.	PFOA (mean = 2.9 ng/mL), PFOS (mean = 20 ng/mL), PFHxS (mean = 1 ng/mL), PFNA (mean = 0.5 ng/mL), PFDA (mean = 0.23 ng/mL)	TC, TGs	Sex, age, education, sample year, BMI, smoking, alcohol, physical activity, and healthy diet score
Lin et al., 2019[10]	Cross-sectional	USA	888	34.1	40–65	Participants were overweight and prediabetic individuals who were recruited for the Diabetes Prevention Program during July 1996 and May 1999 from 27 medical centers across the United States.	PFOA (mean = 4.9 ng/mL), PFOS (mean = 27.2 ng/mL), PFHxS (mean = 2.3 ng/mL), PFNA (mean = 0.6 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, sex, race, marital status, educational attainment, smoking, drinking, physical activity level, percentage of daily calorie from saturated fat intake, and waist circumference at baseline
Li et al., 2020[46]	Cross-sectional	Sweden	*N* = 1,815 (high exposure), *N* = 130 (low exposure)	43	42	Highly exposed residents in Ronneby, Sweden, where drinking water was contaminated from aqueous fire-fighting foams, and controls from a nearby area.	PFOA (residents mean = 8.6 ng/mL, controls mean = 1.6 ng/mL), PFOS (residents mean = 160 ng/mL, controls mean = 4.8 ng/mL), PFHxS (residents mean = 140 ng/mL, controls mean = 1 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, sex, and BMI
Fan et al., 2020[47]	Cross-sectional	USA	1,067	50.3	47.6	Participants' data were continuously collected from the NHANES over two periods (2011–2012 and 2013–2014).	PFOA (mean = 2.6 ng/mL), PFOS (mean = 9.1 ng/mL), PFHxS (mean = 2 ng/mL), PFNA (mean = 1 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, sex, race, education level, poverty/income ratio, BMI, smoking status, alcohol use, energy intake levels, and screen time
Canova et al., 2020[48]	Cross-sectional	Italy	*N* = 8,100 (male), *N* = 7,620 (female)	NA	20–39	Participants were recruited in the regional health surveillance program in the Veneto Region, Italy.	PFOA (male mean = 83.8 ng/mL, female mean = 36.9 ng/mL), PFOS (male mean = 5.7 ng/mL, female mean = 3.6 ng/mL), PFHxS (male mean = 8.9 ng/mL, female mean = 3.2 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, BMI, time-lag between enrollment and the beginning of the study, sex, physical activity, smoking, country of birth, alcohol, education, lab in charge of the serum analyses, and food consumption

Table 1. (*Continued.*)

Author(s) and year of publication	Study design	Country	*N*	Percentage male (%)	Age [y (mean)]	Study population	Exposure(s) and reported serum mean levels	Outcome(s)	Variables adjusted
Starling et al., 2017[49]	Cross-sectional	USA	598	0	27.8	Midpregnancy women (20–34 weeks gestation) who were recruited for the Healthy Start prospective cohort at the University of Colorado Hospital from 2009 to 2014.	PFOA (mean = 1.1 ng/mL), PFOS (mean = 2.4 ng/mL), PFHxS (mean = 0.8 ng/mL), PFDA (mean = 0.4 ng/mL), PFNA (mean = 0.4 ng/mL)	TGs, HDL-C	Age, race/ethnicity, prepregnancy BMI, education, gravidity, smoking, gestational age at blood draw
Starling et al., 2014[50]	Cross-sectional	Norway	891	0	19–44	Pregnant women enrolled in the Norwegian Mother and Child (MoBa) Cohort Study in 2003–2004. 99% of the women provided plasma sample during their second trimester of pregnancy (14–26 weeks).	PFOA (mean = 2.3 ng/mL), PFOS (mean = 13 ng/mL), PFHxS (mean = 0.6 ng/mL), PFNA (mean = 0.4 ng/mL), PFDA (mean = 0.09 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, prepregnant BMI, nulliparous or interpregnancy interval, duration of breastfeeding previous child, education, current smoking at midpregnancy, gestational weeks at blood draw, and daily consumption of oily fish
Kishi et al., 2015[51]	Cross-sectional	Japan	306	0	30.4	Pregnant women recruited for the Hokkaido birth cohort between 2002 and 2005 with their children in Japan. They provided their plasma sample after their second trimester of pregnancy.	PFOA (mean = 1.5 ng/mL), PFOS (mean = 6 ng/mL)	TGs	Age, smoking and alcohol intake during pregnancy, annual household income, parity, and blood sampling period
Yang et al., 2020[52]	Cross-sectional	China	312	0	20–40	Healthy pregnant women at early term of pregnancy (5–15 gestational weeks) recruited for a prospective cohort study in the Maternal and Child Health Care Hospital of Tangshan city of Hebei, China (2013–2014).	PFOA (mean = 7.2 ng/mL), PFOS (mean = 8 ng/mL), PFHxS (mean = 0.4 ng/mL), PFNA (mean = 1.6 ng/mL), PFDA (mean = 1.29 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, BMI at baseline, husband smoking, gestational diabetes mellitus, parity, education, career, income; energy intake and physical activity in the late term of pregnancy; gestational weeks, carbohydrate, protein, SFA, MUFA, and PUFA intake in the late term of pregnancy
Tian et al., 2020[53]	Longitudinal	China	306	0	28.1	Pregnant women recruited for a prospective cohort study (Shanghai-Minhang Birth Cohort Study) in Shanghai, China, between April and December 2012. They provided their cord blood sample at delivery for lipid measurement, and PFAS concentrations were measured in plasma.	PFOA (mean = 19.6 ng/mL), PFOS (mean = 10.5 ng/mL), PFHxS (mean = 2.7 ng/mL), PFNA (mean = 1.8 ng/mL), PFDA (mean = 2.15 ng/mL)	TC, TGs, HDL-C, LDL-C	Maternal age, prepregnancy BMI, per capita household income, infant sex, and gestational age
Dalla Zuanna et al., 2021[54]	Cross-sectional	Italy	319	0	14–48	Pregnant women enrolled in the regional health surveillance program in the Veneto Region, Italy (2017–2020). 31.7% were in their first trimester of gestation, 27.6% in the second trimester, and 40.8% in the third trimester.	PFOA (mean = 26.2 ng/mL), PFOS (mean = 3.2 ng/mL), PFHxS (mean = 2.7 ng/mL)	TC, HDL-C, LDL-C	Age, number of previous deliveries, BMI, physical activity, smoking, country of birth, education, lab in charge of the serum lipid analyses, gestation weeks, and reported fish consumption

Table 1. (*Continued.*)

