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PFAS Exposures and the Human Metabolome: A Systematic Review of Epidemiological Studies

Sandra India-Aldana[1], **Meizhen Yao**[1], **Vishal Midya**[1], **Elena Colicino**[1], **Leda Chatzi**[2], **Jaime Chu**[3], **Chris Gennings**[1], **Dean P. Jones**[4], **Ruth J. F. Loos**[1,5,6], **Veronica W. Setiawan**[2], **Mathew Ryan Smith**[4,7], **Ryan W. Walker**[1], **Dinesh Barupal**[1], **Douglas I. Walker**[1], **Damaskini Valvi**[1]

[1]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1057, New York, NY 10029, USA

[2]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

[3]Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[4]Clinical Biomarkers Laboratory, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University, Atlanta, GA, USA

[5]Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[6]Faculty of Health and Medical Sciences, Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark

[7]Veterans Affairs Medical Center, Decatur, GA, USA

Abstract

Purpose of Review—There is a growing interest in understanding the health effects of exposure to per- and polyfluoroalkyl substances (PFAS) through the study of the human metabolome. In this systematic review, we aimed to identify consistent findings between PFAS and metabolomic signatures. We conducted a search matching specific keywords that was independently reviewed by two authors on two databases (EMBASE and PubMed) from their inception through July 19, 2022 following PRISMA guidelines.

Recent Findings—We identified a total of 28 eligible observational studies that evaluated the associations between 31 different PFAS exposures and metabolomics in humans. The most common exposure evaluated was legacy long-chain PFAS. Population sample sizes ranged from 40 to 1,105 participants at different stages across the lifespan. A total of 19 studies used a non-

✉Damaskini Valvi, dania.valvi@mssm.edu.

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targeted metabolomics approach, 7 used targeted approaches, and 2 included both. The majority of studies were cross-sectional (n = 25), including four with prospective analyses of PFAS measured prior to metabolomics.

Summary—Most frequently reported associations across studies were observed between PFAS and amino acids, fatty acids, glycerophospholipids, glycerolipids, phosphosphingolipids, bile acids, ceramides, purines, and acylcarnitines. Corresponding metabolic pathways were also altered, including lipid, amino acid, carbohydrate, nucleotide, energy metabolism, glycan biosynthesis and metabolism, and metabolism of cofactors and vitamins. We found consistent evidence across studies indicating PFAS-induced alterations in lipid and amino acid metabolites, which may be involved in energy and cell membrane disruption.

Keywords

PFAS; Metabolomics; Human metabolome; Endocrine-disrupting chemicals; Systematic review

Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a group of widespread human-made fluorinated compounds that can contribute to deleterious health effects and chronic diseases in humans [1, 2]. Estimates from recent data derived from the National Health And Nutrition Examination Survey (NHANES) show that PFAS can be detected in nearly every sample [3, 4], with perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexanesulfonic acid (PFHxS) being present in at least 99% of the U.S. population [5]. While certain long-chain, or so-called legacy PFAS, such as PFOS and PFOA are being phased out in many countries [6], a new generation of short-chain PFAS chemicals are being introduced with limited knowledge on their short- and long-term health effects in humans. Early indications in observational studies point at the persistent nature of these chemicals through overall long half-life, bioaccumulation, and slow degradation rate in the environment and in the human body [7–9]. In prior research, PFAS exposures have been linked to a wide array of diseases including, but not limited to, increased risk of cancer [10, 11], asthma [12], altered immune [13], thyroid [14, 15], or liver function [16], kidney damage [17], altered pregnancy outcomes [18], and cardiometabolic disease [19–21]. These effects are observed in occupational and non-occupational settings and in both adult and child cohorts. Particular attention has been placed on the metabolic effects of PFAS in metabolic syndrome [1], a complex combination of metabolic abnormalities including insulin resistance, dyslipidemia, glucose intolerance, hypertension, and obesity [22]. Mechanisms underlying PFAS toxicity in humans are not yet fully understood, but exposure to PFAS has been hypothesized to play a role in pathways modulating insulin resistance and lipid metabolism, such as oxidative stress, inflammation, peroxisome proliferator-activated receptor (PPAR) signaling, metabolic hormones (i.e., adipokines, insulin) or sex steroid hormones [21, 23–27].

Newly available emerging high-throughput technologies have made possible the investigation of the human metabolome as a novel way to understand mechanisms of health and disease [28]. Metabolomics is the study of metabolites (or small molecules) within the body, tissues, and cells, at a large-scale. Metabolomic approaches have the ability to

characterize the human exposome and are considered a promising tool to potentially unravel the etiology of certain diseases [29–31]. Only one scoping review has been conducted on PFAS and metabolomics previously, including untargeted metabolomics studies only [32]. To our knowledge, we compile for the first time a systematic review of all epidemiological studies that have examined PFAS exposures and metabolomics using both targeted and untargeted approaches. In this review, we summarized the human metabolite pathways associated with PFAS exposure, highlighting the major and common pathways identified across studies to gain more insight into biological responses of PFAS exposures in humans. We also discuss current research gaps and possible avenues of future research.

What Are PFAS? Definition and Types

PFAS are a group of ubiquitously manufactured chemicals that have been broadly used worldwide in consumer and industrial products for their properties as surfactants and their coating resistance to heat, oil, stains, or water. PFAS are aliphatic substances made of strong carbon-fluoride bonds that give these compounds their slow degradation rate and enduring properties in the environment and within the human body [33]. PFAS half-lives in humans reported in published literature to date are summarized in Table S1. PFAS compounds have a characteristic perfluoroalkyl moiety, where for one or more carbon atoms the hydrogens have been replaced by fluorine atoms, as well as a functional group [34] conferring them both hydrophobic and lipophobic properties [35, 36]. Depending on the number of carbons, a PFAS compound is referred to as either long-chain or short-chain (Table 1). Long-chain PFAS usually refer to any perfluoroalkyl carboxylic acid containing 8 carbons or greater, or any perfluoroalkyl sulfonic acid containing 6 carbons or greater. Perfluoroalkyl carboxylic acids and sulfonic acids containing less than 8 and 6 per-fluorinated carbons, respectively, are commonly referred to as short-chain PFAS [34, 37]. The longer their fluorinated carbon chain the more PFAS are thought to bioaccumulate, as suggested in previous animal studies [38–40], and thus are more subjected to monitoring [41]. PFOA and PFOS are two of the most common long-chain PFAS studied. While regulation tends to focus more on long-chain PFAS [42], short-chain PFAS also present a wide array of concerns. Short-chain PFAS can be considered toxic [43] and as persistent as long-chain PFAS [44]. They have a potential long-range transport in both biotic and abiotic environments compared to their long-chain counterparts [45, 46]. This high mobility [47, 48] means that they may reach bodies of water from which they are harder to remove than long-chain PFAS due to their lower adsorption potential [46, 49]. A limited number of PFAS have been considered in biomonitoring and health studies to date. However, it is estimated that more than 4700 PFAS exist [50–52] and at least 3000 are readily available in products currently on the market [53, 54].

Sources of Human Exposure to PFAS

PFAS have been in use in industry and consumer products since their introduction in the 1940s [55]. Common PFAS sources range from site-specific and occupational exposures (military bases, airport sites, fire-fighting foams) to everyday consumer products, such as cookware, food packaging, impermeable gear, furniture, carpeting, coatings and paint, or cosmetics, among others [56–58]. The most prevalent PFAS exposure routes in humans are via dietary sources or contaminated water (oral route), followed by inhalation of dust or air particles, and dermal absorption [59, 60]. To date, PFAS have been detected in rivers, rain

water, soil, and ambient air of major cities around the world, as well as in remote areas [61]. There are no current adequate safety limits to PFOS or other PFAS in drinking water in most countries, and there are no proven safe levels of PFAS at lower dosages. For instance, even low doses of PFAS have been linked to adverse health effects in humans, such as decreased antibody response [62–64]. Additional routes of exposure also include early life exposure routes via the placenta and breastfeeding [65–67]. Prenatal and early-life PFAS exposures are particularly important, yet understudied, as they may contribute significantly to programming of later chronic health outcomes in adulthood [68].

PFAS Transport and Clearance in Human Body

Given the persistent nature of PFAS, with an average half-life ranging from a few days or months to several decades (Table S1), bioaccumulation in humans has raised concerns. PFAS are structurally similar to fatty acids, but unlike other persistent organic pollutants, such as organochlorine and brominated compounds, PFAS compounds do not tend to accumulate in lipid tissue. Instead, due to their polar hydrophobic fluorine content, PFAS have a higher affinity for proteins [69–71]. After ingestion, PFAS tend to concentrate in high protein density tissues, such as compounds in blood, binding to serum albumin [72]. Protein-rich tissues, such as the liver and blood, are major repositories of perfluorinated acids [73, 74]. Interestingly, an intervention study showed a decrease in serum and plasma PFAS levels of Australian firefighters after blood donation [75]. Not surprisingly, PFAS are also commonly detected in human breast milk [76], which has high antimicrobial and digestive enzymatic activity [77, 78]. In addition to primarily accumulating after adsorption in media with high-protein content, such as liver and serum, PFAS can also accumulate in other organs, including the lungs, bone, brain, and kidney [79, 80]. While the primary route of PFAS clearance is through the kidney in animal studies [72, 81], renal urine excretion in humans has been modeled to be low for these compounds [82] highlighting the persistent nature and difficult elimination of these compounds, particularly long-chain PFAS. Despite PFAS secretion via urine, an albumin-based reabsorption mechanism in the kidneys contributes to low elimination rates [83]. Sex steroid hormones have also been observed to take part in facilitating renal clearance in animals [84]. Additionally, fecal excretion has been suggested as a potential route of PFAS elimination [85, 86]. In women, lactation, parity, and menstruation are other alternative excretion routes that may provide an advantage, compared to males, in terms of more rapid PFAS secretion from the body [87–90]. This is consistent with the higher levels of some PFAS found in males compared to women [3], yet this sex difference in clearance may narrow as a function of age and menopausal status [91, 92].

Characterization of Exposure–Disease Mechanisms via Metabolomics

The metabolome refers to the collection of all the molecules (organic or inorganic) playing a role in physiological processes in the body or present in cells and tissues. The human metabolome can include metabolites involved in endogenous cellular processes, as well as metabolites external to the body such as dietary factors, xenobiotics, and environmental contaminants. Analytical methods using high-throughput technologies have emerged as novel tools to examine comprehensively both exogenous chemicals as well as endogenous metabolites in the body at a granular level. Targeted methods have been developed for

a priori preselected metabolites while untargeted methods holistically and systematically analyze a wide array of metabolites in an organism by maximizing the number of metabolite features detected. Numerous laboratory methods, such as nuclear magnetic resonance (NMR) and liquid chromatography-mass spectrometry (LC–MS), enable the detection of metabolites. Recent advances, particularly in high-resolution metabolomics (HRM), such as ultra-high-resolution mass spectrometry (UHRMS), have allowed for an even more comprehensive characterization of exogenous and endogenous metabolites present at lower concentrations in the body [28, 93]. The use of metabolomics as a tool to better understand the mechanisms associated with disease is still at its early stages. So far, metabolomics has facilitated the assessment of the effects from PFAS exposure in humans in recent studies, indicating putative intermediary markers for the initiation and progression of various diseases, such as cardiometabolic disease [29], diabetes [30], and cancer [31]. For instance, candidate metabolites like glucose or creatine have been hypothesized as biomarkers for diagnosis or prognosis of diseases [94] as metabolomics data encompass the downstream phenotypic product after gene transcription and translation [95], as well as suggest possible interaction effects or cross-talk between the exposome and endogenous biological systems.

Methods

We conducted a systematic review following PRISMA guidelines [96] and selected studies that investigated human PFAS exposures (either studied as single compounds or as a mixture) in relation to metabolic profiling using high-throughput metabolomics technologies. Inclusion criteria were detailed in advance and registered in PROSPERO (ID: 327,196; access registration via https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=327196).

Search Strategy

We searched research articles found on EMBASE and PubMed databases from their inception through July 19, 2022. Two reviewers independently performed a study selection of eligible epidemiological research articles. Our search was based on matching words contained in the title, abstract, or as keywords including “PFAS” or “perfluoroalkyl” or “polyfluoroalkyl,” and “metabolomics” or “metabolome” or “metabolic profiles,” among others. A full list of terms and search strategy is provided in the Supplementary Material (Supplementary Material, Methods) as well as in PROSPERO.

Study Selection

Eligible studies included original epidemiological research articles reported as full-text articles in English that predominantly focused on at least one PFAS exposure and with metabolomics data (either as a primary or secondary outcome, or either as targeted or untargeted). Lipidomics studies were also included under the targeted study category. All research studies made use of high-throughput approaches for metabolite profiling. Research articles that focused solely on metabolic biomarkers with no metabolomic analytic approach used were excluded from this review. Studies with metabolomics data were eligible from any human biofluid sample as long as the study was epidemiological; animal studies, as well

as experimental studies with human samples conducted *in vitro* or *in vivo* were ineligible (Supplementary Material, Methods).

Data Extraction from Eligible Studies

Data extraction of eligible studies included first-author, year of publication, study design, sample size, participant characteristics and location, years of follow-up (if applicable), number and nomenclature of PFAS examined, window of exposure (and year), number of metabolites measured (outcome), metabolomics analytical method (including reported level of confidence in metabolites [97]), data pre-processing, statistical methods (including false discovery rate correction), chemical databases used for identification or classification of the metabolites and pathways, summary of findings (analyzed metabolites and pathways), biological significance, adjusted confounders, effect modifiers, limitations, and additional findings. When possible, we classified each PFAS-associated metabolite using the criteria denoted by the human metabolome database (HMDB) (https://hmdb.ca/) and pathways using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (https://www.genome.jp/kegg/pathway.html). When a particular metabolite identifier was not found in the HMDB database, the Chemical Entities of Biological Interest (ChEBI) (https://www.ebi.ac.uk/chebi/) and LipidMaps (https://www.lipidmaps.org/) were used instead.

Quality Assessment

We evaluated the quality of each study based on their limitations and potential biases. We created a quality score following 5-point criteria based on epidemiological [98] and metabolomics guidelines [99, 100] where points were assigned for each of the following: sample size (≥ 100 vs < 100 participants), adjustment for confounders (adjusted vs. none), false discovery rate (FDR-adjustment vs. no correction), study design (prospective vs. not prospective), and reporting of confidence level 1 metabolites identified according to the Metabolomics Standards Initiative (MSI). A higher score indicated a higher quality of evidence.

Data Synthesis

We summarized the evidence for reported PFAS associations with individual metabolites or dysregulated metabolic pathways to identify consistent findings and research gaps. In this review, we refer to consistent findings as those metabolites, metabolite classes, or pathways reported most frequently across studies (Figs. 2–6, Table S5), but we also report consistent directionalities based on the total number of metabolite associations independent of study number (Figs. S1–S3, Table S3–S4); we either presented the number of studies reporting specific PFAS-metabolite associations or the total number of reported PFAS-metabolite associations in all studies. We classified each reported metabolite by HMDB superclass, class, and subclass categories. We also specified the directionality of the association reported, as well as the PFAS exposure (either a combination of several PFAS mixtures or the individual PFAS studied) and metabolomics approach followed (either targeted or untargeted). Pathway analyses across studies were also summarized by KEGG modules and submodules. In our summary, we included results from correlation analyses, analyses adjusting for covariates, and analyses implementing FDR-correction. If a study presented more than one type of analysis, we extracted the results that were considered more

rigorous (FDR-corrected and/or covariate-adjusted). In order to complement the summary of pathways reported across studies, we extracted each reported metabolite by study and conducted an independent pathway analysis using a systematic method with Reactome (https://reactome.org) [101]. We extracted each identified metabolite name reported in the articles and converted them to KEGG IDs. In the case of lipids, when unsure, we searched on LipidMaps, and if a *m/z* ratio was provided, we matched it with what was reported by the study. Studies were included in Reactome analyses if they reported any PFAS-metabolite association with an available metabolite KEGG ID recognizable by Reactome ($n = 26$). We then used the KEGG IDs for each compound and uploaded them in Reactome to evaluate the pathways inferred from positive associations, negative associations, and all associations for each study separately. Lastly, we calculated combined *p*-values for top pathways across studies [240, 241]. Quantitative summaries for descriptive statistics and visualizations for main findings were implemented in R (version 4.1.2).

Results

Description of Studies included in the Review

Out of 358 records retrieved from EMBASE ($n = 207$) and PubMed ($n = 151$), a total of 28 unique records for original studies evaluating PFAS exposures and human metabolomics that were observational in design and in English language were eligible for this systematic review (Fig. 1). Effects of 31 different PFAS exposures (including isomers) have been evaluated in relation to the human metabolome across studies, with the most common exposure being legacy long-chain PFAS, such as PFOA, PFOS, and PFHxS (Table 1). We accounted for PFAS that are included in the final analytic dataset across studies (Table S2) and described their reported distributions in Table 1. While the majority of studies examined single and mixed exposures to PFAS, there are several studies that examined other pollutants as well [31, 102–110]. Only one study [109] examined PFAS-metabolite associations adjusting for other pollutants in partial correlation analyses and another two studies (Li et al. [31] and Matta et al. [104]) implemented multi-pollutant models (PCBs in combination with PFAS). Most PFAS were measured in samples collected during the 2000s and only four studies had samples measured prior to 1999 [31, 111–113]. The majority of studies measured PFAS exposures during adulthood ($n = 15$), followed by prenatally or perinatally ($n = 9$), and/or in childhood or adolescence ($n = 7$) (Tables 2 and 3, Table S2). Sample sizes across eligible studies also ranged widely from 40 to 1,105 participants recruited across three different continents as follows: America ($n = 11$ in the USA), Asia ($n = 9$), and Europe ($n = 2$ in Sweden, $n = 2$ in Finland, $n = 1$ in France, $n = 1$ in Spain, and $n = 2$ across Europe).

A total of 19 studies reported a non-targeted metabolomics approach, 7 studies used a targeted metabolomics approach, and 2 studies included both approaches. The most common analytical method used in samples was LC–MS or LC-HRMS ($n = 11$), followed by UHPLC-, UPLC-, HPLC-, or LC-qTOF-MS ($n = 7$), HPLC-, UPLC-, or LC–MS/MS ($n = 7$), and LC/Orbitrap-MS or UPLC-Q-Orbitrap HRMS ($n = 2$). Other methods such as ^{1}H-NMR ($n = 1$) or GC–MS ($n = 1$) were less commonly used for metabolomics analyses.

Metabolomics data were collected from several media across studies: in serum (n = 16), plasma (n = 10), urine (n = 2), or semen samples (n = 1). Most studies measured metabolomics in a single sample collected from participants, with only two studies integrating repeated metabolomics measures in plasma [114] or urine [102].

The majority of studies were cross-sectional (n = 25), including four [30, 102, 114, 115] with additional prospective analyses of PFAS measured prior to metabolomics. Several studies focused as well on examining associations with a specific disease or biomarker for disease (n = 18). Cardiometabolic outcomes were the most studied diseases in relation to PFAS exposure, including overall diabetes [105], type 2 diabetes [111, 113] type 1 diabetes [30], obesity [105], hypertension [105], dyslipidemia [105], hyperuricemia [105], non-alcoholic fatty liver disease or steatohepatitis [108, 116], in addition to cardiometabolic markers (insulin resistance, lipids, glucose level, adiposity, BMI, or liver injury) [29, 106, 109, 115, 117, 118]. A few other studies also examined reproductive outcomes (semen quality [107] or endometriosis [104]), birth weight or small-for-gestational age [119], breast cancer [31], celiac disease [114], and COVID-19 [120]. Overall, most articles had a medium to high-level quality score with Kingsley et al. [121], Maitre et al. [102], Salihovic et al. [117], Hu et al. [112], and Chang et al. [119] studies scoring the highest based on the aforementioned criteria (Table S2).

Summary of Individual Metabolites Linked to PFAS Exposures Across Studies

A total of 546 unique metabolite features, either classifiable or identifiable under HMDB, ChEBI, or LipidMaps (with reported names), were found to be dysregulated by PFAS exposures across studies. PFAS were associated more frequently with lipid metabolites, followed by organic acids and derivatives (Fig. 2, Figures S1-S3). More specifically, metabolites that appeared significant most frequently across all studies pertained to the class of chemicals fatty acyls (present in n = 26 studies), carboxylic acids and derivatives (n = 26 studies), glycerophospholipids (n = 23 studies), steroids and steroid derivatives (n = 18 studies), or sphingolipids (n = 16 studies) (Fig. 2). Overall, a positive association between PFAS and metabolites was more frequently reported across studies, particularly for fatty acyls, imidazopyrimidines, and benzene and substituted derivatives, whereas a negative association was reported for sphingolipids in more studies. A sensitivity descriptive analysis was conducted restricting to studies that included a metabolite confidence level 1 in their results (Figure S4), which yielded consistent findings for most metabolite classes; PFAS had an overall positive association with imidazopyrimidines, benzene and substituted derivatives, organooxygen and organonitrogen compounds, while a negative association was found for sphingolipids across studies. Other metabolite classes had approximately a similar positive-to-negative association number ratio ± 1 study, with the exception of fatty acyls which were observed to revert in directionality with respect to PFAS but the number of studies in our sensitivity analysis was reduced significantly (from n = 26 studies that initially reported any PFAS-metabolite associations to only n = 11). Among all untargeted metabolomics data, the most common metabolites reported were glycerophospholipids (40.3%), fatty acyls (23.2%), sphingolipids (9.3%), carboxylic acids and derivatives (8.1%), glycerolipids (6.1%), and steroids (4.7%) (Figure S1). A similar distribution of metabolites was also observed in studies reporting a targeted approach, where PFAS were found to be related the most

to the following metabolite classes: glycerophospholipids (33.6%), glycerolipids (15.6%), sphingolipids (13.0%), carboxylic acids and derivatives (10.0%), steroids (9.1%), and fatty acyls (6.2%) (Figure S2). Overall, the most frequent PFAS-metabolite associations were observed with respect to glycerophospholipids, followed by fatty acyls (Figure S3).

Long-chain legacy PFAS were the predominant PFAS compound forms that were most examined in relation to metabolomics and also the most frequently associated with different metabolic profiles (Table S3). These include primarily PFOA, PFOS, and PFHxS, followed by PFDA, PFNA, and PFUnDA. We observed a fewer number of associations for other long-chain PFAS such as PFTrDA, PFHpS, and EtFOSAA, short-chain PFAS (PFHpA, PFPeA), or novel PFAS (Cl-PFESAs). In terms of the total number of metabolites, an overall consistency in the directionality of associations was particularly observed between PFAS homologues and increased number of fatty acids [17, 29, 105, 110, 113, 117, 120, 122, 123], glycerophospholipids (glycerophosphocholines and glycerophosphoethanolamines) [105–108, 111, 115, 117, 124, 125], glycerolipids (triradylcglycerols, diradylglycerols, monoradylglycerols) [106, 108, 111, 113, 114, 124], bile acids [31, 105, 108, 109, 114, 119, 124], and to a lesser extent, for fatty acid esters (acylcarnitines) [17, 105, 107, 112, 118, 120], amino acids [17, 29, 102, 105, 106, 108, 111, 112, 115, 116, 119, 120], phosphosphingolipids (sphingomyelins) [105, 111, 115, 124, 125], purines [17, 105, 112, 117, 119], sulfated steroids [105, 119], glycerophosphoinositols [105], carnitine [105, 112], and benzoic acids [105, 106, 120]. On the other hand, cholestane steroids [105, 108, 112], quinone, and hydroquinone lipids [105] appeared to be consistently downregulated in relation to PFAS. Ceramides were frequently reported as being potentially altered by PFAS, though with unclear or inconsistent directionality [105, 108, 124].

At the metabolite-level, we found an overlap in the number of significant metabolites across studies (Table S4). A particularly high number of metabolites that were reported in at least three studies in relation to PFAS exposures were an increase in docosahexaenoic acid (Schillemans et al. [113], Li et al. [122], Salihovic et al. [117]), phosphatidylcholine (PC) 40:6 (Salihovic et al. [117], Sinisalu et al. [124], You et al. [105]), creatine (Jin et al. [116], Hu et al. [112], You et al. [105]), and uric acid (Salihovic et al. [117], You et al. [105], Chang et al. [119]). Overall, an additional 15 metabolites were consistently upregulated (PC 35:1, PC 36:5, PC 38:5, PC 38:6, PC 40:5, ether-linked phosphatidylcholines PC O-38:5, PC O-40:4, triacylglycerols TG 54:2, TG 54:5, TG 54:1, glycochenodeoxycholic acid, pyroglutamic acid, phenylalanine, succinate or succinic acid, carnitine), two were downregulated (glycine, betaine), and two were either upregulated and downregulated (deoxycholic acid) or for which directionality was not reported (methionine) across several studies.

Summary of Dysregulated Pathways Linked to PFAS Exposures Across Studies

In pathway analyses, a total of 101 different pathways were reported to be significantly altered in relation to PFAS exposures. In Table S5, we classified these PFAS-related pathways based on KEGG identifiers. There were 10 untargeted studies (Jin et al. [116], Lu et al. [17], Kingsley et al. [121], Li et al. [31], Alderete et al. [29], Li et al. [122], Salihovic et al. [117], Hu et al. [112], Chang et al. [119], Chen et al. [118]) and 3 targeted studies (Sen

et al. [108], Ji et al. [120], Stratakis et al. [115]) that examined metabolic pathways related to PFAS using Mummichog, pathway enrichment analysis in MetaboAnalyst, or the KEGG database. Out of these 13 studies, the majority (8 studies) conducted analyses adjusting for confounders and incorporating FDR-correction (Jin et al. [116], Kingsley et al. [121], Alderete et al. [29], Li et al. [122], Salihovic et al. [117], Hu et al. [112], Chang et al. [119], Ji et al. [120]).

The most frequently reported alteration of metabolism in most studies was among amino acids followed by lipid, carbohydrate, and metabolism of cofactors and vitamins, accounting for 27%, 25%, 15%, and 9% of the total significant PFAS-induced pathway associations across studies, respectively (Table S5, Fig. 3). The predominant pathways of amino acid metabolism included alanine and aspartate ($n = 7$), aspartate and asparagine ($n = 6$), arginine and proline ($n = 6$), urea cycle ($n = 5$), lysine ($n = 5$), and glutamate ($n = 5$). The predominant pathways of lipid metabolism involved glycerophospholipid ($n = 8$), linoleate/linoleic acid ($n = 6$), glycosphingolipid ($n = 5$), glycosphingolipid biosynthesis ($n = 5$), bile acid-related pathways ($n = 3$), or fatty acid-related pathways ($n = 15$). The most prevalent pathways of carbohydrate metabolism involved butanoate ($n = 4$), TCA cycle ($n = 3$), sialic acid ($n = 3$), glycolysis/gluconeogenesis ($n = 3$), glyoxylate and dicarboxylate ($n = 3$). The most frequent pathways of vitamin and cofactor metabolism involved vitamin A ($n = 3$), vitamin B3 ($n = 4$), and vitamin D3 ($n = 3$). In addition, PFAS exposure also contributed to the alteration of several additional pathways: nucleotide metabolism (5%, i.e., purine and pyrimidine metabolism), glycan biosynthesis and metabolism (5%, i.e., N-glycan degradation/biosynthesis, keratan/chondroitin/heparin sulfate degradation), energy metabolism (4%, i.e., nitrogen metabolism), metabolism of other amino acids (3%, i.e., beta-alanine metabolism), or xenobiotic metabolism (3%). Results for other pathways were reported less consistently across studies.

Similar pathway results were found in our analyses using Reactome where metabolites participating in membrane transport, lipid-related, or amino acid-related mechanisms were predominant across studies (Fig. 4A–C and Tables S6-S8). A complete list of Reactome pathways including those that appeared less frequently across studies were also shown in Tables S9-S11. Top pathways associated with metabolites involved in the potential deleterious effects of PFAS belonged to transmembrane transport, transport of bile salts and organic acids, metal ions and amine compounds, plasma lipoprotein remodeling pathways (including HDL), phospholipid and phospholipase-related pathways (PLC beta mediated events or phospho-PLA2), phagocytosis, amino acid transport across the plasma membrane, Golgi-to-ER transport, glucose-dependent insulinotropic polypeptide, or acyl chain remodeling of lipids, among others (Fig. 4C, Table S6). Additional pathways were observed when we conducted analyses separately with metabolites from positive and negative PFAS associations (Fig. 4A, B, Tables S7-S8). For instance, while pathways implicated in triglyceride metabolism were present in studies that reported positive PFAS-metabolite associations (Table S7), immune system or ceramide signaling pathways, as well as amino acid transport across the plasma membrane, were predominant across studies that reported metabolites with inverse PFAS associations (Table S8). In addition to the top pathways (present in 25% of the studies and with an FDR < 0.05), summaries for Reactome pathways specific to lipid and amino acid metabolism are shown in Figs. 5 and 6. It is

noteworthy that at least 3 studies showed a pathway enrichment for PPAR-αregulation of lipid metabolism, lipid particle organization, sphingolipid, and phospholipid metabolism (Fig. 5), as well as catabolism of tryptophan, threonine, and choline, creatine metabolism, and carnitine synthesis (Fig. 6).