Author(s) and year of publication	Study design	Country	*N*	Percentage male (%)	Age [y (mean)]	Study population	Exposure(s) and reported serum mean levels	Outcome(s)	Variables adjusted
Kobayashi et al., 2021[55]	Cross-sectional	Japan	504	0	30.4	Mothers in a birth cohort between 2002 and 2005 with their children in Japan (Hokkaido Study on Environment and Children's Health).	PFOS (median = 5.4 ng/mL	TGs	Age, maternal smoking, alcohol consumption during pregnancy, annual household income, parity, and sampling period
Cong et al., 2021[56]	Cross-sectional	China	$N = 893$ (BMI <25), $N = 345$ (BMI ≥25)	54.9	62.0	Adults from the Isomers of C8 Health Project (2015–2016), a cross-sectional study in China.	PFOA (median = 4.79 ng/mL), PFOS (median = 10.33 ng/mL	TC, TGs, HDL-C, LDL-C	Age, sex, ethnicity, education, annual household income, career, smoking, alcohol drinking, and regular exercise
Batzella et al., 2022[57]	Cross-sectional	Italy	232	100	57.3	Former workers of an Italian chemical factory exposed to elevated PFAS levels.	PFOA (mean = 624.7 ng/mL), PFOS (mean = 15.6 ng/mL), PFHxS (mean = 30.0 ng/mL), PFNA (mean = 1.0 ng/mL	TC, HDL-C, LDL-C	Age, smoke habit, alcohol, education level, and dyslipidemia
Mi et al., 2022[58]	Cross-sectional	China	1,336	40.1	53.4	Residents recruited in Guangzhou, China, between 2018 and 2019.	PFOA (median = 5.4 ng/mL), PFOS (median = 7.8 ng/mL)	TC, TGs, HDL-C, LDL-C	Age, sex, annual household income, educational level, marital status, smoking status, alcohol drinking, and physical activity
Vuong et al., 2021[59]	Cross-sectional	USA	388	0	25–34	Pregnant women from the Health Outcomes and Measures of the Environment (HOME) study, a prospective pregnancy and birth cohort in Ohio (2003–2006).	PFOA (median = 5.4 ng/mL), PFOS (median = 13.3 ng/mL), PFHxS (median = 1.5 ng/mL), PFNA (median = 0.9 ng/mL)	TC, TGs	Age, race/ethnicity, household income, smoking status, marijuana use, serum concentrations of the sum of polychlorinated biphenyls (ΣPCBs), prepregnancy BMI, and parity

Note: BMI, body mass index; CDC, Centers for Disease Control and Prevention; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MUFA, monounsaturated fat; NA, not available; NHANES, National Health Nutrition Examination Survey; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PUFA, polyunsaturated fatty acid; SES, socioeconomic status; SFA, saturated fatty acid; TC, total cholesterol; TG, triacylglycerol.

observed in 7 studies that enrolled workers with professional exposure history to PFAS or residents living near PFAS plants. Blood levels of TC were measured in most studies, HDL-C were measured in 23 studies, and only 21 studies examined LDL-C and TGs.

PFAS, Lipids, and Subgroup Results

Table 2 summarizes the associations of interest across all studies and also in subgroups defined by average baseline PFAS levels. A summary of individual data points (effect size ± SE) in each study can be found in Table S1. Figure 1A shows that, overall, per IQR increase of blood PFOA, exposure was significantly associated with higher levels of TC, TGs, and LDL-C, with modest-to-high heterogeneity across studies (I^2 ranging from 59.6% to 87.9%; p for heterogeneity <0.01). The pooled estimates were 2.1-mg/dL TC (95% CI: 1.2, 3.0), 1.3-mg/dL TGs (95% CI: 0.1, 2.4), and 1.4-mg/dL LDL-C (95% CI: 0.6, 2.2) increment per IQR increase of blood PFOA levels. For HDL-C, the effects were not significant in either high- or low-exposure groups. The associations between PFOA and blood lipid levels seemed to be stronger among highly exposed populations, except for HDL-C and LDL-C. However, the differences in effect size between the high- vs. low-PFOA groups did not reach significance, except for TGs.

Similar positive associations were observed between PFOS and blood lipids (Figure 1B). Overall, a per IQR increase of blood PFOS exposure was significantly associated with higher levels of TC [2.6 mg/dL (95% CI: 1.5, 3.6)], and LDL-C [1.9 mg/dL (95% CI: 0.9, 3.1)], with significant heterogeneity (I^2 ranging from 74.2% to 92.6%; p for heterogeneity <0.01). There were insignificant associations between PFOS and HDL-C. For TC and LDL-C, the associations were stronger in the high-exposure group. None of the differences in associations between the high- vs. low-PFOS groups reached statistical significance.

Figure S2 shows associations for PFHxS, PFDA, and PFNA. Increased exposure to PFHxS was positively associated with higher levels of HDL-C [0.8 mg/dL (95% CI: 0.5, 1.2)]. An inverse association was observed between PFDA and TGs [−5.0 (95% CI: −8.1, −1.9)], whereas the association was positive between PFDA and HDL-C [1.4 (95% CI: 0.1, 2.7)]. PFNA was negatively associated with TGs [−1.7 (95% CI: −3.5, −0.02)].

For PFOA and PFOS, neither the exclusion of any single study nor the addition of a single study by mean PFAS levels at a time substantially changed the main findings (Figures S3 and S4). We also conducted secondary analyses by excluding industrially funded studies or longitudinal studies and the results remained persistent (Table S2). Furthermore, the heterogeneity among PFOS–lipid studies could be explained jointly by variables considered in the meta-regression to various degrees ($R^2 = 0\%$–61.8%). For example, cross-sectional studies tended to report stronger associations of interest. Age, study design, and number of covariates adjusted in the original analysis were significant predictors of study estimates in some PFOS–lipid associations, such as the PFOS–HDL-C association. Heterogeneity among PFOA–lipid studies, however, was not well explained by these variables (Table S3).

Dose–Response Meta-Analysis

Figure 2 shows the dose–response relationship between PFOA or PFOS and blood lipid levels. Given that the mean PFOA levels across different populations ranged from 2.3 to 10,126 ng/mL, we applied natural log-transformation to PFOA and PFOS values to accommodate all studies. We observed some potential dose–response relationships, such as between PFOS and HDL-C or PFOA and LDL-C, although none of the p-values for nonlinearity reached statistical significance (Table 3).

Table 2. Summary of meta-analysis and subgroup analysis results, which are differences in lipids (mg/dL) per 1-IQR increase of PFAS (95% confidence intervals).

		TC		TG		HDL-C		LDL-C	
Exposure	Outcome	No. of studies	Difference (95% CI)	No. of studies	Difference (95% CI)	No. of studies	Difference (95% CI)	No. of studies	Difference (95% CI)
PFOA	High PFOA group (≥100 ng/mL)	$n = 10$	3.35 (−0.54, 7.23)	$n = 8$	6.66 (1.43, 11.88)[†]	$n = 13$	−0.24 (−0.60, 0.13)	$n = 8$	1.21 (0.00, 2.42)
	Low-PFOA group (<100 ng/mL)	$n = 24$	2.11 (0.90, 3.32)[†]	$n = 21$	0.73 (−0.59, 2.05)	$n = 21$	0.38 (−0.08, 0.83)	$n = 19$	1.30 (0.22, 2.39)[†]
	p-Value for subgroup difference[‡]		$p = 0.69$		$p = 0.03$		$p = 0.07$		$p = 0.66$
	Overall	$N = 34$	2.11 (1.23, 3.00)[†]	$N = 29$	1.26 (0.08, 2.43)[†]	$N = 34$	0.16 (−0.18, 0.50)	$N = 27$	1.40 (0.61, 2.19)[†]
PFOS	High PFOS group (≥20 ng/mL)	$n = 8$	3.29 (1.85, 4.73)[†]	$n = 4$	−0.55 (−7.78, 6.68)	$n = 5$	0.24 (−0.32, 0.80)	$n = 4$	2.05 (0.35, 3.76)[†]
	Low-PFOS group (<20 ng/mL)	$n = 17$	2.39 (0.93, 3.85)[†]	$n = 18$	−1.06 (−1.59, −0.54)[†]	$n = 17$	0.42 (−0.39, 1.24)	$n = 16$	1.89 (0.85, 2.93)[†]
	p-Value for subgroup difference[‡]		$p = 0.57$		$p = 0.37$		$p = 0.83$		$p = 0.89$
	Overall	$N = 25$	2.55 (1.48, 3.61)[†]	$N = 22$	−0.99 (−2.16, 0.18)	$N = 22$	0.33 (−0.05, 0.71)	$N = 20$	1.94 (0.92, 2.96)[†]
PFHxS		$N = 18$	0.94 (−0.20, 2.08)	$N = 16$	−0.90 (−2.18, 0.38)	$N = 17$	0.82 (0.47, 1.16)[†]	$N = 16$	0.47 (−0.55, 1.49)
PFNA		$N = 13$	2.18 (−0.11, 4.47)	$N = 12$	−1.74 (−3.47, −0.02)[†]	$N = 12$	0.47 (−0.18, 1.13)	$N = 11$	1.92 (−0.01, 3.86)
PFDA		$N = 8$	0.94 (−3.01, 4.89)	$N = 9$	−4.97 (−8.08, −1.87)[†]	$N = 8$	1.40 (0.09, 2.70)[†]	$N = 7$	0.14 (−2.42, 2.70)

Note: All analyses were run using the random effects model. Total number of studies = 29, total number of data points = 360. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; TC, total cholesterol; TG, triacylglycerol.