PFAS-Metabolomic Associations Reported Between Disease and Control Populations

Nearly half of the studies included in this review (n = 13) made reference to populations with a specific disease or populations at increased risk for disease for whom metabolomics data were analyzed. Three studies evaluated metabolomics in patient populations: Jin et al. [116] in children with nonalcoholic fatty liver disease (NAFLD), Ji et al. in COVID-19 patients [120], and Sen et al. [108] in NAFLD patients undergoing a laparoscopic bariatric surgery. Another three metabolomics studies were conducted in population subgroups at high risk for disease: Chen et al. [118] focused on children who had a history of being overweight or obese but did not have diabetes or other disease, Mitro et al. [111] focused on adult participants at higher risk for diabetes (with BMIs of above 24 and with high levels of fasting plasma glucose), and Alderete et al. [29] focused on children with high risk of T2D but without clinical diagnosis. Lastly, nearly seven studies reported PFAS-associated metabolite features separately in disease patients (or at increased risk for disease) and control populations: Stratakis et al. [115] compared children with high vs. low liver injury risk, Schillemans et al. [113] compared T2D and control pairs, Li et al. [31] and Hu et al. [112] examined breast cancer cases and controls but no metabolomics comparison was conducted, You et al. [105] compared cases with hyperuricemia and controls, Matta et al. [104] compared women with and without endometriosis, and Sinisalu et al. [114] evaluated metabolomics on celiac disease patients and healthy controls. When comparing PFAS-metabolite associations in a cardiometabolic disease population with a healthy control group, Stratakis et al. [115] found primarily increases in several branched-amino acids, and lipid alterations (glycerophospholipids and sphingomyelins), Schillemans et al. [113] study observed primarily increases of glycerophospholipids and diacylglycerols linked to T2D odds ratios, and You et al. [105] compared differential metabolites in hyperuricemia patients versus controls (but disregarding PFAS exposure status) showing alteration in several lipids and aminoacids. Sinisalu et al. [114] conducted metabolomics analyses with respect to celiac patients and controls and showed alterations in lipid and bile acid metabolism triggered by PFAS exposure in infants who developed celiac disease later in life in comparison to healthy controls. Lastly, Matta et al. [104] observed a differential metabolome (lipids and functional metabolite ratios) between cases of endometriosis and controls but disregarding PFAS exposure levels between groups.

PFAS Effects During Susceptible Windows of Exposure

Given the different ages from populations included in reviewed studies, we evaluated potential differential patterns across life stages focusing on early life exposures or sensitive windows of exposure. We observed reports of alterations to amino acids during the prenatal period [102, 119], as well as alterations in the metabolism of several vitamins (B3, D, and retinol) [112, 119, 122] and dysregulation of imidazopyrimidines in pregnant women [112, 119]. These findings (dysregulation of imidazopyrimidines, amino acids, and vitamins) were also consistent with findings in adults. Additionally, we observed that aromatic amino acids

[29, 116] and arginine or related pathways [29, 116, 121], were particularly specific to associations found in children across studies in this review.

Discussion

This systematic review highlights the potential for PFAS exposures to alter several metabolic pathways in humans as reported by recent investigations of the human metabolome. The studies summarized in this review were recently published, with the oldest publication being in 2017, highlighting the relevance of this emerging field. We found consistent evidence across several observational studies suggesting that PFAS exposures are associated with dysregulations in lipid and amino acid metabolites and related pathways particularly relevant to metabolic disease in humans. Many of these pathways may be involved in energy and cell membrane disruption. We additionally observed both potentially similar and divergent effects of PFAS by age or developmental stages. Research gaps from the reviewed studies include the lack of prospective studies or longitudinal measures of PFAS and metabolomics over the life-course, as well as limited adjustment for relevant confounders. The majority of studies to date have evaluated long-chain legacy PFAS. Therefore, future research to study emerging and shorter chain PFAS, either as individual compounds or as exposure mixtures, is warranted.

Potential Dysregulated Pathways Linked with PFAS Exposures in Humans

Growing evidence from previous epidemiological and experimental studies indicate that PFAS can alter health via increased oxidative stress, inflammation, peroxisome proliferator-activated receptor (PPAR) signaling, or sex steroid hormone mechanisms [23–26, 126]. PPARs are nuclear receptors that regulate fatty acids, lipids, and glucose metabolism [127]. A variety of PFAS have been shown to activate PPARα, primarily expressed in the liver, in human cells *in vitro* [128–130]. Several mechanisms for PFAS toxicity in mammals also show that PFAS can incur damage via non-PPARα-dependent pathways, such as other nuclear receptors (i.e., PPARγ, CAR, ERα) [131–135] inducing gene expression changes, altering mitochondrial function [136–138] modifying membrane fluidity [139], or inhibiting gap junction intercellular communication [131, 140, 141]. Similarly, findings from Reactome pathway analyses in this review also highlighted that PFAS may modify transmembrane, lipid, and amino acid metabolism. Of note, alterations in PPAR-mediated mechanisms were also among the most recurrent (present in at least 3 studies with FDR < 0.05) PFAS-induced pathways related to lipid metabolism in this review.

At the molecular level, the potential for PFAS as endocrine disruptors is reflected in their capacity to bind to other proteins, their structure similar to that of fatty acids, and their putative involvement in the displacement of endogenous ligands, which could explain their high retention in human serum and the potential to alter lipid metabolism and the hormonal system. For instance, PFAS can interfere with binding to albumin [142, 143], sex hormone-binding globulin [144], corticosteroid-binding globulin [71], and liver fatty acid-binding protein (L-FABP) [145]. PFAS also can compete with thyroxine in binding to thyroid hormone transport protein or receptors [146, 147], which could lead to a potential decrease in the normal levels of circulating hormones and derivatives (i.e., thyroid hormone,

SHBG) resulting in hormone dysregulation. In our review, we found that PFAS altered levels of steroid-related and bile acid-related pathways and metabolites, such as pregnane steroids [102, 122], overall levels of sulfated steroids [105, 119], and bile acids were increased [105, 106, 108, 109, 114, 119, 122, 124], and levels of cholestane steroids were decreased [105, 108, 112]. Similarly, previous metabolomic studies on PFAS toxicity in animals indicated that PFAS exposures modulated metabolic pathways related to sterols and bile acids in mice [148]. This is consistent with findings from pathway analyses in Reactome indicating bile acid transport dysregulation and a moderate alteration of steroid metabolism. Overall, the findings from our systematic review parallel prior findings in animal studies, which together support a causal role for PFAS on disrupting endocrine pathways.

Our review detected a disproportionately higher number of lipids and membrane function-related pathways across studies and across pathway analyses. Glycerophospholipids, the main type of lipid in the cell membrane, may be an important component in driving cellular accumulation of PFAS. More specifically, in our review an overall increase in glycerophosphocholines, and in particular of phosphatidylcholines, may indicate mitochondrial membrane disruption with a subsequent hydrolysis of phospholipids [149]. Furthermore, glycosphingolipid and sphingolipid metabolism were recurrent in pathway analyses across the studies [29, 31, 118, 119, 121]; related metabolites (altered ceramides and increased phosphosphingolipids, such as sphingomyelin) were also reported frequently across the studies [29, 104, 105, 108, 111, 115, 124, 125] and corroborated in Reactome showing consistent pathways related to ceramide signaling, phospholipids, sphingolipids, and phospholipase activity which may exacerbate inflammatory response [150]. Furthermore, given that sphingolipids constitute a major part of the fluidity, structure, and permeability of membranes and are involved in cell-to-cell signaling [151–154], a PFAS-induced membrane alteration mechanism may be a common pathway by which PFAS may exert cellular damage.

We also found a relative consistent positive association with PFAS among glycerolipids, particularly with triacylglycerides (TGs). While the association between PFAS and increased levels of unhealthy lipids, including triglycerides or LDL-cholesterol, has not been consistent across animal [155, 156] and epidemiological studies [157–161], the majority of overall PFAS-TG associations across human metabolomics studies included in this systematic review were positive in directionality [105, 108, 111, 114, 124]. Furthermore, pathway analyses in Reactome confirmed that mechanisms related to TG metabolism were involved in the positive association between higher PFAS exposure levels and increased TGs. Similarly, lipoprotein pathways, including dysregulation of healthy cholesterol pathways such as high-density lipoprotein (HDL), were observed to be predominant across studies reporting PFAS-TG associations [105, 108, 111, 114, 124]. In humans, PFAS associations with serum triglycerides rendered inconsistent effects across different PFAS in previous non-metabolomics epidemiological studies [158, 160, 162, 163], though more positive associations were observed for PFOA [157, 158, 164–166], PFOS [157, 165, 167, 168], PFHxS [166, 169], or PFNA [165, 166] exposures across various populations of healthy and unhealthy adults, children, and adolescents. Moreover, lipidomics studies in mice and rats have suggested more consistent associations with hepatic triglycerides for several long-chain PFAS (PFDoDA, PFOS, PFHxS, APFO, PFNA) [131,

170–173]. The mechanism underlying a potential PFAS-induced alteration in triglycerides points at initiation by PPARs. An *in vitro* study with PFAS-exposed human liver cells where PFOS, PFOA, and PFNA activated PPARα signaling, suggested that the subsequent observed increase in cellular triglyceride levels could be due to an induction of lipid droplet-associated proteins or glyceroneogenesis [174]. PPARγ could be also implicated in the PFAS-induced lipid alteration as a regulator of lipids and triglyceride fat storage in adipose tissue [175], though mechanisms for PFAS-induced damage via changes in triglyceride levels are poorly understood.

PFAS may contribute to lipid dysregulation by alterations in energy metabolism. Across studies, we observed that PFAS were positively associated with acylcarnitines [17, 105, 107, 112, 118, 120], which are intermediate metabolites involved in the transport of fatty acids and long-chain acyl-CoA from the cytosol into the mitochondria. Hence, the potential for acylcarnitines to be used as a marker of mitochondrial functioning and fatty acid oxidation [176], given that elevated levels could reflect either mitochondrial dysfunction or an adaptive change to disturbed lipid metabolism. Our findings across the reviewed studies are consistent with the studies in mice, the latter suggesting an overall increase in acylcarnitines (particularly hepatic) in relation to PFAS [148, 177]. Similarly, we observed an implication of PFAS exposures on fatty acid metabolism, carbohydrate, and amino acid metabolism. Binding of PFAS to fatty acid binding proteins may be implicated in the reduction of bioavailable binding sites for endogenous fatty acids resulting in higher concentrations of fatty acids. Fatty acids may interact with PPARs [178] and liver X receptors and could be involved in the regulation of gene expression and inflammation. Furthermore, several branched-chain amino acids (leucine, isoleucine, and valine), relevant in fatty acid oxidation and prevalent in the metabolome of those suffering from obesity-related conditions [179], were overall increased across reviewed studies [111, 115]. Similarly, aromatic amino acids, namely tyrosine and phenylalanine, which have been shown to be related to insulin resistance or diabetes [180, 181], were also increased across studies [29, 115, 116]. Pathway analyses in Reactome for metabolites sharing a negative association with PFAS, implicated pathways related to acyl-chain remodeling and amino acid transport across the plasma membrane, which could explain abundant levels of amino acids in obese subjects via dysregulation of key metabolites helping in the processing of fatty acids and amino acids. It is hypothesized that impaired branched-chain amino acid metabolism could lead to accumulation of toxic branched-chain keto acids and acyl-CoA precursors facilitating conversions into acylcarnitines [182, 183], which are increased in obese and T2D individuals [180, 184], consistent with our findings across studies in this review. Increased levels of acylcarnitines may reflect incomplete long-chain fatty acid beta-oxidation and limited intermediates or tricarboxylic acid (TCA) cycle utilization [184]. Furthermore, glycan-related pathways were also recurrent across studies in this review. Glycans are polysaccharides and alterations in glycosylation (a post-translational modification) have been suggested to be involved in diabetes etiology in prior epidemiological studies [185–187]. Perturbations of several metabolites associated with the TCA cycle, along with the presence of enriched carbohydrate metabolism across studies in our review, such as electron transport chain, glycolysis and gluconeogenesis, or beta-oxidation, is also consistent with the notion of the toxicity exerted by PFAS. Thus, changes in energy metabolism may have

widespread implications on development, growth, aging, protection against infectious and toxic exposures, and multiple disease processes.

PFAS and Increased Disease Risk in Human Metabolomic Studies

In humans, a myriad of studies have linked environmental endocrine-disrupting chemicals to a variety of diseases and metabolic dysregulations. *In vitro* studies with animal and human cells, have shown that PFAS can exert immunotoxicity [188], hepatic toxicity [172], developmental [189], and endocrine toxicity [147]. Research indicates that PFAS affect cardiometabolic markers of disease, can increase cancer risk, alter immune response, and impair reproductive health, thyroid, liver, and kidney function, among others [4, 10, 12, 14, 18, 190–192]. For instance, various PFAS, such as PFOA, PFBS, or PFNA have been linked to diabetes across different populations and epidemiological study designs [193–195]. Interestingly, Reactome pathways related to disease, the immune system, and glucose-dependent insulinotropic polypeptide (GIP), which is a hormone regulating insulin secretion, were shared across reviewed studies.

Several of the studies included in our review indicated that PFAS increased the risk of multiple cardiometabolic conditions. Given that prior epidemiological studies not including metabolomics reported inconsistent findings on PFAS and cardiometabolic outcomes [1, 196–200], either due to their cross-sectional design or heterogeneous populations, epidemiological studies including metabolomics are warranted to elucidate potential mechanisms at the metabolite-level in the plausible link between PFAS exposure and cardiometabolic outcomes. In the liver, PFAS increased liver enzymes characterizing injury risk in Stratakis et al.'s study [115]. In Jin et al.'s study [116], PFOS and PFHxS were associated with increased odds for liver fibrosis, lobular inflammation, or nonalcoholic steatohepatitis (NASH) [116]. PFAS exposure mixtures together with other environmental chemicals increased NAFLD risk in Sen et al.'s study [108]. A potential mechanism for liver injury could be via increased oxidative stress, as reflected in increased liver function biomarkers (i.e., ALT, AST) [201, 202]. Furthermore, PFAS was associated as well with increased glucose in several studies in our review [29, 118]. Mitro et al. 2021 [111] identified particularly several sphingomyelins, phosphatidylethanolamines, and DGs and TGs related to legacy PFAS (PFOA and PFOS) in a population at high risk of developing T2D. Similarly, increased T2D risk was also reported for PFNA-associated diacylglycerols in Schillemans et al. 2021 [113]. Lipids are mainly stored in mature white adipocytes in the form of TGs. Increased circulating free fatty acids and accumulation of TGs and derivatives, such as diacylglycerols, are deemed contributing factors to insulin resistance [203]. Along with TGs, diacylglycerols were overall increased across the studies in this review [105, 108, 113]. Furthermore, prenatal PFAS exposure contributed to increased postnatal risk of type 1 diabetes in neonates in one other study (McGlinchey et al. [30]), and PFHxS contributed to metabolic syndrome and lower levels of healthy cholesterol (HDL) in Bessonneau et al.'s study in occupationally-exposed adult women [109]. Elevated levels of acylcarnitines, which were increased across studies in our review ("Potential Dysregulated Pathways Linked with PFAS Exposures in Humans"), have been linked to risk of cardiovascular disease in prior cohort studies [204, 205]. Other metabolic disorders such as hyperuricemia were found to increase in risk upon PFAS exposures [105]. This is consistent with findings from several

large cohorts from US and Chinese populations where PFOA, PFNA, PFOS, and PFHxS were reported to increase risk of hyperuricemia [2, 206, 207].

There was evidence across the included studies from this review that PFAS exposures also altered reproductive outcomes and immune-related diseases. PFNA concentration was significantly associated with higher odds of small-for-gestational age (SGA) birth in a population of African-American women in Chang et al.'s study [119], and PFHxS was linked to lower sperm concentration in Chinese males in Huang et al.'s study [107]. Chemical mixtures including PFAS exposures also exacerbated conditions like endometriosis in Matta et al.'s study [104], suggesting that an endometriosis metabolic pattern could be characterized by dysregulation of bile acid homeostasis. PFAS was also found to increase risk of COVID-19 in one metabolomics study via impaired kynurenine metabolism (involved in immune responses), and eicosanoids (involved in inflammatory responses) [120], consistent with previous research linking PFAS and impaired immune system.

Overall, we observed consistent findings for reported PFAS-metabolite associations between studies conducted in population subgroups with a specific disease compared to population-based studies, particularly in regard to alterations in lipid metabolites (glycerolipids [104, 105, 108, 111, 113, 114, 117, 124], sphingolipids [29, 30, 104–106, 108, 111, 115, 124, 125], and fatty acyls [17, 29, 104–107, 109, 110, 112, 113, 117–120, 122–124]), bile acids [105, 106, 108, 109, 114, 119, 122, 124], and amino acids [17, 29, 30, 102, 105, 106, 108, 111–113, 115–120, 123]. Additionally, the field of metabolomics is at its early stages and could have the potential to become a key tool for disease biomarker detection and help elucidate pre-diagnostic stages of disorders that could be amenable to intervention. The lack of multi-omics studies integrating metabolomics with genomics, epigenomics, toxicogenomics, transcriptomics, proteomics, the microbiome, and other fields, highlights the need to advance this area of research as multi-omics may be a promising avenue of exposomics research where combined applications can provide mechanistic explanations for differential levels of environmental contaminants in the body and corresponding phenotypic states across individuals.

Effects of PFAS Exposures in the Developing Human Fetal Metabolome

Different populations may undergo distinct effects from PFAS at different stages throughout their life course. Of particular concern are the effects of PFAS in the womb due to the critical windows of exposure increasing the risk of disease onset in the offspring. Based on experimental research in mice, it is hypothesized that PFAS exposures lead to a reduction in transport of amino acid analogues from mothers to the fetus [208]. Though across studies we observed a perturbation of amino acids in mothers, we observed inconsistent results throughout pregnancy; for instance, amino acids, such as glycine, were increased in mothers at 8–14 weeks in the Chang et al. study [119]; in the Maitre et al. study, glycine decreased at trimester 3 [102]. Consequences of amino acid perturbation in the developing fetus could indicate improper nutrition, affect fetal growth, and contribute to small gestational size [119, 209, 210].

An association between PFAS and disrupted metabolism related to cofactors and vitamins B and D was also observed across studies and are key contributors to proper fetus development. Metabolism for vitamin B3 (nicotinate and nicotinamide) [29, 112, 119, 121], retinol [17, 121, 122], and vitamin D [109, 112, 118, 119, 121] were reported consistently across studies, three of them being conducted in pregnant women [112, 119, 122]. In pregnant women, vitamin A (retinol) and its analogs can regulate gene transcription impacting embryonic development [211] and the immune system [212–214]. Moreover, vitamin B is a well-known antioxidant for fetal growth (i.e., folate), and Vitamin D can be implicated also in oxidative stress and inflammatory response mechanisms, as well as in the metabolism of glucose and fetal growth skeletal development or placental function [215–217].

An overall increase of imidazopyrimidines [17, 105, 112, 117, 119], including increased uric acid [117, 119], was observed across studies in this review, with two studies being conducted in pregnant women [112, 119]. In pregnant women, it is hypothesized that PFAS may lead to decreases in uric acid secretion, resulting in elevated serum uric acid concentrations, which in turn, may trigger placental inflammation and oxidative stress, inhibit amino acid transport to placentas, alter the development of endothelial and trophoblast cell development in the fetus, or lead to higher risk for pre-eclampsia [119, 218–221].

Effects of PFAS Exposures on the Child's Metabolome

Seven studies in total have focused on PFAS and metabolomics and were conducted in a population of children or adolescents [29, 106, 114, 116, 118, 121, 125]. Interestingly, out of these studies, three [116, 121, 29] performed pathway analyses with PFAS-associated metabolites and numerous amino acid pathways were reported in all three studies: tyrosine metabolism, aspartate and asparagine metabolism, glycine, serine, alanine and threonine metabolism, urea cycle/amino group metabolism, arginine and proline metabolism, alanine and aspartate metabolism, and glutamate metabolism. We did not see consistent associations between PFAS-induced alterations on branched-amino acids (valine, isoleucine, and leucine) and related pathways across reviewed studies in children, contrary to previous findings from adult studies [105, 111]. However, an alteration in aromatic amino acids was evident in children. Tyrosine and phenylalanine are aromatic metabolites that were primarily increased in children populations across reviewed studies [29, 116]. Aromatic amino acids, as well as associated pathways, have been previously linked to increased risk of developing insulin resistance or obesity in children [222–226], or increased liver injury in adolescents [227]. We also observed that arginine or arginine-related pathways, previously linked to diabetes [228], were recurrent across the reviewed studies in children [29, 116, 121]. These findings are consistent with the hypothesis that environmental contaminants, namely PFAS, could alter the susceptible metabolism of children in a more remarkable way than at other developmental stages across the lifespan suggesting a potential window of susceptibility on certain amino acid types, particularly aromatic. A possible avenue of future research could also focus on infant PFAS exposures and other environmental contaminants via breast milk.

Differential Effects Across PFAS Groups

This review also intended to discern any potential patterns of effects across PFAS subtypes. Sulfonic acids are considered more potent than carboxylic acids [229], and it is hypothesized that longer carbon-chain PFAS may exert more deleterious effects [230], however, this premise has been contested [231] as novel PFAS emerge. We observed similar effects across the major studied PFAS (PFOS, PFOA, PFHxS), though a more clear-cut positive association seems to be apparent between the long-chain sulfonate PFOS and amino acids, fatty acid esters, or glycerophosphocholines. Overall, the findings observed across studies indicated that PFAS with longer half-lives were associated with relatively more metabolites. Similarly, we found that more legacy or long-chain PFAS were associated with more metabolites compared to short-chain or novel PFAS [113, 122], yet this could also be due to the frequency of the chemical being studied across studies and/or their detectability, where novel shorter-chain PFAS have lower exposure levels across samples, and their exposure assessment could be more prone to measurement error due to shorter half-lives. Animal studies have shown that PPARα receptor activation was increased the longer the carbon chain of the PFAS chemical [128, 232]. Furthermore, inhibition of gap junction intercellular communication is also considered more prominent for longer chain PFAS than in shorter chain PFAS [140]. Although animal studies can provide some validity as to the reason why we may be encountering different potency across PFAS groups, we would need more evidence for emerging or short-chain PFAS, which may be similarly toxic but are understudied, to further assess their deleterious effects on the human metabolome and involvement in disease.

Common Limitations of Previous Studies, Risk of Bias, and Future Directions

Several common limitations were found across studies rendering a lower quality score. These included confounding factors not accounted for, lack of false discovery rate (FDR) adjustment, a cross-sectional design introducing potential reverse causation bias, a small sample size, or not reporting a high confidence level for metabolites. Out of all 28 studies included in the review, no study reached a maximum quality score of 5, meaning that no study accounted altogether for a longitudinal study design, a large sample size, multiple testing correction, MSI metabolite confidence level 1, and covariate adjustment in the study design. Future PFAS-metabolomics studies may consider addressing these limitations in their design. Longitudinal measures of PFAS and metabolomics with longer follow-up from birth through adulthood are needed to better capture metabolite variability and to elucidate persistent effects over the life-course.

Metabolomics approaches handling repeated exposures and longitudinal -omics data are also needed to corroborate potential windows of enhanced vulnerability. Variability encountered in the laboratory methods for metabolomics profiling as well as the intra-individual variability in the samples could have also reduced the power to detect associations [233], so it is likely that the observed associations may be an underestimate of the true associations. We also expect that technical methods are more reliable than intra-individual correlation, which could have low reliability over time, as metabolites may be dependent on sex, age, fasting status, and diet of the individual.

On the other hand, there could be potential false positives (type I error) due to lack of multiple testing correction or lack of covariate-adjustment in metabolomics analyses. Overall, in metabolomics analyses, 16 studies included in the review reported FDR-correction (Tables 2 and 3, Table S2). Similarly, only 8 studies reporting pathway analyses both applied FDR-correction and adjusted for any covariates (Table S5). Moreover, nearly 40% of the studies in this review (n = 11) report to have included metabolites with a confidence level 1. Our sensitivity analyses including only these studies that reported the highest confidence level indicated a similar pattern of PFAS-associated metabolites for most metabolite groups examined (Figure S4). Given that more than half of the studies either did not include MSI confidence level 1, or did not mention at all confidence levels, caution when interpreting both findings should be given. Compliance with the Metabolomics Standards Initiative when reporting metabolomics methods is needed in future studies [99, 100].

Confounding bias could be present in reviewed studies that examined an association without controlling for sociodemographic and lifestyle variables, such as diet or exposure to other correlated chemicals. Diet was included as a confounder in the metabolomic analyses for only 2 studies [102, 117]. Interestingly, high level of docosahexaenoic acid (DHA) was observed across several studies [113, 117, 122]. Evidence from animal studies indicated that undergoing fish oil supplements prevented the PFOA-induced increase in hepatic triglyceride content by depressing the formation of triglycerides by DHA [234]. This suggests that potential deleterious effects exerted by PFAS exposures may be attenuated if fish consumption, a potential negative confounder of PFAS and omega-3 fatty acids, is not adjusted for in the analyses. Given that fish is a DHA-rich food source but also has high PFAS content [235–237], findings cannot be attributed to PFAS exposures as the only causative factor. The same would apply to a high correlation between packaged foods with high caloric density content and PFAS contamination [238], which could instead skew results over-representing lipid metabolism. Similarly, the presence of several benzenoids and xenobiotic metabolism across studies may indicate that PFAS may act in conjunction with other exogenous chemicals to alter metabolite levels in humans. Therefore, it is not possible to parse out whether findings are due to the effects from PFAS exposures solely, or instead, stem in part from potential confounders, a combination of both (mixture), or effect modification. Of note, there is a research gap regarding co-exposures since most of the reviewed articles on PFAS and metabolomics do not adjust for other pollutants in their analyses and correlated exposures are not systematically taken into account.

The vast majority of studies presented in this review were conducted in White and Asian populations with only a few studies including Hispanic and African-American populations in the US [29, 119]. Increased representation of minority ethnic groups with potentially different socioeconomic backgrounds, lifestyle, and dietary behaviors is needed in future studies to reassure generalizability of findings to minority populations that are disproportionally affected by metabolic and other chronic diseases. Moreover, most of the evidence compiled in this review is drawn from blood samples and additional studies comparing PFAS effects via the metabolome across tissues and other biofluid matrices can be informative. Additionally, genetic susceptibility to PFAS exposure in relation to metabolomics was taken into account in only one study [30]. Emerging evidence suggest gene-PFAS interactions in disease risk in humans [239]. To that end, an emerging field of

"multi-omics" data incorporating both metabolomics and genomics has just recently started to be applied in the investigation of environmental exposures and disease. Together with novel PFAS exposures, effect modification by genetic variations or incorporating "multi-omics" approaches could be a focus of future research. Improvements in the sensitivity of analytic tools (i.e., HRM) and harmonization in chemical annotation and standardization of pre-processing and data preparation (i.e., imputation, transformations, CV %) can help address these limitations in this field of research and enable a better reproducibility of metabolomic studies.

Limitations and Strengths of this Systematic Review

This review included metabolite classifications from the HMDB and ChEBI databases and KEGG pathway classifications, which are not fully comprehensive, challenging the summary and classification of findings across specific metabolite groups. About a third of unique metabolite features reported in our review, were either unmatched to a KEGG ID (not found) or their KEGG ID was not recognized by Reactome. Conversions were not possible particularly for several lipid metabolites and vitamins and were underrepresented when performing pathway analyses compared to other molecules, in spite of appearing frequently in results across studies. Thus, we can expect that lipid metabolism, yet present across studies in a significant manner, is underestimated in Reactome pathway analyses, although this also seems to be the case for individual studies conducting other pathway enrichment analyses. We also recognize that differentiation of targeted and untargeted studies is arguable in the field of metabolomics, so we attempted to refer to this classification as reported by the studies. Additionally, laboratory methods likely influencing quality assessment are not reported systematically throughout each study, and therefore, we were not able to account for other factors into the quality score. One important strength is that despite the high heterogeneity noted across epidemiology and laboratory methods, study design, and populations (i.e., country of study, sex, race, age, occupational, unhealthy), we found consistent findings for several metabolites and pathways across studies, and thus, results are more likely to reflect true associations. Furthermore, our study provides a comprehensive systematic review of all human studies published on PFAS and metabolomics, including both targeted and untargeted metabolomics, as well as lipidomics studies. Lastly, by using Reactome we provided a pathway analysis, which is considered a more systematic method to summarize and visualize findings.

Conclusion

PFAS are ubiquitous chemicals that can alter health via disruption of key metabolites and pathways in the human body. In this review, we summarized and identified alterations in several metabolites (amino acids, fatty acids, glycerophospholipids, glycerolipids, phosphosphingolipids, bile acids, ceramides, purines, and acylcarnitines) and related metabolic pathways that could underlie PFAS-associated diseases in humans, including lipid, amino acid, carbohydrate, nucleotide, glycan, or energy metabolism, and metabolism of cofactors and vitamins. Future studies should consider prospective designs optimizing methods for exposure-metabolomics analyses with longitudinal measures, additional

confounder adjustment, or assessment of emerging PFAS and mixture effects to address existing limitations in this field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

All data extracted from studies included in this review is available in the electronic supplementary material.