[†]Effect estimates $p < 0.05$.

[‡]p-Values for subgroup difference were obtained using Cochrane's Q test, and $p < 0.05$ indicates statistically significant heterogeneity detected across studies.

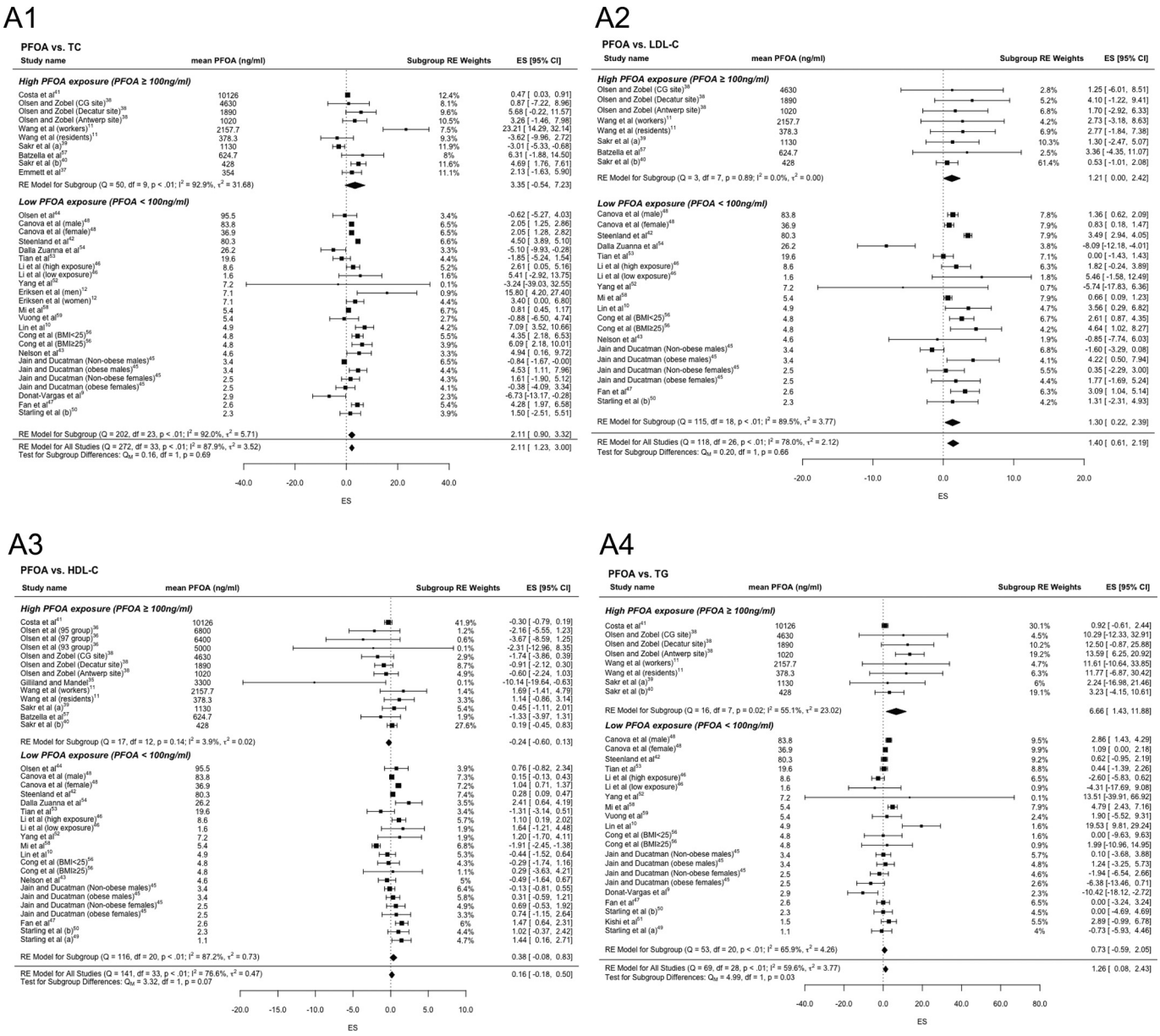

Figure 1. (A1–A4) Forrest plot of pooled estimates of increment (95% CI) of lipids per IQR increase of PFOA, overall and stratified by PFOA level (≥100 ng/mL, <100 ng/mL), using random effects models. (B1–B4) Forrest plot of pooled estimate of increment (95% CI) of lipids per IQR increase of PFOS, overall and stratified by PFOS level (≥20 ng/mL, <20 ng/mL), using random effects models. Note: CI, confidence interval; ES, effect size; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; RE, random effects; TC, total cholesterol; TG, triacylglycerol.

Assessment of Publication Bias

Both visual inspection and the results from Eggers' tests did not indicate possible publication bias of PFOA–lipids or PFOS–lipids studies selected (Figure S5). Potential publication bias was identified only in the associations between the PFDA and HDL-C and PFDA and TGs, although the findings remained largely unchanged in the trim-and-fill analyses (Figure S6).

Discussion

Study Findings

Our analysis summarized results from 29 epidemiological studies and suggested that, overall, PFOA and PFOS were positively associated with certain blood lipid measurements, especially TC, TGs, and LDL-C, and significant heterogeneity was detected for most of the associations. The relationships between other PFAS and lipids were less clear, but the data were relatively sparse. Some of the positive associations between PFAS and blood lipids might potentially be dose dependent, although the nonlinearity tests did not achieve statistical significance. To our knowledge, the present study provides, thus far, the most comprehensive quantitative summary on the association between PFAS and blood lipids.

Notably, the associations identified in the meta-analysis are broadly consistent with previous narrative reviews.[15,16] Both PFOA and PFOS exposures were consistently linked to higher blood TC and LDL-C levels across studies with different PFAS exposures. Of note, studies that examined PFAS and blood lipids repeatedly over time also found a significant correlation between PFOA and TC levels.[30,31,39,41] In contrast, in occupational studies, null associations between PFOA/PFOS and HDL-C levels were observed,[10,30,37,38,40,43] whereas in general populations, a