Abbreviations

AAs
Amino acids

ALT
Alanine transaminase

AST
Aspartate transferase

APFO
Ammonium perfluorooctanoate

BMI
Body mass index

CAR
Constitutive androstane receptor

CHDS
Child Health and Development Studies

ChEBI
Chemical Entities of Biological Interest

Cl-PFESAs
Chlorinated polyfluorinated ether sulfonic acids

COVID-19
Coronavirus disease 2019

CV

Coefficient of variation

DHA
Docosahexaenoic acid

EMBASE
Excerpta Medica database

ER
Endoplasmic reticulum

ERα
Estrogen receptor alpha

EtFOSAA
Ethyl perfluorooctane sulfonamido acetic acid

FDR
False discovery rate

FIA
Flow injection analysis

GC × GC–TOFMS
Comprehensive two-dimensional gas chromatography/time-of-flight mass spectrometry

GC-MS
Gas chromatography-mass spectrometry

GIP
Glucose-dependent insulinotropic polypeptide

HDL
High-density lipoprotein

HMDB
Human metabolome database

HPLC
High-performance liquid chromatography

H-NMR
Proton nuclear magnetic resonance

HRM
High-resolution metabolomics

KEGG
Kyoto Encyclopedia of Genes and Genomes

LC ESI–MS/MS
Liquid chromatography-electrospray ionization tandem mass spectrometry

LDL
Low-density lipoprotein

L-FABP
Liver fatty acid-binding protein

LC-MS
Liquid chromatography-mass spectrometry

LC–MS/MS
Liquid chromatography-tandem mass spectrometry

LC-HRMS
Liquid chromatography-high-resolution mass spectrometry

LC/Orbitrap-MS
Liquid chromatography/orbitrap-mass spectrometry

LC-qTOF-MS
Liquid chromatography-quadrupole time-of-flight mass spectrometry

MeFOSAA
Methyl perfluorooctanesulfonamidoacetic acid

MS/MS
Tandem mass spectrometry

MSI
Metabolomics Standards Initiative

NAFLD
Nonalcoholic fatty liver disease

NASH
Nonalcoholic steatohepatitis

NHANES
National Health and Nutrition Examination Survey

NIEHS
National Institute of Environmental Health Science

NIH
National Institutes of Health

NMR
nuclear magnetic resonance

PC
Phosphatidylcholine

PLA2
Phospholipase A2

PLC
Phospholipase C

PFAS
Perfluoroalkyl and polyfluoroalkyl substances

PFBA
Perfluorobutyric acid or perfluorobutanoic acid

PFBS
Perfluorobutane sulfonic acid

PFDA/PFDeA
Perfluorodecanoic acid

PFDoA/PFDoDA
Perfluorododecanoic acid

PFDoDS
Perfluorododecane sulfonate

PFDS
Pefluorodecane sulfonic acid

PFECHS
Potassium perfluoro-4-ethylcyclohexanesulfonate

PFHpA
Perfluoroheptanoic acid

PFHpS
Perfluoroheptane sulfonic acid

PFHxA
Perfluorohexanoic acid

PFHxS
Perfluorohexanesulfonic acid

PFNA
Perfluorononanoic acid

PFNS
Perfluorononane sulfonate

PFOA
Perfluorooctanoic acid

PFOS
Perfluorooctane sulfonate

PFOSA
Perfluorooctanesulfonamide

PFPeA
Perfluoropentanoic acid

PFPeS
Perfluoropentane sulfonic acid

PFTeDA/PFTDA
Perfluorotetradecanoic acid

PFTrDA
Perfluorotridecanoic acid

PFUnA/PFUnDA/PFUdA
Perfluoroundecanoic acid

PPAR
Peroxisome proliferator-activated receptor

PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO
International Prospective Register of Systematic Reviews

RPC
Reversed-phase chromatography

SHBG
Sex hormone-binding globulin

SGA
Small-for-gestational age

T2D
Type 2 diabetes

TCA
Tricarboxylic acid

TG
Triacylglycerides

UHPLC
Ultra-high-performance liquid chromatography

UHPLC-QQQMS
Ultra-high-performance liquid chromatography method coupled with triple quadrupole mass spectrometry

UHPLC-qTOF/MS or UHPLC-QTOFMS
Ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry

UHRMS
Ultra-high-resolution mass spectrometry

UPLC
Ultra-performance liquid chromatography

UPLC/MS/MS or UPLC-MS/MS
Ultra-performance liquid chromatography-tandem mass spectrometry

UPLC-Q-Orbitrap HRMS
Ultra-high-performance liquid chromatography-quadrupole orbitrap high-resolution mass spectrometry

UPLC-QTOF-MS
Ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry

VIP
Västerbotten Intervention Programme

References

1. Christensen KY, Raymond M, Meiman J. Perfluoroalkyl substances and metabolic syndrome. Int J Hyg Environ Health. 2019;222(1):147–53. 10.1016/jijheh.2018.08.014. [PubMed: 30290996]
2. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A review of the pathways of human exposure to poly- and Perfluoroalkyl substances (PFASs) and present understanding of health effects. J Eposure Sci Environ Epidemiol. 2019;29(2):131–47. 10.1038/s41370-018-0094-1.
3. Calafat AM, Wong L-Y, Kuklenyik Z, Reidy JA, Needham LL. Poly-fluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ Health Perspect. 2007;115(11):1596–602. 10.1289/ehp.10598. [PubMed: 18007991]
4. Lewis RC, Johns LE, Meeker JD. Serum biomarkers of exposure to Perfluoroalkyl substances in relation to serum testosterone and measures of thyroid function among adults and adolescents from NHANES 2011–2012. Int J Environ Res Public Health. 2015;12(6):6098–114. 10.3390/ijerph120606098. [PubMed: 26035660]
5. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey. 2017–2018 Data Documentation, Codebook, and Frequencies. Perfluoroalkyl and Poly-fluoroalkyl Substances (PFAS_J). 2020.
6. (EPA) EPA. Multi-Industry Per- and Poly-fluoroalkyl Substances (PFAS) Study −2021 Preliminary Report. 2021.

7. Cousins IT, DeWitt JC, Glüge J, Goldenman G, Herzke D, Lohmann R, et al. The high persistence of PFAS is sufficient for their management as a chemical class. Environ Sci Process Impacts. 2020;22(12):2307–12. 10.1039/d0em00355g. [PubMed: 33230514]

8. Wang Z, DeWitt JC, Higgins CP, Cousins IT. A Never-ending story of per- and Poly-fluoroalkyl substances (PFASs)? Environ Sci Technol. 2017;51(5):2508–18. 10.1021/acs.est.6b04806. [PubMed: 28224793]

9. Xu Y, Fletcher T, Pineda D, Lindh CH, Nilsson C, Glynn A, et al. Serum half-lives for short- and long-chain Perfluoroalkyl acids after ceasing exposure from drinking water contaminated by firefighting foam. Environm Health Perspect. 2020;128(7):077004. 10.1289/EHP6785.

10. Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect. 2013;121(11–12):1313–8. 10.1289/ehp.1306615. [PubMed: 24007715]

11. Steenland K, Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ Res. 2021;194:110690. 10.1016/jenvres.2020.110690. [PubMed: 33385391]

12. Jackson-Browne MS, Eliot M, Patti M, Spanier AJ, Braun JM. PFAS (per- and Poly-fluoroalkyl substances) and asthma in young children: NHANES 2013–2014. Int J Hyg Environ Health. 2020;229:113565. 10.1016/jijheh.2020.113565. [PubMed: 32485600]

13. Dong GH, Tung KY, Tsai CH, Liu MM, Wang D, Liu W, et al. Serum Poly-fluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children. Environ Health Perspect. 2013;121(4):507–13. 10.1289/ehp.1205351. [PubMed: 23309686]

14. Lopez-Espinosa MJ, Mondal D, Armstrong B, Bloom MS, Fletcher T. Thyroid function and Perfluoroalkyl acids in children living near a chemical plant. Environ Health Perspect. 2012;120(7):1036–41. 10.1289/ehp.1104370. [PubMed: 22453676]

15. Webster GM, Rauch SA, Marie NS, Mattman A, Lanphear BP, Venners SA. Cross-Sectional Associations of Serum Perfluoroalkyl Acids and Thyroid Hormones in U.S. Adults: Variation According to TPOAb and Iodine Status (NHANES 2007–2008). Environ Health Perspect. 2016;124(7):935–42. 10.1289/ehp.1409589. [PubMed: 26517287]

16. Costello E, Rock S, Stratakis N, Eckel SP, Walker DI, Valvi D, et al. Exposure to per- and Poly-fluoroalkyl Substances and Markers of Liver Injury: A Systematic Review and Meta-Analysis. Environmental Health Perspectives. 2022;130(4):046001. 10.1289/EHP10092. [PubMed: 35475652]

17. Lu Y, Gao K, Li X, Tang Z, Xiang L, Zhao H, et al. Mass Spectrometry-Based Metabolomics Reveals Occupational Exposure to Per- and Poly-fluoroalkyl Substances Relates to Oxidative Stress, Fatty Acid β-Oxidation Disorder, and Kidney Injury in a Manufactory in China. Environ Sci Technol. 2019;53(16):9800–9. 10.1021/acs.est.9b01608. [PubMed: 31246438]

18. Bommarito PA, Ferguson KK, Meeker JD, McElrath TF, Cantonwine DE. Maternal Levels of Perfluoroalkyl Substances (PFAS) during Early Pregnancy in Relation to Preeclampsia Subtypes and Biomarkers of Preeclampsia Risk. Environ Health Perspect. 2021;129(10):107004. 10.1289/ehp9091. [PubMed: 34637358]

19. Lin PD, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, et al. Per- and Poly-fluoroalkyl substances and blood lipid levels in pre-diabetic adults-longitudinal analysis of the diabetes prevention program outcomes study. Environ Int. 2019;129:343–53. 10.1016/j.envint.2019.05.027. [PubMed: 31150976]

20. Meneguzzi A, Fava C, Castelli M, Minuz P. Exposure to Perfluoroalkyl Chemicals and Cardiovascular Disease: Experimental and Epidemiological Evidence. Front Endocrinol (Lausanne). 2021;12:706352. 10.3389/fendo.2021.706352. [PubMed: 34305819]

21. Margolis R, Sant KE. Associations between Exposures to Perfluoroalkyl Substances and Diabetes, Hyperglycemia, or Insulin Resistance: A Scoping Review. J Xenobiot. 2021;11(3):115–29. 10.3390/jox11030008. [PubMed: 34564296]

22. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. The Lancet. 2005;365(9468):1415–28. 10.1016/S0140-6736(05)66378-7.

23. Xu Y, Li Y, Scott K, Lindh CH, Jakobsson K, Fletcher T, et al. Inflammatory bowel disease and biomarkers of gut inflammation and permeability in a community with high exposure to

Perfluoroalkyl substances through drinking water. Environmental Research. 2020;181:108923. 10.1016/jenvres.2019.108923. [PubMed: 31759646]

24. Petersen MS, Halling J, Jørgensen N, Nielsen F, Grandjean P, Jensen TK, et al. Reproductive Function in a Population of Young Faroese Men with Elevated Exposure to Polychlorinated Biphenyls (PCBs) and Perfluorinated Alkylate Substances (PFAS). Int J Environ Res Public Health. 2018;15(9):1880. [PubMed: 30200252]
25. Bodin J, Groeng EC, Andreassen M, Dirven H, Nygaard UC. Exposure to perfluoroundecanoic acid (PFUnDA) accelerates insulitis development in a mouse model of type 1 diabetes. Toxicol Rep. 2016;3:664–72. 10.1016/j.toxrep.2016.08.009. [PubMed: 28959590]
26. Kamendulis LM, Wu Q, Sandusky GE, Hocevar BA. Perfluorooctanoic acid exposure triggers oxidative stress in the mouse pancreas. Toxicol Rep. 2014;1:513–21. 10.1016/jtoxrep.2014.07.015. [PubMed: 28962265]
27. Ding N, Karvonen-Gutierrez CA, Herman WH, Calafat AM, Mukherjee B, Park SK. Associations of Perfluoroalkyl and Poly-fluoroalkyl substances (PFAS) and PFAS mixtures with adipokines in midlife women. Int J Hyg Environ Health. 2021;235:113777. 10.1016/jijheh.2021.113777. [PubMed: 34090141]
28. Walker DI, Valvi D, Rothman N, Lan Q, Miller GW, Jones DP. The metabolome: A key measure for exposome research in epidemiology. Curr Epidemiol Rep. 2019;6:93–103. [PubMed: 31828002]
29. Alderete TL, Jin R, Walker DI, Valvi D, Chen Z, Jones DP, et al. Perfluoroalkyl substances, metabolomic profiling, and alterations in glucose homeostasis among overweight and obese Hispanic children: A proof-of-concept analysis. Environ Int. 2019;126:445–53. 10.1016/jenvint.2019.02.047. [PubMed: 30844580]
30. McGlinchey A, Sinioja T, Lamichhane S, Sen P, Bodin J, Siljander H, et al. Prenatal exposure to Perfluoroalkyl substances modulates neonatal serum phospholipids, increasing risk of type 1 diabetes. Environ Int. 2020;143:105935. 10.1016/j.envint.2020.105935. [PubMed: 32634666]
31. Li S, Cirillo P, Hu X, Tran V, Krigbaum N, Yu S, et al. Understanding mixed environmental exposures using metabolomics via a hierarchical community network model in a cohort of California women in 1960's. Reprod Toxicol. 2020;92:57–65. 10.1016/j.reprotox.2019.06.013. [PubMed: 31299210]
32. Guo P, Furnary T, Vasiliou V, Yan Q, Nyhan K, Jones DP, et al. Non-targeted metabolomics and associations with per- and Poly-fluoroalkyl substances (PFAS) exposure in humans: A scoping review. Environ Int. 2022;162:107159. 10.1016/j.envint.2022.107159. [PubMed: 35231839]
33. (NIEHS) NIoEHS: Perfluoroalkyl and Poly-fluoroalkyl Substances (PFAS). https://www.niehs.nih.gov/health/topics/agents/pfc/index.cfm (2022). Accessed 2022.
34. Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, et al. Perfluoroalkyl and Poly-fluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag. 2011;7(4):513–41. 10.1002/ieam.258. [PubMed: 21793199]
35. Conder JM, Hoke RA, Wolf Wd, Russell MH, Buck RC. Are PFCAs Bioaccumulative? A Critical Review and Comparison with Regulatory Criteria and Persistent Lipophilic Compounds. Environmental Science & Technology. 2008;42(4):995–1003. 10.1021/es070895g. [PubMed: 18351063]
36. Kissa E Fluorinated surfactants and repellents. CRC Press; 2001.
37. (OECD) OfEC-oaD: Portal on Per and Poly Fluorinated Chemicals-About PFAS. https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/aboutpfass/ Accessed 2022.
38. Martin JW, Mabury SA, Solomon KR, Muir DC. Dietary accumulation of perfluorinated acids in juvenile rainbow trout (Oncorhynchus mykiss). Environ Toxicol Chem. 2003;22(1):189–95. [PubMed: 12503764]
39. Russell MH, Nilsson H, Buck RC. Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey. Chemosphere. 2013;93(10):2419–25. 10.1016/jchemosphere.2013.08.060. [PubMed: 24050716]
40. Ohmori K, Kudo N, Katayama K, Kawashima Y. Comparison of the toxicokinetics between perfluorocarboxylic acids with different carbon chain length. Toxicology. 2003;184(2–3):135–40. 10.1016/s0300-483x(02)00573-5. [PubMed: 12499116]

41. Land M, de Wit CA, Cousins IT, Herzke D, Johansson J, Martin JW. What is the effect of phasing out long-chain per- and Poly-fluoroalkyl substances on the concentrations of Perfluoroalkyl acids and their precursors in the environment? A systematic review protocol. Environmental Evidence. 2015;4(1):3. 10.1186/2047-2382-4-3.

42. Brennan NM, Evans AT, Fritz MK, Peak SA, von Holst HE. Trends in the Regulation of Per- and Poly-fluoroalkyl Substances (PFAS): A Scoping Review. Int J Environ Res Public Health. 2021;18(20):10900. 10.3390/ijerph182010900. [PubMed: 34682663]

43. (EPA) EPA. Draft Human Health Toxicity Assessments for Hexafluoropropylene Oxide Dimer Acid and Its Ammonium Salt (GenX Chemicals) and for Perfluorobutane Sulfonic Acid (PFBS) and Related Compound Potassium Perfluorobutane Sulfonate. EPA Washinton, DC, USA; 2018.

44. Vierke L, Staude C, Biegel-Engler A, Drost W, Schulte C. Perfluorooctanoic acid (PFOA) — main concerns and regulatory developments in Europe from an environmental point of view. Environ Sci Eur. 2012;24(1):16. 10.1186/2190-4715-24-16.