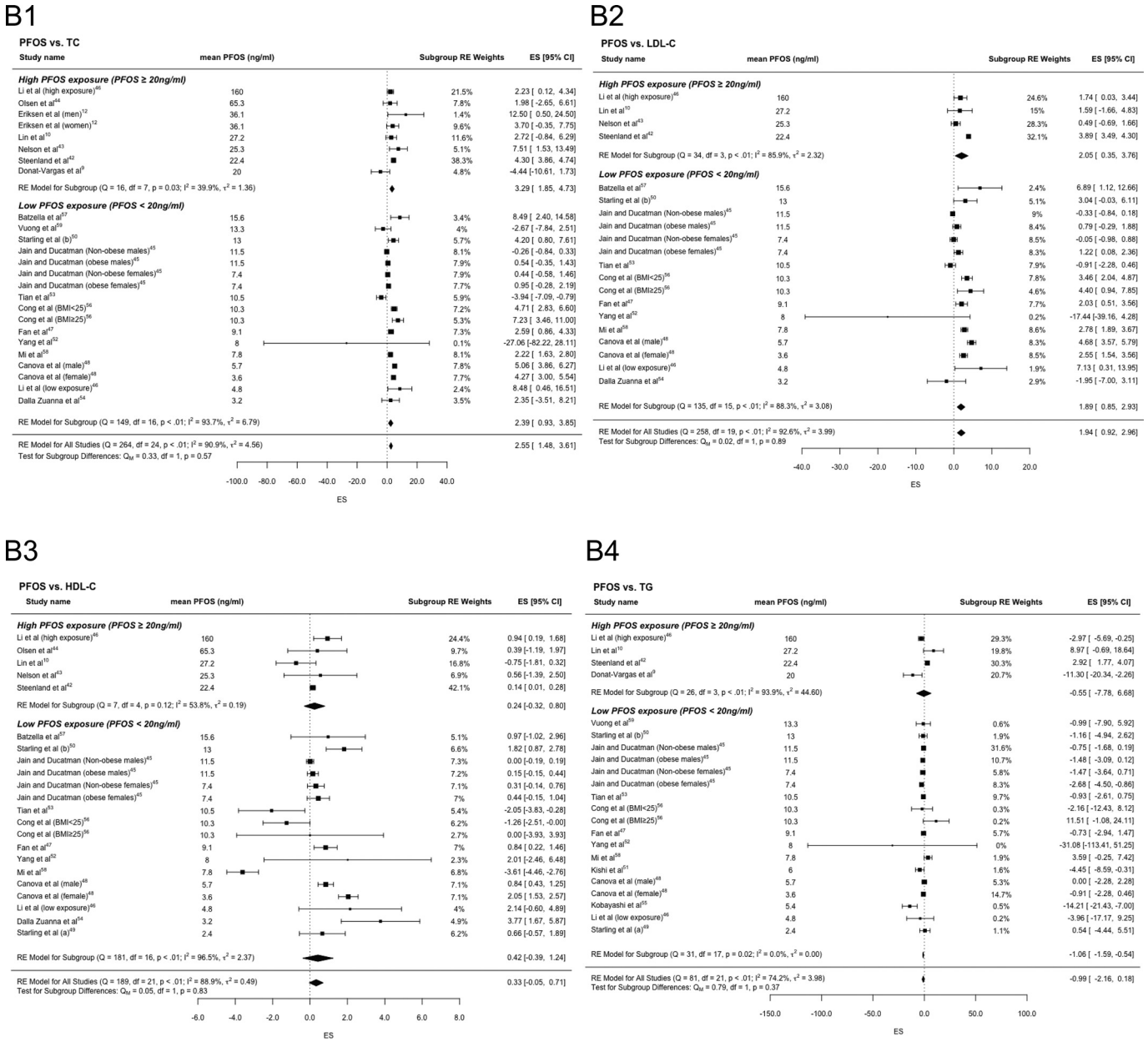

Figure 1. (*Continued.*)

positive association was more likely to be observed.[24,60] Our dose–response analyses and analyses stratified by PFOS/PFOA exposure levels largely reflected these observations in previous individual studies or narrative reviews. In addition, our dose–response analyses also demonstrated potential nonlinear relationships in PFOA–LDL-C and PFOS–HDL-C associations that were not explained in previous reviews. These possible nonlinear associations may underscore the complexity in PFAS–lipids associations, although further epidemiological and mechanistic studies are needed to substantiate these findings.

Besides dose, cross-sectional study design and industrial funding may also explain part of the heterogeneity for PFOS–lipid studies. Even though industrial funding was not a significant factor in meta-regression, the strength of its prediction still ranked second among eight predictors in the models. Several previous studies demonstrated potential effect modifications by sex[22,45,48,61]; however, we did not find sex explaining the heterogeneity of PFAS–lipid associations. Jain and Ducatman[45] also reported differential associations by adiposity level, although we were unable to explore the role of obesity because the data on BMI were missing for 14 studies. In general, the majority of heterogeneity was still unexplained by these factors, especially for PFOA associations. Nevertheless, it is worth noting that the associations were largely consistent among nationwide representative samples in the U.S. National Health and Nutrition Examination Survey (NHANES) at the lower range of PFAS exposures.[43,47] Publication bias was also spotted in a few PFAS–lipid associations, although results from the trim-and-fill analysis did not support the notion that the publication bias might explain our findings.

Clinical Significance

Blood lipids are causal risk factors for CVD. It is estimated that each 1-mg/dL increase in LDL-C was associated with a 25% increased risk of developing coronary heart disease (CHD).[62] Based on our findings, every 1-IQR increase in PFOA or PFOS

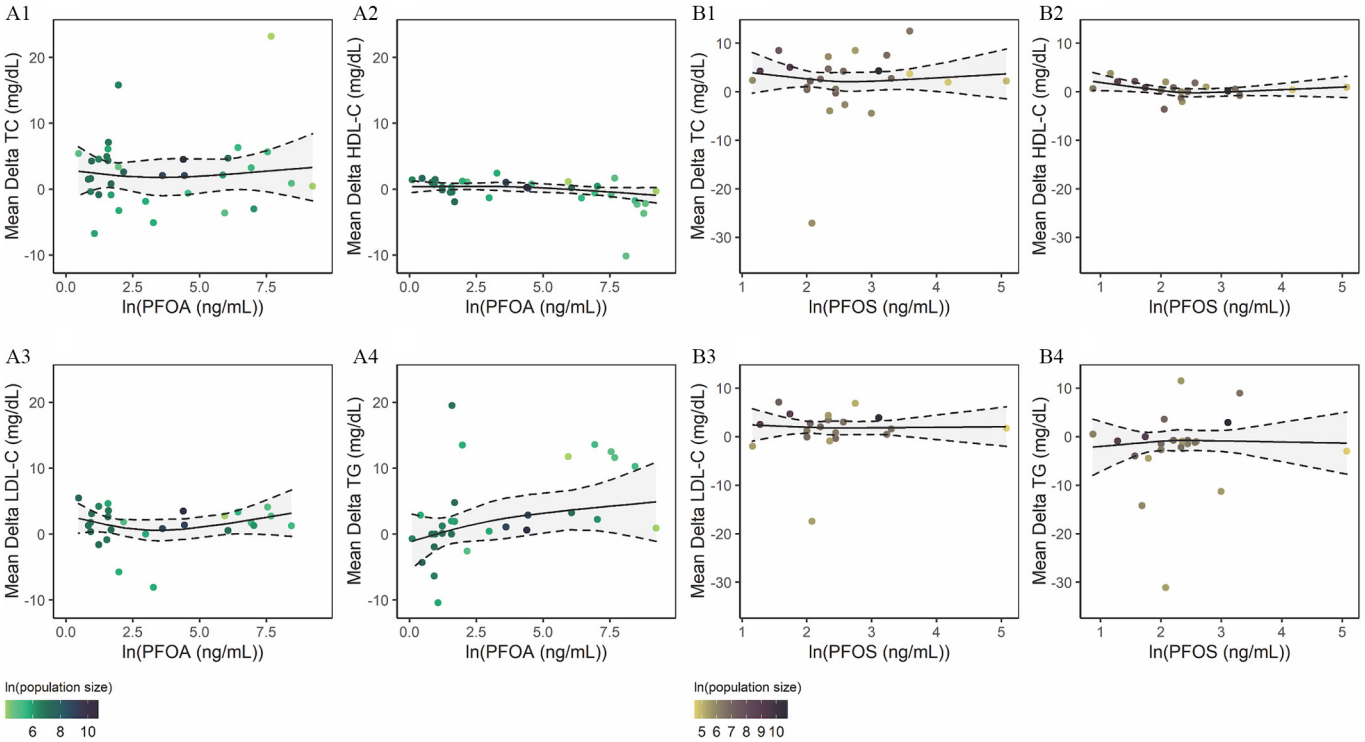

Figure 2. Dose–response relation between (A1–A4) PFOA and (B1–B4) PFOS levels and blood lipid levels. Solid lines represent point estimates of changes of lipids per 1-IQR increase in PFAS (Delta); dashed lines are 95% confidence intervals. Each solid dot represents a study included, and the density of their color represent the sample sizes. A summary of individual data points (effect size ± SE) in this plot can be found in Table S1. Note: HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; SE, standard error; TC, total cholesterol; TG, triacylglycerol.