45. Gellrich V, Stahl T, Knepper TP. Behavior of perfluorinated compounds in soils during leaching experiments. Chemosphere. 2012;87(9):1052–6. 10.1016/j.chemosphere.2012.02.011. [PubMed: 22391048]

46. Brendel S, Fetter É, Staude C, Vierke L, Biegel-Engler A. Short-chain Perfluoroalkyl acids: environmental concerns and a regulatory strategy under REACH. Environmental sciences Europe. 2018;30(1):9-. 10.1186/s12302-018-0134-4. [PubMed: 29527446]

47. Scheurer M, Nödler K, Freeling F, Janda J, Happel O, Riegel M, et al. Small, mobile, persistent: Trifluoroacetate in the water cycle - Overlooked sources, pathways, and consequences for drinking water supply. Water Res. 2017;126:460–71. 10.1016/j.watres.2017.09.045. [PubMed: 28992593]

48. Kotthoff M, Bücking M. Four Chemical Trends Will Shape the Next Decade's Directions in Perfluoroalkyl and Poly-fluoroalkyl Substances Research. Front Chem. 2018;6:103-. 10.3389/fchem.2018.00103. [PubMed: 29675408]

49. Zhang C, Yan H, Li F, Hu X, Zhou Q. Sorption of short- and long-chain Perfluoroalkyl surfactants on sewage sludges. J Hazard Mater. 2013;260:689–99. 10.1016/j.jhazmat.2013.06.022. [PubMed: 23834900]

50. The Federal Role in the Toxic PFAS Chemical Crisis. Senate Committee on Homeland Security and Governmental Affairs: National Institute of Environmental Health Sciences (NIEHS, NIH),; 2018.

51. OECD/UNEP: Toward a new comprehensive global database of per- and Poly-fluoroalkyl substances (PFASs): Summary report on updating the OECD 2007 list of per- and Poly-fluoroalkyl substances (PFASs), Organisation for Economic Co-operation and Development, Portal for Per and Poly Fluorinated Chemicals. http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/ (2018). Accessed.

52. (NIEHS) NIoEHS: Perfluoroalkyl and Poly-fluoroalkyl Substances (PFAS). https://www.niehs.nih.gov/health/topics/agents/pfc/index.cfm#footnote2 (2021). Accessed.

53. Glüge J, Scheringer M, Cousins IT, DeWitt JC, Goldenman G, Herzke D, et al. An overview of the uses of per- and Poly-fluoroalkyl substances (PFAS). Environ Sci Process Impacts. 2020;22(12):2345–73. 10.1039/D0EM00291G. [PubMed: 33125022]

54. Xu L, Shi Y, Li C, Song X, Qin Z, Cao D, et al. Discovery of a Novel Poly-fluoroalkyl Benzenesulfonic Acid around Oilfields in Northern China. Environ Sci Technol. 2017;51(24):14173–81. 10.1021/acs.est.7b04332. [PubMed: 29218982]

55. (EPA) EPA: Our Current Understanding of the Human Health and Environmental Risks of PFAS. https://www.epa.gov/pfas/our-current-understanding-human-health-and-environmental-risks-pfas (2022). Accessed 1/26/2022.

56. Savvaides T, Koelmel JP, Zhou Y, Lin EZ, Stelben P, Aristizabal-Henao JJ, et al. Prevalence and Implications of Per- and Poly-fluoroalkyl Substances (PFAS) in Settled Dust. Curr Environ Health Rep. 2021;8(4):323–35. 10.1007/s40572-021-00326-4. [PubMed: 34985714]

57. Affairs USDoV: PFAS - Perfluoroalkyl and Poly-fluoroalkyl substances. https://www.publichealth.va.gov/exposures/pfas.asp#:~:text=Perfluoroalkyl%20and%20Poly-fluoroalkyl%20substances%20%28PFAS%29%20are%20synthetic%20chemicals,adhesives%2C%

20paper%20packaging%20for%20food%2C%20and%20heat-resistant%2Fnon-stick%20cookware. (2022). Accessed 6/19/2022.

58. Whitehead HD, Venier M, Wu Y, Eastman E, Urbanik S, Diamond ML, et al. Fluorinated Compounds in North American Cosmetics. Environ Sci Technol Lett. 2021;8(7):538–44. 10.1021/acs.estlett.1c00240.
59. Haug LS, Huber S, Becher G, Thomsen C. Characterisation of human exposure pathways to perfluorinated compounds–comparing exposure estimates with biomarkers of exposure. Environ Int. 2011;37(4):687–93. 10.1016/j.envint.2011.01.011. [PubMed: 21334069]
60. Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbühler K. Estimating Consumer Exposure to PFOS and PFOA. Risk Anal. 2008;28(2):251–69. 10.1111/j.1539-6924.2008.01017.x. [PubMed: 18419647]
61. Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. Perfluoroalkyl Acids: A Review of Monitoring and Toxicological Findings. Toxicol Sci. 2007;99(2):366–94. 10.1093/toxsci/kfm128. [PubMed: 17519394]
62. Mogensen UB, Grandjean P, Heilmann C, Nielsen F, Weihe P, Budtz-Jørgensen E. Structural equation modeling of immunotoxicity associated with exposure to perfluorinated alkylates. Environ Health. 2015;14:47. 10.1186/s12940-015-0032-9. [PubMed: 26041029]
63. Grandjean P, Heilmann C, Weihe P, Nielsen F, Mogensen UB, Budtz-Jørgensen E. Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds. Environ Health Perspect. 2017;125(7):077018. 10.1289/ehp275. [PubMed: 28749778]
64. (ATSDR) AfTSaDR: Toxicological Profile for Perfluoroalkyls. https://www.atsdr.cdc.gov/toxprofiles/tp200-c2.pdf (2021). Accessed.
65. Blake BE, Fenton SE. Early life exposure to per- and Poly-fluoroalkyl substances (PFAS) and latent health outcomes: A review including the placenta as a target tissue and possible driver of peri- and postnatal effects. Toxicology. 2020;443:152565. 10.1016/j.tox.2020.152565. [PubMed: 32861749]
66. Bangma J, Eaves LA, Oldenburg K, Reiner JL, Manuck T, Fry RC. Identifying Risk Factors for Levels of Per- and Poly-fluoroalkyl Substances (PFAS) in the Placenta in a High-Risk Pregnancy Cohort in North Carolina. Environ Sci Technol. 2020;54(13):8158–66. 10.1021/acs.est.9b07102. [PubMed: 32469207]
67. Mogensen UB, Grandjean P, Nielsen F, Weihe P, Budtz-Jørgensen E. Breastfeeding as an Exposure Pathway for Perfluorinated Alkylates. Environ Sci Technol. 2015;49(17):10466–73. 10.1021/acs.est.5b02237. [PubMed: 26291735]
68. Valvi D, Højlund K, Coull BA, Nielsen F, Weihe P, Grandjean P. Life-course Exposure to Perfluoroalkyl Substances in Relation to Markers of Glucose Homeostasis in Early Adulthood. J Clin Endocrinol Metab. 2021;106(8):2495–504. 10.1210/clinem/dgab267. [PubMed: 33890111]
69. Vanden Heuvel JP, Kuslikis BI, Peterson RE. Covalent binding of perfluorinated fatty acids to proteins in the plasma, liver and testes of rats. Chem Biol Interact. 1992;82(3):317–28. 10.1016/0009-2797(92)90003-4. [PubMed: 1606626]
70. Luebker DJ, Hansen KJ, Bass NM, Butenhoff JL, Seacat AM. Interactions of flurochemicals with rat liver fatty acid-binding protein. Toxicology. 2002;176(3):175–85. 10.1016/S0300-483X(02)00081-1. [PubMed: 12093614]
71. Jones PD, Hu W, De Coen W, Newsted JL, Giesy JP. Binding of perfluorinated fatty acids to serum proteins. Environ Toxicol Chem. 2003;22(11):2639–49. 10.1897/02-553. [PubMed: 14587903]
72. Han X, Snow TA, Kemper RA, Jepson GW. Binding of perfluorooctanoic acid to rat and human plasma proteins. Chem Res Toxicol. 2003;16(6):775–81. 10.1021/tx034005w. [PubMed: 12807361]
73. Vanden Heuvel JP, Kuslikis BI, Van Rafelghem MJ, Peterson RE. Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. J Biochem Toxicol. 1991;6(2):83–92. 10.1002/jbt.2570060202. [PubMed: 1941903]
74. Martin JW, Mabury SA, Solomon KR, Muir DC. Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (Oncorhynchus mykiss). Environ Toxicol Chem. 2003;22(1):196–204. [PubMed: 12503765]

75. Gasiorowski R, Forbes MK, Silver G, Krastev Y, Hamdorf B, Lewis B, et al. Effect of Plasma and Blood Donations on Levels of Perfluoroalkyl and Poly-fluoroalkyl Substances in Firefighters in Australia: A Randomized Clinical Trial. JAMA Network Open. 2022;5(4):e226257–e. 10.1001/jamanetworkopen.2022.6257. [PubMed: 35394514]
76. LaKind JS, Verner M-A, Rogers RD, Goeden H, Naiman DQ, Marchitti SA, et al. Current Breast Milk PFAS Levels in the United States and Canada: After All This Time, Why Don't We Know More? Environ Health Perspect. 2022;130(2):025002. 10.1289/EHP10359. [PubMed: 35195447]
77. Hamosh M, Henderson TR, Ellis LA, Mao JI, Hamosh P. Digestive enzymes in human milk: stability at suboptimal storage temperatures. J Pediatr Gastroenterol Nutr. 1997;24(1):38–43. 10.1097/00005176-199701000-00010. [PubMed: 9093984]
78. Dallas DC, Guerrero A, Khaldi N, Castillo PA, Martin WF, Smilowitz JT, et al. Extensive in vivo human milk peptidomics reveals specific proteolysis yielding protective antimicrobial peptides. J Proteome Res. 2013;12(5):2295–304. 10.1021/pr400212z. [PubMed: 23586814]
79. Pérez F, Nadal M, Navarro-Ortega A, Fàbrega F, Domingo JL, Barceló D, et al. Accumulation of Perfluoroalkyl substances in human tissues. Environ Int. 2013;59:354–62. 10.1016/jenvint.2013.06.004. [PubMed: 23892228]
80. Cao Y, Ng C. Absorption, distribution, and toxicity of per- and Poly-fluoroalkyl substances (PFAS) in the brain: a review. Environ Sci Process Impacts. 2021;23(11):1623–40. 10.1039/d1em00228g. [PubMed: 34533150]
81. Cui L, Liao CY, Zhou QF, Xia TM, Yun ZJ, Jiang GB. Excretion of PFOA and PFOS in male rats during a subchronic exposure. Arch Environ Contam Toxicol. 2010;58(1):205–13. 10.1007/s00244-009-9336-5. [PubMed: 19468665]
82. Harada K, Inoue K, Morikawa A, Yoshinaga T, Saito N, Koizumi A. Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environ Res. 2005;99(2):253–61. 10.1016/j.envres.2004.12.003. [PubMed: 16194675]
83. Birn H, Christensen EI. Renal albumin absorption in physiology and pathology. Kidney Int. 2006;69(3):440–9. 10.1038/sj.ki.5000141. [PubMed: 16514429]
84. Kudo N, Katakura M, Sato Y, Kawashima Y. Sex hormone-regulated renal transport of perfluorooctanoic acid. Chem Biol Interact. 2002;139(3):301–16. 10.1016/s0009-2797(02)00006-6. [PubMed: 11879818]
85. Genuis SJ, Birkholz D, Ralitsch M, Thibault N. Human detoxification of perfluorinated compounds. Public Health. 2010;124(7):367–75. 10.1016/j.puhe.2010.03.002. [PubMed: 20621793]
86. Ma J, Zhu H, Kannan K. Fecal Excretion of Perfluoroalkyl and Poly-fluoroalkyl Substances in Pets from New York State, United States. Environ Sci Technol Lett. 2020;7(3):135–42. 10.1021/acs.estlett.9b00786.
87. Seo S-H, Son M-H, Choi S-D, Lee D-H, Chang Y-S. Influence of exposure to Perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects. Environ Int. 2018;113:149–61. 10.1016/j.envint.2018.01.025. [PubMed: 29425899]
88. Ding N, Harlow SD, Batterman S, Mukherjee B, Park SK. Longitudinal trends in Perfluoroalkyl and Poly-fluoroalkyl substances among multiethnic midlife women from 1999 to 2011: The Study of Women's Health Across the Nation. Environ Int. 2020;135:105381. 10.1016/j.envint.2019.105381. [PubMed: 31841808]
89. Wong F, MacLeod M, Mueller JF, Cousins IT. Enhanced Elimination of Perfluorooctane Sulfonic Acid by Menstruating Women: Evidence from Population-Based Pharmacokinetic Modeling. Environ Sci Technol. 2014;48(15):8807–14. 10.1021/es500796y. [PubMed: 24943117]
90. Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C, Stewart B, et al. Serum levels of Perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ Res. 2008;108(1):56–62. 10.1016/j.envres.2008.06.001. [PubMed: 18649879]
91. Ruark CD, Song G, Yoon M, Verner MA, Andersen ME, Clewell HJ 3rd, et al. Quantitative bias analysis for epidemiological associations of Perfluoroalkyl substance serum concentrations and early onset of menopause. Environ Int. 2017;99:245–54. 10.1016/j.envint.2016.11.030. [PubMed: 27927583]

92. Lorber M, Eaglesham GE, Hobson P, Toms LML, Mueller JF, Thompson JS. The effect of ongoing blood loss on human serum concentrations of perfluorinated acids. Chemosphere. 2015;118:170–7. 10.1016/j.chemosphere.2014.07.093. [PubMed: 25180653]

93. Go YM, Walker DI, Liang Y, Uppal K, Soltow QA, Tran V, et al. Reference Standardization for Mass Spectrometry and High-resolution Metabolomics Applications to Exposome Research. Toxicol Sci. 2015;148(2):531–43. 10.1093/toxsci/kfv198. [PubMed: 26358001]

94. Medina S, Dominguez-Perles R, Gil JI, Ferreres F, Gil-Izquierdo A. Metabolomics and the diagnosis of human diseases–a guide to the markers and pathophysiological pathways affected. Curr Med Chem. 2014;21(7):823–48. 10.2174/09298673206613119124056. [PubMed: 24251573]

95. Mamas M, Dunn WB, Neyses L, Goodacre R. The role of metabolites and metabolomics in clinically applicable biomarkers of disease. Arch Toxicol. 2011;85(1):5–17. 10.1007/s00204-010-0609-6. [PubMed: 20953584]

96. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89. 10.1186/s13643-021-01626-4. [PubMed: 33781348]

97. Schymanski EL, Jeon J, Gulde R, Fenner K, Ruff M, Singer HP, et al. Identifying small molecules via high resolution mass spectrometry: communicating confidence. Environ Sci Technol. 2014;48(4):2097–8. 10.1021/es5002105. [PubMed: 24476540]

98. Ryan RHS. How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group; 2016.

99. Kodra D, Pousinis P, Vorkas PA, Kademoglou K, Liapikos T, Pechlivanis A, et al. Is Current Practice Adhering to Guidelines Proposed for Metabolite Identification in LC-MS Untargeted Metabolomics? A Meta-Analysis of the Literature. J Proteome Res. 2022;21(3):590–8. 10.1021/acsjproteome.1c00841. [PubMed: 34928621]

100. Sumner LW, Amberg A, Barrett D, Beale MH, Beger R, Daykin CA, et al. Proposed minimum reporting standards for chemical analysis Chemical Analysis Working Group (CAWG) Metabolomics Standards Initiative (MSI). Metabolomics. 2007;3(3):211–21. 10.1007/s11306-007-0082-2. [PubMed: 24039616]

101. Gillespie M, Jassal B, Stephan R, Milacic M, Rothfels K, Senff-Ribeiro A, et al. The reactome pathway knowledgebase 2022. Nucleic Acids Res. 2021;50(D1):D687–92. 10.1093/nar/gkab1028.

102. Maitre L, Robinson O, Martinez D, Toledano MB, Ibarluzea J, Marina LS, et al. Urine Metabolic Signatures of Multiple Environmental Pollutants in Pregnant Women: An Exposome Approach. Environ Sci Technol. 2018;52(22):13469–80. 10.1021/acs.est.8b02215. [PubMed: 30285427]

103. Chen Q, Zhang Y, Ye L, Gong S, Sun H, Su G. Identifying active xenobiotics in humans by use of a suspect screening technique coupled with lipidomic analysis. Environ Int. 2021;157:106844. 10.1016/j.envint.2021.106844. [PubMed: 34455192]

104. Matta K, Lefebvre T, Vigneau E, Cariou V, Marchand P, Guitton Y, et al. Associations between persistent organic pollutants and endometriosis: A multiblock approach integrating metabolic and cytokine profiling. Environ Int. 2022;158:106926. 10.1016/j.envint.2021.106926. [PubMed: 34649050]

105. You L, Zheng F, Su C, Wang L, Li X, Chen Q, et al. Metabolome-wide association study of serum exogenous chemical residues in a cohort with 5 major chronic diseases. Environ Int. 2022;158:106919. 10.1016/j.envint.2021.106919. [PubMed: 34634623]

106. Yu M, Teitelbaum SL, Dolios G, Dang L-HT, Tu P, Wolff MS, et al. Molecular Gatekeeper Discovery: Workflow for Linking Multiple Exposure Biomarkers to Metabolomics. Environmental Science & Technology. 2022;56(10):6162–71. 10.1021/acs.est.1c04039. [PubMed: 35129943]

107. Huang Q, Liu L, Wu Y, Wang X, Luo L, Nan B, et al. Seminal plasma metabolites mediate the associations of multiple environmental pollutants with semen quality in Chinese men. Environ Int. 2019;132:105066. 10.1016/j.envint.2019.105066. [PubMed: 31394396]

108. Sen P, Qadri S, Luukkonen PK, Ragnarsdottir O, McGlinchey A, Jäntti S, et al. Exposure to environmental contaminants is associated with altered hepatic lipid metabolism in non-alcoholic

fatty liver disease. J Hepatol. 2022;76(2):283–93. 10.1016/j.jhep.2021.09.039. [PubMed: 34627976]

109. Bessonneau V, Gerona RR, Trowbridge J, Grashow R, Lin T, Buren H, et al. Gaussian graphical modeling of the serum exposome and metabolome reveals interactions between environmental chemicals and endogenous metabolites. Sci Rep. 2021;11(1):7607. 10.1038/s41598-021-87070-9. [PubMed: 33828161]
110. Panagopoulos Abrahamsson D, Wang A, Jiang T, Wang M, Siddharth A, Morello-Frosch R, et al. A Comprehensive Non-targeted Analysis Study of the Prenatal Exposome. Environ Sci Technol. 2021;55(15):10542–57. 10.1021/acs.est.1c01010. [PubMed: 34260856]
111. Mitro SD, Liu J, Jaacks LM, Fleisch AF, Williams PL, Knowler WC, et al. Per- and Poly-fluoroalkyl substance plasma concentrations and metabolomic markers of type 2 diabetes in the Diabetes Prevention Program trial. Int J Hygiene Environ Health. 2021;232:113680. 10.1016/j.ijheh.2020.113680.
112. Hu X, Li S, Cirillo PM, Krigbaum NY, Tran V, Jones DP, et al. Metabolome Wide Association Study of Serum Poly and Perfluoroalkyl Substances (PFASs) in Pregnancy and Early Postpartum. Reprod Toxicol. 2019;87:70–8. 10.1016/j.reprotox.2019.05.058. [PubMed: 31121237]
113. Schillemans T, Shi L, Donat-Vargas C, Hanhineva K, Tornevi A, Johansson I, et al. Plasma metabolites associated with exposure to Perfluoroalkyl substances and risk of type 2 diabetes – A nested case-control study. Environ Int. 2021;146:106180. 10.1016/j.envint.2020.106180. [PubMed: 33113464]
114. Sinisalu L, Sen P, Salihović S, Virtanen SM, Hyöty H, Ilonen J, et al. Early-life exposure to perfluorinated alkyl substances modulates lipid metabolism in progression to celiac disease. Environmental Research. 2020;188:109864. 10.1016/j.envres.2020.109864. [PubMed: 32846648]
115. Stratakis N, V. Conti D, Jin R, Margetaki K, Valvi D, Siskos AP, et al. Prenatal Exposure to Perfluoroalkyl Substances Associated With Increased Susceptibility to Liver Injury in Children. Hepatology. 2020;72(5):1758–70. 10.1002/hep.31483. [PubMed: 32738061]
116. Jin R, McConnell R, Catherine C, Xu S, Walker DI, Stratakis N, et al. Perfluoroalkyl substances and severity of nonalcoholic fatty liver in Children: An untargeted metabolomics approach. Environ Int. 2020;134:105220. 10.1016/jenvint.2019.105220. [PubMed: 31744629]
117. Salihovic S, Fall T, Ganna A, Broeckling CD, Prenni JE, Hyötyläinen T, et al. Identification of metabolic profiles associated with human exposure to Perfluoroalkyl substances. J Eposure Sci Environ Epidemiol. 2019;29(2):196–205. 10.1038/s41370-018-0060-y.
118. Chen Z, Yang T, Walker DI, Thomas DC, Qiu C, Chatzi L, et al. Dysregulated lipid and fatty acid metabolism link Perfluoroalkyl substances exposure and impaired glucose metabolism in young adults. Environ Int. 2020;145:106091. 10.1016/j.envint.2020.106091. [PubMed: 32892005]
119. Chang C-J, Barr DB, Ryan PB, Panuwet P, Smarr MM, Liu K, et al. Per- and Poly-fluoroalkyl substance (PFAS) exposure, maternal metabolomic perturbation, and fetal growth in African American women: A meet-in-the-middle approach. Environ Int. 2022;158:106964. 10.1016/jenvint.2021.106964. [PubMed: 34735953]
120. Ji J, Song L, Wang J, Yang Z, Yan H, Li T, et al. Association between urinary per- and poly-fluoroalkyl substances and COVID-19 susceptibility. Environ Int. 2021;153:106524. 10.1016/j.envint.2021.106524. [PubMed: 33773143]
121. Kingsley SL, Walker DI, Calafat AM, Chen A, Papandonatos GD, Xu Y, et al. Metabolomics of childhood exposure to Perfluoroalkyl substances: a cross-sectional study. Metabolomics. 2019;15(7):95. 10.1007/s11306-019-1560-z. [PubMed: 31227916]
122. Li Y, Lu X, Yu N, Li A, Zhuang T, Du L, et al. Exposure to legacy and novel Perfluoroalkyl substance disturbs the metabolic homeostasis in pregnant women and fetuses: A metabolome-wide association study. Environ Int. 2021;156:106627. 10.1016/j.envint.2021.106627. [PubMed: 33991873]
123. Wang X, Liu L, Zhang W, Zhang J, Du X, Huang Q, et al. Serum metabolome biomarkers associate low-level environmental per-fluorinated compound exposure with oxidative /nitrosative stress in humans. Environ Pollut. 2017;229:168–76. 10.1016/j.envpol.2017.04.086. [PubMed: 28599201]

124. Sinisalu L, Yeung LWY, Wang J, Pan Y, Dai J, Hyotylainen T. Prenatal exposure to poly-/Perfluoroalkyl substances is associated with alteration of lipid profiles in cord-blood. Metabolomics. 2021;17(12):103. 10.1007/s11306-021-01853-9. [PubMed: 34816353]

125. Lee S-H, Tseng W-C, Du Z-Y, Lin W-Y, Chen M-H, Lin C-C, et al. Lipid responses to environmental Perfluoroalkyl substance exposure in a Taiwanese Child cohort. Environmental Pollution. 2021;283:117007. 10.1016/j.envpol.2021.117007. [PubMed: 33845286]

126. Takacs ML, Abbott BD. Activation of Mouse and Human Peroxisome Proliferator-Activated Receptors (α, β/δ, γ) by Perfluo-rooctanoic Acid and Perfluorooctane Sulfonate. Toxicol Sci. 2006;95(1):108–17. 10.1093/toxsci/kfl135. [PubMed: 17047030]

127. Montaigne D, Butruille L, Staels B. PPAR control of metabolism and cardiovascular functions. Nat Rev Cardiol. 2021;18(12):809–23. 10.1038/s41569-021-00569-6. [PubMed: 34127848]

128. Bjork JA, Wallace KB. Structure-activity relationships and human relevance for Perfluoroalkyl acid-induced transcriptional activation of peroxisome proliferation in liver cell cultures. Toxicol Sci. 2009;111(1):89–99. 10.1093/toxsci/kfp093. [PubMed: 19407336]

129. Bjork JA, Butenhoff JL, Wallace KB. Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes. Toxicology. 2011;288(1–3):8–17. 10.1016/j.tox.2011.06.012. [PubMed: 21723365]

130. Shipley JM, Hurst CH, Tanaka SS, DeRoos FL, Butenhoff JL, Seacat AM, et al. trans-activation of PPARalpha and induction of PPARalpha target genes by perfluorooctane-based chemicals. Toxicol Sci. 2004;80(1):151–60. 10.1093/toxsci/kfh130. [PubMed: 15071170]

131. United States Agency for Toxic Substances and Disease Registry. Toxicological profile for Perfluoroalkyls. Health Effects. 2021.

132. Rosen MB, Das KP, Rooney J, Abbott B, Lau C, Corton JC. PPARα-independent transcriptional targets of Perfluoroalkyl acids revealed by transcript profiling. Toxicology. 2017;387:95–107. 10.1016/j.tox.2017.05.013. [PubMed: 28558994]

133. Cheng X, Klaassen CD. Perfluorocarboxylic acids induce cytochrome P450 enzymes in mouse liver through activation of PPAR-alpha and CAR transcription factors. Toxicol Sci. 2008;106(1):29–36. 10.1093/toxsci/kfn147. [PubMed: 18648086]

134. Vanden Heuvel JP, Thompson JT, Frame SR, Gillies PJ. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-alpha, -beta, and -gamma, liver X receptor-beta, and retinoid X receptor-alpha. Toxicol Sci. 2006;92(2):476–89. 10.1093/toxsci/kfl014. [PubMed: 16731579]

135. Zhang L, Ren XM, Wan B, Guo LH. Structure-dependent binding and activation of perfluorinated compounds on human peroxisome proliferator-activated receptor γ. Toxicol Appl Pharmacol. 2014;279(3):275–83. 10.1016/j.taap.2014.06.020. [PubMed: 24998974]

136. Choi EM, Suh KS, Rhee SY, Oh S, Woo JT, Kim SW, et al. Perfluorooctanoic acid induces mitochondrial dysfunction in MC3T3-E1 osteoblast cells. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2017;52(3):281–9. 10.1080/10934529.2016.1253402. [PubMed: 27901621]

137. Suh KS, Choi EM, Kim YJ, Hong SM, Park SY, Rhee SY, et al. Perfluorooctanoic acid induces oxidative damage and mitochondrial dysfunction in pancreatic β-cells. Mol Med Rep. 2017;15(6):3871–8. 10.3892/mmr.2017.6452. [PubMed: 28440430]

138. Quist EM, Filgo AJ, Cummings CA, Kissling GE, Hoenerhoff MJ, Fenton SE. Hepatic Mitochondrial Alteration in CD-1 Mice Associated with Prenatal Exposures to Low Doses of Perfluorooctanoic Acid (PFOA). Toxicol Pathol. 2015;43(4):546–57. 10.1177/0192623314551841. [PubMed: 25326589]

139. Starkov AA, Wallace KB. Structural determinants of fluorochemical-induced mitochondrial dysfunction. Toxicol Sci. 2002;66(2):244–52. 10.1093/toxsci/66.2.244. [PubMed: 11896291]

140. Upham BL, Deocampo ND, Wurl B, Trosko JE. Inhibition of gap junctional intercellular communication by perfluorinated fatty acids is dependent on the chain length of the fluorinated tail. Int J Cancer. 1998;78(4):491–5. 10.1002/(sici)1097-0215(19981109)78:4<491::aid-ijc16>3.0.co;2-9. [PubMed: 9797139]

141. Hu W, Jones PD, Upham BL, Trosko JE, Lau C, Giesy JP. Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney

epithelial cell lines in vitro and Sprague-Dawley rats in vivo. Toxicological sciences : an official journal of the Society of Toxicology. 2002;68(2):429–36. 10.1093/toxsci/68.2.429. [PubMed: 12151638]