levels would be associated with a 37% and 54% increased risk of developing CHD, respectively. Likewise, the risk of developing CHD increased by 0.7% per mg/dL increase in TG levels.[63] In contrast, HDL-C levels were robustly associated with a lower risk of developing CHD.[64,65] It is difficult to extrapolate the present findings regarding various blood lipids to potential changes in CVD risk, and, as such, further studies are needed to directly address associations between PFAS and CVD risk in longitudinal studies. It is also worth mentioning that recent studies demonstrated that lipoprotein particles are a heterogeneous group of subspecies that bear different functions.[66] In particular, HDL-C particles that do not carry apolipoprotein C-III (apoC-III) were associated with a lower risk of developing CHD. In contrast, LDL-C and HDL-C particles that carry apoC-III were associated with an elevated risk of developing CHD. Interestingly, in the Prevention of Obesity Using Novel Dietary Strategies (POUNDS Lost) trial, PFOA levels were significantly associated with higher concentrations of HDL-C and LDL-C that carry apoC-III.[67] Thus, it is critical to further examine the associations between PFAS and the subspecies of blood lipoproteins defined by apolipoproteins and whether PFAS are associated with CVD risk.

Table 3. Dose–response analysis parameters.

	PFAS	TC	TGs	HDL-C	LDL-C
p-Values for nonlinearity	PFOA	0.66	0.67	0.39	0.20
	PFOS	0.43	0.68	0.05	0.75
p-Values for linearity	PFOA	0.88	0.08	0.06	0.88
	PFOS	0.98	0.90	0.49	0.90

Note: Dose–response analysis was performed using meta-regression with study effect size as the outcome and restricted cubic spline terms of mean PFAS levels as the independent variable (number of knots = 3). *p*-Values were obtained using Wald tests for nonlinearity as the significance of restricted cubic spline terms, and *p*-values for linearity as the significance of the linear term. All eligible studies were used for this analysis. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; TC, total cholesterol; TG, triacylglycerol.

Potential Mechanisms

The mechanisms underlying the associations between PFAS and blood lipids in humans are still poorly understood. It is well understood that, in animal models, PFAS disrupt lipid metabolism by interfering with PPARα, which plays an essential role in fatty acid metabolism.[68,69] PFAS may also influence blood lipid metabolism by interfering with bile acid metabolism.[70,71] In addition, PFAS may disrupt the expression of genes involved in the cholesterol clearance pathway, although findings were not entirely consistent.[6,72,73] Human metabolomics studies are instrumental to elucidate mechanisms that might be directly relevant to humans.[74] For example, Alderete et al.[75] reported that plasma PFAS disrupted metabolic pathways of glycosphingolipid, palmitic acid, linoleic acid, tyrosine, and arginine, which have been associated with β-cell signaling pathways or insulin resistance in previous studies.[76–79] PFOA was also positively associated with acyl-carnitines, such as acetyl-carnitine (C2) and 3-hydroxybutyrylcarnitine (C4-OH).[79] Apparently, more multi-omics studies are needed to deepen the understanding of potential pathways between PFAS exposures and blood lipid metabolism.

Strengths and Limitations

This meta-analysis is among the first meta-analyses that quantitatively summarized associations between PFAS and lipids in adults. We have included multiple studies among populations residing at various geological locations and with various levels of PFAS exposure. The limitations and strengths of individual studies may vary across studies. The common strengths include that the methods of blood collection and PFAS/lipid measurement were, in general,

well described and standardized and that the statistical analyses were appropriate and clearly described in the publications. The common weaknesses of these studies are that participants were usually selected groups of people exposed to PFAS, except for some large nationwide cohorts. Meanwhile, the present meta-analysis is also subject to a few other limitations. Most studies included were cross-sectional studies, thus lending little evidence to support a causal interpretation of study findings. An alternate interpretation of our findings is reverse causation, given that it has been suggested that PFAS may be bound to lipoproteins and transported to target organs that regulate plasma lipid levels, although the percentage of PFAS bound to human serum lipoproteins is low.[80] As such, it is unlikely that blood lipids levels lead to higher PFAS levels in the circulation.[81] Furthermore, it is worth noting that our findings are in line with evidence from other prospective studies; that is, that reductions of PFAS levels are associated with reduction of lipids, indicating potential causal relationships.[28,31] In addition, baseline blood PFAS concentrations were found to be significantly associated with a higher incidence of hyperlipidemia.[10] We also made several statistical assumptions in data processing to harmonize raw data obtained from studies using different data transformations. For example, to calculate changes of lipids per IQR difference in PFAS in each study, we assumed that the PFAS or log-PFAS distribution follows a normal distribution in study participants within each study, depending on the regression methods they used.[12,30,37] Several studies were excluded in the data standardization process owing to a lack of transformable data or use of logistic regression. However, these studies would account for a small percentage of our total data points. Last, our meta-analysis focused on five PFAS that were most widely examined in the literature. As such, whether the findings hold true for other PFAS shall be examined in future studies.

In conclusion, the present meta-analysis shows overall positive associations of PFOA and PFOS with blood lipid levels in adults, especially LDL-C and TC, and such associations might potentially be dose dependent. Data for other minor PFAS that are currently examined in the literature are relatively sparse. Future studies are warranted to extend this research to other newly emerged PFAS and to examine whether the findings can be translated into changes in CVD risk.

Acknowledgments

Q.S. supervised the research project; B.L. and L.Z. conducted the research and wrote the manuscript; M.W. provided support on methodology development. All authors read and approved the final manuscript.

This research was supported by the National Institutes of Health (NIH) grant ES022981 (to Q.S.). This work was also supported by the Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH Award UL1 TR002541 (to Q.S.) and financial contributions from Harvard University and its affiliated academic health care centers). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the NIH. The funding source had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

References

1. ATSDR (Agency for Toxic Substances and Disease Registry). 2021. Toxicological Profile for Perfluoroalkyls. https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=1117&tid=237 [accessed 7 July 2022].
2. Brennan NM, Evans AT, Fritz MK, Peak SA, von Holst HE. 2021. Trends in the regulation of per- and polyfluoroalkyl substances (PFAS): a scoping review. Int J Environ Res Pubic Health 18(20):10900, PMID: 34682663, https://doi.org/10.3390/ijerph182010900.
3. Cousins IT, Johansson JH, Salter ME, Sha B, Scheringer M. 2022. Outside the safe operating space of a new planetary boundary for per- and polyfluoroalkyl substances (PFAS). Environ Sci Technol 56(16):11172–11179, PMID: 35916421, https://doi.org/10.1021/acs.est.2c02765.
4. Rigamonti E, Chinetti-Gbaguidi G, Staels B. 2008. Regulation of macrophage functions by PPAR-α, PPAR-γ, and LXRs in mice and men. Arterioscler Thromb Vasc Biol 28(6):1050–1059, PMID: 18323516, https://doi.org/10.1161/ATVBAHA.107.158998.
5. Behr AC, Plinsch C, Braeuning A, Buhrke T. 2020. Activation of human nuclear receptors by perfluoroalkylated substances (PFAS). Toxicol In Vitro 62:104700, PMID: 31676336, https://doi.org/10.1016/j.tiv.2019.104700.
6. Fletcher T, Galloway TS, Melzer D, Holcroft P, Cipelli R, Pilling LC, et al. 2013. Associations between PFOA, PFOS and changes in the expression of genes involved in cholesterol metabolism in humans. Environ Int 57–58:2–10, PMID: 23624243, https://doi.org/10.1016/j.envint.2013.03.008.
7. Soppert J, Lehrke M, Marx N, Jankowski J, Noels H. 2020. Lipoproteins and lipids in cardiovascular disease: from mechanistic insights to therapeutic targeting. Adv Drug Deliv Rev 159:4–33, PMID: 32730849, https://doi.org/10.1016/j.addr.2020.07.019.
8. Dong J, Yang S, Zhuang Q, Sun J, Wei P, Zhao X, et al. 2021. The associations of lipid profiles with cardiovascular diseases and death in a 10-year prospective cohort study. Front Cardiovasc Med 8:745539, PMID: 34901209, https://doi.org/10.3389/fcvm.2021.745539.
9. Donat-Vargas C, Bergdahl IA, Tornevi A, Wennberg M, Sommar J, Koponen J, et al. 2019. Associations between repeated measure of plasma perfluoroalkyl substances and cardiometabolic risk factors. Environ Int 124:58–65, PMID: 30639908, https://doi.org/10.1016/j.envint.2019.01.007.
10. Lin PID, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, et al. 2019. *Per-* and polyfluoroalkyl substances and blood lipid levels in pre-diabetic adults—longitudinal analysis of the diabetes prevention program outcomes study. Environ Int 129:343–353, PMID: 31150976, https://doi.org/10.1016/j.envint.2019.05.027.
11. Wang J, Zhang Y, Zhang W, Jin Y, Dai J. 2012. Association of perfluorooctanoic acid with HDL cholesterol and circulating miR-26b and miR-199–3p in workers of a fluorochemical plant and nearby residents. Environ Sci Technol 46(17):9274–9281, PMID: 22862179, https://doi.org/10.1021/es300906q.
12. Eriksen KT, Raaschou-Nielsen O, McLaughlin JK, Lipworth L, Tjønneland A, Overvad K, et al. 2013. Association between plasma PFOA and PFOS levels and total cholesterol in a middle-aged Danish population. PLoS One 8(2):e56969, PMID: 23441227, https://doi.org/10.1371/journal.pone.0056969.
13. Kirk M, Smurthwaite K, Braunig J, Trevenar S, D'Este C, Lucas R, et al. The PFAS Health Study: systematic literature review. https://rsph.anu.edu.au/files/PFAS%20Health%20Study%20Systematic%20Review_1.pdf [accessed 9 February 2022].
14. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. 2019. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. J Expo Sci Environ Epidemiol 29(2):131–147, PMID: 30470793, https://doi.org/10.1038/s41370-018-0094-1.
15. Meneguzzi A, Fava C, Castelli M, Minuz P. 2021. Exposure to perfluoroalkyl chemicals and cardiovascular disease: experimental and epidemiological evidence. Front Endocrinol (Lausanne) 12:706352, PMID: 34305819, https://doi.org/10.3389/fendo.2021.706352.
16. Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, et al. 2021. Per- and polyfluoroalkyl substance toxicity and human health review: current state of knowledge and strategies for informing future research. Environ Toxicol Chem 40(3):606–630, PMID: 33017053, https://doi.org/10.1002/etc.4890.
17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 283(15):2008–2012, PMID: 10789670, https://doi.org/10.1001/jama.283.15.2008.
18. Bull S, Burnett K, Vassaux K, Ashdown L, Brown T, Rushton L. 2014. Extensive literature search and provision of summaries of studies related to the oral toxicity of perfluoroalkylated substances (PFASs), their precursors and potential replacements in experimental animals and humans. Area 1: data on toxicokinetics (absorption, distribution, metabolism, excretion) in *in vitro* studies, experimental animals and humans. Area 2: data on toxicity in experimental animals. Area 3: data on observations in humans. EFSA Support Publ 11(4):572E, https://doi.org/10.2903/sp.efsa.2014.EN-572.
19. Swat MJ, Grenon P, Wimalaratne S. 2016. ProbOnto: ontology and knowledge base of probability distributions. Bioinformatics 32(17):2719–2721, PMID: 27153608, https://doi.org/10.1093/bioinformatics/btw170.

20. Durrleman S, Simon R. 1989. Flexible regression models with cubic splines. Stat Med 8(5):551–561, PMID: 2657958, https://doi.org/10.1002/sim.4780080504.
21. Fu Y, Wang T, Fu Q, Wang P, Lu Y. 2014. Associations between serum concentrations of perfluoroalkyl acids and serum lipid levels in a Chinese population. Ecotoxicol Environ Saf 106:246–252, PMID: 24863755, https://doi.org/10.1016/j.ecoenv.2014.04.039.
22. He X, Liu Y, Xu B, Gu L, Tang W. 2018. PFOA is associated with diabetes and metabolic alteration in US men: National Health and Nutrition Examination Survey 2003–2012. Sci Total Environ 625:566–574, PMID: 29291571, https://doi.org/10.1016/j.scitotenv.2017.12.186.
23. Honda-Kohmo K, Hutcheson R, Innes KE, Conway BN. 2019. Perfluoroalkyl substances are inversely associated with coronary heart disease in adults with diabetes. J Diabetes Complications 33(6):407–412, PMID: 30928231, https://doi.org/10.1016/j.jdiacomp.2019.02.004.
24. Château-Degat ML, Pereg D, Dallaire R, Ayotte P, Dery S, Dewailly É. 2010. Effects of perfluorooctanesulfonate exposure on plasma lipid levels in the Inuit population of Nunavik (Northern Quebec). Environ Res 110(7):710–717, PMID: 20696425, https://doi.org/10.1016/j.envres.2010.07.003.
25. Seo SH, Son MH, Choi SD, Lee DH, Chang YS. 2018. Influence of exposure to perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects. Environ Int 113:149–161, PMID: 29425899, https://doi.org/10.1016/j.envint.2018.01.025.
26. Lin TW, Chen MK, Lin CC, Chen MH, Tsai MS, Chan DC, et al. 2020. Association between exposure to perfluoroalkyl substances and metabolic syndrome and related outcomes among older residents living near a science park in Taiwan. Int J Hyg Environ Health 230:113607, PMID: 32919137, https://doi.org/10.1016/j.ijheh.2020.113607.
27. Lin CY, Lee HL, Hwang YT, Su TC. 2020. The association between total serum isomers of per- and polyfluoroalkyl substances, lipid profiles, and the DNA oxidative/nitrative stress biomarkers in middle-aged Taiwanese adults. Environ Res 182:109064, PMID: 31884197, https://doi.org/10.1016/j.envres.2019.109064.
28. Fitz-Simon N, Fletcher T, Luster MI, Steenland K, Calafat AM, Kato K, et al. 2013. Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid. Epidemiology 24(4):569–576, PMID: 23685825, https://doi.org/10.1097/EDE.0b013e31829443ee.
29. Liu HS, Wen LL, Chu PL, Lin CY. 2018. Association among total serum isomers of perfluorinated chemicals, glucose homeostasis, lipid profiles, serum protein and metabolic syndrome in adults: NHANES, 2013–2014. Environ Pollut 232:73–79, PMID: 28923343, https://doi.org/10.1016/j.envpol.2017.09.019.
30. Olsen GW, Burris JM, Burlew MM, Mandel JH. 2003. Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. J Occup Environ Med 45(3):260–270, PMID: 12661183, https://doi.org/10.1097/01.jom.0000052958.59271.10.
31. Dunder L, Lind PM, Salihovic S, Stubleski J, Kärrman A, Lind L. 2022. Changes in plasma levels of per- and polyfluoroalkyl substances (PFAS) are associated with changes in plasma lipids—a longitudinal study over 10 years. Environ Res 211:112903, PMID: 35231461, https://doi.org/10.1016/j.envres.2022.112903.
32. Han X, Meng L, Zhang G, Li Y, Shi Y, Zhang Q, et al. 2021. Exposure to novel and legacy per- and polyfluoroalkyl substances (PFASs) and associations with type 2 diabetes: a case–control study in East China. Environ Int 156:106637, PMID: 33993001, https://doi.org/10.1016/j.envint.2021.106637.
33. Cakmak S, Lukina A, Karthikeyan S, Atlas E, Dales R. 2022. The association between blood PFAS concentrations and clinical biochemical measures of organ function and metabolism in participants of the Canadian Health Measures Survey (CHMS). Sci Total Environ 827:153900, PMID: 35218824, https://doi.org/10.1016/j.scitotenv.2022.153900.
34. Schillemans T, Donat-Vargas C, Lindh CH, de Faire U, Wolk A, Leander K, et al. 2022. Per- and polyfluoroalkyl substances and risk of myocardial infarction and stroke: a nested case-control study in Sweden. Environ Health Perspect 130(3):37007, PMID: 35285690, https://doi.org/10.1289/EHP9791.
35. Gilliland FD, Mandel JS. 1996. Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins, and cholesterol: a study of occupationally exposed men. Am J Ind Med 29(5):560–568, PMID: 8732932, https://doi.org/10.1002/(SICI)1097-0274(199605)29:5<560::AID-AJIM17>3.0.CO;2-Z.
36. Olsen GW, Burris JM, Burlew MM, Mandel JH. 2000. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem Toxicol 23(4):603–620, PMID: 11071397, https://doi.org/10.1081/dct-100101973.
37. Emmett EA, Zhang H, Shofer FS, Freeman D, Rodway NV, Desai C, et al. 2006. Community exposure to perfluorooctanoate: relationships between serum levels and certain health parameters. J Occup Environ Med 48(8):771–779, PMID: 16902369, https://doi.org/10.1097/01.jom.0000233380.13087.37.
38. Olsen GW, Zobel LR. 2007. Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. Int Arch Occup Environ Health 81(2):231–246, PMID: 17605032, https://doi.org/10.1007/s00420-007-0213-0.
39. Sakr CJ, Leonard RC, Kreckmann KH, Slade MD, Cullen MR. 2007. Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. J Occup Environ Med 49(8):872–879, PMID: 17693785, https://doi.org/10.1097/JOM.0b013e318124a93f.
40. Sakr CJ, Kreckmann KH, Green JW, Gillies PJ, Reynolds JL, Leonard RC. 2007. Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonium perfluorooctanoate or APFO) as part of a general health survey in a cohort of occupationally exposed workers. J Occup Environ Med 49(10):1086–1096, PMID: 18000414, https://doi.org/10.1097/JOM.0b013e318156eca3.
41. Costa G, Sartori S, Consonni D. 2009. Thirty years of medical surveillance in perfluorooctanoic acid production workers. J Occup Environ Med 51(3):364–372, PMID: 19225424, https://doi.org/10.1097/JOM.0b013e3181965d80.
42. Steenland K, Jin C, MacNeil J, Lally C, Ducatman A, Vieira V, et al. 2009. Predictors of PFOA levels in a community surrounding a chemical plant. Environ Health Perspect 117(7):1083–1088, PMID: 19654917, https://doi.org/10.1289/ehp.0800294.
43. Nelson JW, Hatch EE, Webster TF. 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. Environ Health Perspect 118(2):197–202, PMID: 20123614, https://doi.org/10.1289/ehp.0901165.
44. Olsen GW, Ehresman DJ, Buehrer BD, Gibson BA, Butenhoff JL, Zobel LR. 2012. Longitudinal assessment of lipid and hepatic clinical parameters in workers involved with the demolition of perfluoroalkyl manufacturing facilities. J Occup Environ Med 54(8):974–983, PMID: 22842914, https://doi.org/10.1097/JOM.0b013e31825461d2.
45. Jain RB, Ducatman A. 2019. Roles of gender and obesity in defining correlations between perfluoroalkyl substances and lipid/lipoproteins. Sci Total Environ 653:74–81, PMID: 30408670, https://doi.org/10.1016/j.scitotenv.2018.10.362.
46. Li Y, Barregard L, Xu Y, Scott K, Pineda D, Lindh CH, et al. 2020. Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water. Environ Health 19(1):33, PMID: 32169067, https://doi.org/10.1186/s12940-020-00588-9.
47. Fan Y, Li X, Xu Q, Zhang Y, Yang X, Han X, et al. 2020. Serum albumin mediates the effect of multiple per- and polyfluoroalkyl substances on serum lipid levels. Environ Pollut 266(pt 2):115138, PMID: 32717635, https://doi.org/10.1016/j.envpol.2020.115138.
48. Canova C, Barbieri G, Zare Jeddi M, Gion M, Fabricio A, Daprà F, et al. 2020. Associations between perfluoroalkyl substances and lipid profile in a highly exposed young adult population in the Veneto Region. Environ Int 145:106117, PMID: 32971418, https://doi.org/10.1016/j.envint.2020.106117.
49. Starling AP, Adgate JL, Hamman RF, Kechris K, Calafat AM, Ye X, et al. 2017. Perfluoroalkyl substances during pregnancy and offspring weight and adiposity at birth: examining mediation by maternal fasting glucose in the Healthy Start Study. Environ Health Perspect 125(6):067016, PMID: 28669937, https://doi.org/10.1289/EHP641.
50. Starling AP, Engel SM, Whitworth KW, Richardson DB, Stuebe AM, Daniels JL, et al. 2014. Perfluoroalkyl substances and lipid concentrations in plasma during pregnancy among women in the Norwegian Mother and Child Cohort Study. Environ Int 62:104–112, PMID: 24189199, https://doi.org/10.1016/j.envint.2013.10.004.
51. Kishi R, Nakajima T, Goudarzi H, Kobayashi S, Sasaki S, Okada E, et al. 2015. The association of prenatal exposure to perfluorinated chemicals with maternal essential and long-chain polyunsaturated fatty acids during pregnancy and the birth weight of their offspring: the Hokkaido Study. Environ Health Perspect 123(10):1038–1045, PMID: 25840032, https://doi.org/10.1289/ehp.1408834.
52. Yang J, Wang H, Du H, Fang H, Han M, Xu L, et al. 2021. Serum perfluoroalkyl substances in relation to lipid metabolism in Chinese pregnant women. Chemosphere 273:128566, PMID: 33097232, https://doi.org/10.1016/j.chemosphere.2020.128566.
53. Tian Y, Miao M, Ji H, Zhang X, Chen A, Wang Z, et al. 2021. Prenatal exposure to perfluoroalkyl substances and cord plasma lipid concentrations. Environ Pollut 268(pt A):115426, PMID: 33152632, https://doi.org/10.1016/j.envpol.2020.115426.
54. Dalla Zuanna T, Savitz DA, Barbieri G, Pitter G, Zare Jeddi M, Daprà F, et al. 2021. The association between perfluoroalkyl substances and lipid profile in exposed pregnant women in the Veneto Region, Italy. Ecotoxicol Environ Saf 209:111805, PMID: 33360787, https://doi.org/10.1016/j.ecoenv.2020.111805.
55. Kobayashi S, Sata F, Goudarzi H, Araki A, Miyashita C, Sasaki S, et al. 2021. Associations among perfluorooctanesulfonic/perfluorooctanoic acid levels, nuclear receptor gene polymorphisms, and lipid levels in pregnant women in the Hokkaido Study. Sci Rep 11(1):9994, PMID: 33976266, https://doi.org/10.1038/s41598-021-89285-2.
56. Cong J, Chu C, Li QQ, Zhou Y, Min Qian Z, Dee Geiger S, et al. 2021. Associations of perfluorooctane sulfonate alternatives and serum lipids in

Chinese adults. Environ Int 155:106596, PMID: 33940391, https://doi.org/10.1016/j.envint.2021.106596.
57. Batzella E, Girardi P, Russo F, Pitter G, Da Re F, Fletcher T, et al. 2022. Perfluoroalkyl substance mixtures and cardio-metabolic outcomes in highly exposed male workers in the Veneto Region: a mixture-based approach. Environ Res 212(pt A):113225, PMID: 35390304, https://doi.org/10.1016/j.envres.2022.113225.
58. Mi X, Wu LY, Liu JJ, Fang QL, Qian ZM, Chu C, et al. 2022. The effects of Cl-PFESAs exposure on blood lipids—a community-based large population study in Guangzhou. Sci Total Environ 806(pt 2):150634, PMID: 34597565, https://doi.org/10.1016/j.scitotenv.2021.150634.
59. Vuong AM, Braun JM, Sjödin A, Calafat AM, Yolton K, Lanphear BP, et al. 2021. Exposure to endocrine disrupting chemicals (EDCs) and cardiometabolic indices during pregnancy: the HOME Study. Environ Int 156:106747, PMID: 34425642, https://doi.org/10.1016/j.envint.2021.106747.
60. Fisher M, Arbuckle TE, Wade M, Haines DA. 2013. Do perfluoroalkyl substances affect metabolic function and plasma lipids?—analysis of the 2007–2009, Canadian Health Measures Survey (CHMS) Cycle 1. Environ Res 121:95–103, PMID: 23266098, https://doi.org/10.1016/j.envres.2012.11.006.
61. Frisbee SJ, Shankar A, Knox SS, Steenland K, Savitz DA, Fletcher T, et al. 2010. Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents: results from the C8 Health Project. Arch Pediatr Adolesc Med 164(9):860–869, PMID: 20819969, https://doi.org/10.1001/archpediatrics.2010.163.
62. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. 2011. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes 4(3):337–345, PMID: 21487090, https://doi.org/10.1161/CIRCOUTCOMES.110.959247.
63. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. 2007. Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 Western prospective studies. Circulation 115(4):450–458, PMID: 17190864, https://doi.org/10.1161/CIRCULATIONAHA.106.637793.
64. Shai I, Rimm EB, Hankinson SE, Curhan G, Manson JE, Rifai N, et al. 2004. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. Circulation 110(18):2824–2830, PMID: 15492318, https://doi.org/10.1161/01.CIR.0000146339.57154.9B.
65. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. 2005. Non–high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 112(22):3375–3383, PMID: 16316964, https://doi.org/10.1161/CIRCULATIONAHA.104.532499.
66. Jensen MK, Rimm EB, Furtado JD, Sacks FM. 2012. Apolipoprotein C-III as a potential modulator of the association between HDL-cholesterol and incident coronary heart disease. J Am Heart Assoc 1(2):jah3-e000232, PMID: 23130121, https://doi.org/10.1161/JAHA.111.000232.
67. Liu G, Zhang B, Hu Y, Rood J, Liang L, Qi L, et al. 2020. Associations of perfluoroalkyl substances with blood lipids and apolipoproteins in lipoprotein subspecies: the POUNDS-Lost study. Environ Health 19(1):5, PMID: 31931806, https://doi.org/10.1186/s12940-020-0561-8.
68. Rosen MB, Schmid JR, Corton JC, Zehr RD, Das KP, Abbott BD, et al. 2010. Gene expression profiling in wild-type and PPARα-null mice exposed to perfluorooctane sulfonate reveals PPARα-independent effects. PPAR Res 2010:794739, PMID: 20936131, https://doi.org/10.1155/2010/794739.
69. Chinetti G, Fruchart JC, Staels B. 2000. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. Inflamm Res 49(10):497–505, PMID: 11089900, https://doi.org/10.1007/s000110050622.
70. Steenland K, Fletcher T, Savitz DA. 2010. Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). Environ Health Perspect 118(8):1100–1108, PMID: 20423814, https://doi.org/10.1289/ehp.0901827.
71. Harada KH, Hashida S, Kaneko T, Takenaka K, Minata M, Inoue K, et al. 2007. Biliary excretion and cerebrospinal fluid partition of perfluorooctanoate and perfluorooctane sulfonate in humans. Environ Toxicol Pharmacol 24(2):134–139, PMID: 21783801, https://doi.org/10.1016/j.etap.2007.04.003.
72. Bjork JA, Butenhoff JL, Wallace KB. 2011. Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes. Toxicology 288(1–3):8–17, PMID: 21723365, https://doi.org/10.1016/j.tox.2011.06.012.
73. Marques LR, Diniz TA, Antunes BM, Rossi FE, Caperuto EC, Lira FS, et al. 2018. Reverse cholesterol transport: molecular mechanisms and the non-medical approach to enhance HDL cholesterol. Front Physiol 9:526, PMID: 29867567, https://doi.org/10.3389/fphys.2018.00526.
74. Kingsley SL, Walker DI, Calafat AM, Chen A, Papandonatos GD, Xu Y, et al. 2019. Metabolomics of childhood exposure to perfluoroalkyl substances: a cross-sectional study. Metabolomics 15(7):95, PMID: 31227916, https://doi.org/10.1007/s11306-019-1560-z.
75. Alderete TL, Jin R, Walker DI, Valvi D, Chen Z, Jones DP, et al. 2019. Perfluoroalkyl substances, metabolomic profiling, and alterations in glucose homeostasis among overweight and obese Hispanic children: a proof-of-concept analysis. Environ Int 126:445–453, PMID: 30844580, https://doi.org/10.1016/j.envint.2019.02.047.
76. Boslem E, Meikle PJ, Biden TJ. 2012. Roles of ceramide and sphingolipids in pancreatic β-cell function and dysfunction. Islets 4(3):177–187, PMID: 22847494, https://doi.org/10.4161/isl.20102.
77. Palomer X, Pizarro-Delgado J, Barroso E, Vázquez-Carrera M. 2018. Palmitic and oleic acid: the yin and yang of fatty acids in type 2 diabetes mellitus. Trends Endocrinol Metab 29(3):178–190, PMID: 29290500, https://doi.org/10.1016/j.tem.2017.11.009.
78. Guasch-Ferré M, Hruby A, Toledo E, Clish CB, Martínez-González MA, Salas-Salvadó J, et al. 2016. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. Diabetes Care 39(5):833–846, PMID: 27208380, https://doi.org/10.2337/dc15-2251.
79. Chen Z, Yang T, Walker DI, Thomas DC, Qiu C, Chatzi L, et al. 2020. Dysregulated lipid and fatty acid metabolism link perfluoroalkyl substances exposure and impaired glucose metabolism in young adults. Environ Int 145:106091, PMID: 32892005, https://doi.org/10.1016/j.envint.2020.106091.
80. Butenhoff JL, Bjork JA, Chang SC, Ehresman DJ, Parker GA, Das K, et al. 2012. Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight-day and ninety-day oral gavage studies. Reprod Toxicol 33(4):513–530, PMID: 21878386, https://doi.org/10.1016/j.reprotox.2011.08.004.
81. Forsthuber M, Kaiser AM, Granitzer S, Hassl I, Hengstschläger M, Stangl H, et al. 2020. Albumin is the major carrier protein for PFOS, PFOA, PFHxS, PFNA and PFDA in human plasma. Environ Int 137:105324, PMID: 32109724, https://doi.org/10.1016/j.envint.2019.105324.