142. Lu Y, Meng L, Ma D, Cao H, Liang Y, Liu H, et al. The occurrence of PFAS in human placenta and their binding abilities to human serum albumin and organic anion transporter 4. Environ Pollut. 2021;273:116460. [PubMed: 33485002]
143. Jackson TW, Scheibly CM, Polera ME, Belcher SM. Rapid Characterization of Human Serum Albumin Binding for Per- and Polyfluoroalkyl Substances Using Differential Scanning Fluorimetry. Environ Sci Technol. 2021;55(18):12291–301. 10.1021/acs.est.1c01200. [PubMed: 34495656]
144. Wang Y, Aimuzi R, Nian M, Zhang Y, Luo K, Zhang J. Perfluoroalkyl substances and sex hormones in postmenopausal women: NHANES 2013–2016. Environ Int. 2021;149:106408. 10.1016/j.envint.2021.106408. [PubMed: 33548847]
145. Luebker DJ, Hansen KJ, Bass NM, Butenhoff JL, Seacat AM. Interactions of fluorochemicals with rat liver fatty acid-binding protein. Toxicology. 2002;176(3):175–85. 10.1016/s0300-483x(02)00081-1. [PubMed: 12093614]
146. Kar S, Sepúlveda MS, Roy K, Leszczynski J. Endocrine-disrupting activity of per- and polyfluoroalkyl substances: Exploring combined approaches of ligand and structure based modeling. Chemosphere. 2017;184:514–23. 10.1016/jchemosphere.2017.06.024. [PubMed: 28622647]
147. Ren X-M, Zhang Y-F, Guo L-H, Qin Z-F, Lv Q-Y, Zhang L-Y. Structure–activity relations in binding of perfluoroalkyl compounds to human thyroid hormone T3 receptor. Arch Toxicol. 2015;89(2):233–42. 10.1007/s00204-014-1258-y. [PubMed: 24819616]
148. Roth K, Yang Z, Agarwal M, Liu W, Peng Z, Long Z, et al. Exposure to a mixture of legacy, alternative, and replacement per- and polyfluoroalkyl substances (PFAS) results in sex-dependent modulation of cholesterol metabolism and liver injury. Environ Int. 2021;157:106843. 10.1016/j.envint.2021.106843. [PubMed: 34479135]
149. Hagenaars A, Vergauwen L, Benoot D, Laukens K, Knapen D. Mechanistic toxicity study of perfluorooctanoic acid in zebrafish suggests mitochondrial dysfunction to play a key role in PFOA toxicity. Chemosphere. 2013;91(6):844–56. 10.1016/j.chemosphere.2013.01.056. [PubMed: 23427857]
150. Dinnes DL, Santerre JP, Labow RS. Phospholipase A2 pathway association with macrophage-mediated polycarbonate-urethane biodegradation. Biomaterials. 2005;26(18):3881–9. 10.1016/j.biomaterials.2004.09.064. [PubMed: 15626436]
151. Yasuda T, Al Sazzad MA, Jäntti NZ, Pentikäinen OT, Slotte JP. The Influence of Hydrogen Bonding on Sphingomyelin/Colipid Interactions in Bilayer Membranes. Biophys J. 2016;110(2):431–40. 10.1016/j.bpj.2015.11.3515. [PubMed: 26789766]
152. Baumruker T, Prieschl EE. Sphingolipids and the regulation of the immune response. Semin Immunol. 2002;14(1):57–63. 10.1006/smim.2001.0342. [PubMed: 11884231]
153. Pinto SN, Silva LC, Futerman AH, Prieto M. Effect of ceramide structure on membrane biophysical properties: the role of acyl chain length and unsaturation. Biochim Biophys Acta. 2011;1808(11):2753–60. 10.1016/j.bbamem.2011.07.023. [PubMed: 21835161]
154. Ohanian J, Ohanian V. Sphingolipids in mammalian cell signalling. Cell Mol Life Sci. 2001;58(14):2053–68. 10.1007/pl00000836. [PubMed: 11814056]
155. Schlezinger JJ, Hyötyläinen T, Sinioja T, Boston C, Puckett H, Oliver J, et al. Perfluorooctanoic acid induces liver and serum dyslipidemia in humanized PPARα mice fed an American diet. Toxicol Appl Pharmacol. 2021;426:115644. 10.1016/j.taap.2021.115644. [PubMed: 34252412]
156. Pouwer MG, Pieterman EJ, Chang S-C, Olsen GW, Caspers MPM, Verschuren L, et al. Dose Effects of Ammonium Per-fluorooctanoate on Lipoprotein Metabolism in APOE*3-Leiden.CETP Mice. Toxicological Sciences. 2019;168(2):519–34. 10.1093/toxsci/kfz015. [PubMed: 30657992]
157. Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V. Association of Perfluorooctanoic Acid and Perfluorooctane Sulfonate With Serum Lipids Among Adults Living Near a Chemical Plant. Am J Epidemiol. 2009;170(10):1268–78. 10.1093/aje/kwp279. [PubMed: 19846564]

158. Olsen GW, Zobel LR. Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. Int Arch Occup Environ Health. 2007;81(2):231–46. 10.1007/s00420-007-0213-0. [PubMed: 17605032]

159. Li Y, Barregard L, Xu Y, Scott K, Pineda D, Lindh CH, et al. Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water. Environ Health. 2020;19(1):33. 10.1186/s12940-020-00588-9. [PubMed: 32169067]

160. Canova C, Barbieri G, Zare Jeddi M, Gion M, Fabricio A, Daprà F, et al. Associations between perfluoroalkyl substances and lipid profile in a highly exposed young adult population in the Veneto Region. Environ Int. 2020;145:106117. 10.1016/j.envint.2020.106117. [PubMed: 32971418]

161. Liu G, Zhang B, Hu Y, Rood J, Liang L, Qi L, et al. Associations of Perfluoroalkyl substances with blood lipids and Apolipoproteins in lipoprotein subspecies: the POUNDS-lost study. Environmental health : a global access science source. 2020;19(1):5-. 10.1186/s12940-020-0561-8. [PubMed: 31931806]

162. Château-Degat ML, Pereg D, Dallaire R, Ayotte P, Dery S, Dewailly E. Effects of perfluorooctanesulfonate exposure on plasma lipid levels in the Inuit population of Nunavik (Northern Quebec). Environ Res. 2010;110(7):710–7. 10.1016/jenvres2010.07.003. [PubMed: 20696425]

163. Fu Y, Wang T, Fu Q, Wang P, Lu Y. Associations between serum concentrations of perfluoroalkyl acids and serum lipid levels in a Chinese population. Ecotoxicol Environ Saf. 2014;106:246–52. 10.1016/j.ecoenv.2014.04.039. [PubMed: 24863755]

164. Koshy TT, Attina TM, Ghassabian A, Gilbert J, Burdine LK, Marmor M, et al. Serum perfluoroalkyl substances and cardiometabolic consequences in adolescents exposed to the World Trade Center disaster and a matched comparison group. Environ Int. 2017;109:128–35. 10.1016/j.envint.2017.08.003. [PubMed: 28890218]

165. Zeng XW, Qian Z, Emo B, Vaughn M, Bao J, Qin XD, et al. Association of polyfluoroalkyl chemical exposure with serum lipids in children. Sci Total Environ. 2015;512–513:364–70. 10.1016/j.scitotenv.2015.01.042.

166. Yang Q, Guo X, Sun P, Chen Y, Zhang W, Gao A. Association of serum levels of perfluoroalkyl substances (PFASs) with the metabolic syndrome (MetS) in Chinese male adults: A cross–sectional study. Sci Total Environ. 2018;621:1542–9. 10.1016/jscitotenv.2017.10.074. [PubMed: 29054655]

167. Timmermann CA, Rossing LI, Grøntved A, Ried-Larsen M, Dalgård C, Andersen LB, et al. Adiposity and glycemic control in children exposed to perfluorinated compounds. J Clin Endocrinol Metab. 2014;99(4):E608–14. 10.1210/jc.2013-3460. [PubMed: 24606078]

168. Olsen GW, Burris JM, Burlew MM, Mandel JH. Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. J Occup Environ Med. 2003;45(3):260–70. 10.1097/01.jom.0000052958.59271.10. [PubMed: 12661183]

169. Manzano-Salgado CB, Casas M, Lopez-Espinosa M-J, Ballester F, Iniguez C, Martinez D, et al. Prenatal Exposure to Perfluoroalkyl Substances and Cardiometabolic Risk in Children from the Spanish INMA Birth Cohort Study. Environ Health Perspect. 2017;125(9):097018. 10.1289/EHP1330. [PubMed: 28934720]

170. Zhang H, Shi Z, Liu Y, Wei Y, Dai J. Lipid homeostasis and oxidative stress in the liver of male rats exposed to perfluorododecanoic acid. Toxicol Appl Pharmacol. 2008;227(1):16–25. 10.1016/j.taap.2007.09.026. [PubMed: 18028973]

171. Bijland S, Rensen PCN, Pieterman EJ, Maas ACE, van der Hoorn JW, van Erk MJ, et al. Perfluoroalkyl Sulfonates Cause Alkyl Chain Length-Dependent Hepatic Steatosis and Hypolipidemia Mainly by Impairing Lipoprotein Production in APOE*3-Leiden CETP Mice. Toxicol Sci. 2011;123(1):290–303. 10.1093/toxsci/kfr142. [PubMed: 21705711]

172. Das KP, Wood CR, Lin MT, Starkov AA, Lau C, Wallace KB, et al. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. Toxicology. 2017;378:37–52. 10.1016/j.tox.2016.12.007. [PubMed: 28049043]

173. Wang J, Yan S, Zhang W, Zhang H, Dai J. Integrated proteomic and miRNA transcriptional analysis reveals the hepatotoxicity mechanism of PFNA exposure in mice. J Proteome Res. 2015;14(1):330–41. 10.1021/pr500641b. [PubMed: 25181679]

174. Louisse J, Rijkers D, Stoopen G, Janssen A, Staats M, Hoogenboom R, et al. Perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorononanoic acid (PFNA) increase triglyceride levels and decrease cholesterogenic gene expression in human HepaRG liver cells. Arch Toxicol. 2020;94(9):3137–55. 10.1007/s00204-020-02808-0. [PubMed: 32588087]

175. Majithia AR, Tsuda B, Agostini M, Gnanapradeepan K, Rice R, Peloso G, et al. Prospective functional classification of all possible missense variants in PPARG. Nat Genet. 2016;48(12):1570–5. 10.1038/ng3700. [PubMed: 27749844]

176. McCann MR, George De la Rosa MV, Rosania GR, Stringer KA. L-Carnitine and Acylcarnitines: Mitochondrial Biomarkers for Precision Medicine. Metabolites. 2021;11(1):51. 10.3390/metabo11010051. [PubMed: 33466750]

177. Wang YN T; Gonzalez FJ; Tanaka N PPARs as Metabolic Regulators in the Liver: Lessons from Liver-Specific PPAR-Null Mice. Int J Mol Sci 2020;21(6):2061. 10.3390/ijms21062061. [PubMed: 32192216]

178. Wang G, Bonkovsky HL, de Lemos A, Burczynski FJ. Recent insights into the biological functions of liver fatty acid binding protein 1. J Lipid Res. 2015;56(12):2238–47. 10.1194/jlr.R056705. [PubMed: 26443794]

179. Gaggini M, Carli F, Rosso C, Buzzigoli E, Marietti M, Della Latta V, et al. Altered amino acid concentrations in NAFLD: Impact of obesity and insulin resistance. Hepatology. 2018;67(1):145–58. 10.1002/hep.29465. [PubMed: 28802074]

180. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, et al. A Branched-Chain Amino Acid-Related Metabolic Signature that Differentiates Obese and Lean Humans and Contributes to Insulin Resistance. Cell Metab. 2009;9(4):311–26. 10.1016/jcmet2009.02.002. [PubMed: 19356713]

181. Kimberly WT, O'Sullivan JF, Nath AK, Keyes M, Shi X, Larson MG, et al. Metabolite profiling identifies anandamide as a biomarker of nonalcoholic steatohepatitis. JCI Insight. 2017;2(9). 10.1172/jciinsight.92989.

182. Lynch CJ, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance. Nat Rev Endocrinol. 2014;10(12):723–36. 10.1038/nrendo.2014.171. [PubMed: 25287287]

183. Holeček M. Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutr Metab (Lond). 2018;15:33. 10.1186/s12986-018-0271-1. [PubMed: 29755574]

184. Adams SH, Hoppel CL, Lok KH, Zhao L, Wong SW, Minkler PE, et al. Plasma acylcarnitine profiles suggest incomplete long-chain fatty acid beta-oxidation and altered tricarboxylic acid cycle activity in type 2 diabetic African-American women. J Nutr. 2009;139(6):1073–81. 10.3945/jn.108.103754. [PubMed: 19369366]

185. Torok R, Horompoly K, Szigeti M, Guttman A, Vitai M, Koranyi L, et al. N-Glycosylation Profiling of Human Blood in Type 2 Diabetes by Capillary Electrophoresis: A Preliminary Study. Molecules. 2021;26(21). 10.3390/molecules26216399.

186. Bermingham ML, Colombo M, McGurnaghan SJ, Blackbourn LAK, Vučković F, Pučić Baković M, et al. N-Glycan Profile and Kidney Disease in Type 1 Diabetes. Diabetes Care. 2018;41(1):79–87. 10.2337/dc17-1042. [PubMed: 29146600]

187. Adua E, Memarian E, Russell A, Trbojević-Akmačić I, Gudelj I, Jurić J, et al. High throughput profiling of whole plasma N-glycans in type II diabetes mellitus patients and healthy individuals: A perspective from a Ghanaian population. Arch Biochem Biophys. 2019;661:10–21. 10.1016/j.abb.2018.10.015. [PubMed: 30365935]

188. U.S. Department of Health and Human Services PHS, National Toxicology Program (NTP). NTP Monograph on immunotoxicity associated with exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC 2016.

189. Biegel LB, Liu RC, Hurtt ME, Cook JC. Effects of ammonium perfluorooctanoate on Leydig cell function: in vitro, in vivo, and ex vivo studies. Toxicol Appl Pharmacol. 1995;134(1):18–25. 10.1006/taap.1995.1164. [PubMed: 7676454]

190. Bassler J, Ducatman A, Elliott M, Wen S, Wahlang B, Barnett J, et al. Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines. Environ Pollut. 2019;247:1055–63. 10.1016/j.envpol.2019.01.064. [PubMed: 30823334]

191. Gardener H, Sun Q, Grandjean P. PFAS concentration during pregnancy in relation to cardiometabolic health and birth outcomes. Environ Res. 2021;192:110287. 10.1016/j.envres.2020.110287. [PubMed: 33038367]

192. Pitter G, Zare Jeddi M, Barbieri G, Gion M, Fabricio ASC, Daprà F, et al. Perfluoroalkyl substances are associated with elevated blood pressure and hypertension in highly exposed young adults. Environ Health. 2020;19(1):102. 10.1186/s12940-020-00656-0. [PubMed: 32958007]

193. Xu H, Zhou Q, Zhang J, Chen X, Zhao H, Lu H, et al. Exposure to elevated per- and polyfluoroalkyl substances in early pregnancy is related to increased risk of gestational diabetes mellitus: A nested case-control study in Shanghai, China. Environ Int. 2020;143:105952. 10.1016/j.envint.2020.105952. [PubMed: 32717645]

194. Mancini FR, Rajaobelina K, Praud D, Dow C, Antignac JP, Kvaskoff M, et al. Nonlinear associations between dietary exposures to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS) and type 2 diabetes risk in women: Findings from the E3N cohort study. Int J Hyg Environ Health. 2018;221(7):1054–60. 10.1016/j.ijheh.2018.07.007. [PubMed: 30056006]

195. Lind L, Zethelius B, Salihovic S, van Bavel B, Lind PM. Circulating levels of perfluoroalkyl substances and prevalent diabetes in the elderly. Diabetologia. 2014;57(3):473–9. 10.1007/s00125-013-3126-3. [PubMed: 24337155]

196. Mattsson K, Rignell-Hydbom A, Holmberg S, Thelin A, Jönsson BAG, Lindh CH, et al. Levels of perfluoroalkyl substances and risk of coronary heart disease: Findings from a population-based longitudinal study. Environ Res. 2015;142:148–54. 10.1016/j.envres.2015.06.033. [PubMed: 26142720]

197. Huang M, Jiao J, Zhuang P, Chen X, Wang J, Zhang Y. Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population. Environ Int. 2018;119:37–46. 10.1016/j.envint.2018.05.051. [PubMed: 29933236]

198. Winquist A, Steenland K. Modeled PFOA Exposure and Coronary Artery Disease, Hypertension, and High Cholesterol in Community and Worker Cohorts. Environ Health Perspect. 2014;122(12):1299–305. 10.1289/ehp.1307943. [PubMed: 25260175]

199. Simpson C, Winquist A, Lally C, Steenland K. Relation between perfluorooctanoic acid exposure and strokes in a large cohort living near a chemical plant. Environ Res. 2013;127:22–8. 10.1016/jenvres.2013.10.002. [PubMed: 24199934]

200. Qi W, Clark JM, Timme-Laragy AR, Park Y. Per- and Polyfluoroalkyl Substances and Obesity, Type 2 Diabetes and Non-alcoholic Fatty Liver Disease: A Review of Epidemiologic Findings. Toxicol Environ Chem. 2020;102(1–4):1–36. 10.1080/02772248.2020.1763997. [PubMed: 33304027]

201. Liu J-J, Cui X-X, Tan Y-W, Dong P-X, Ou Y-Q, Li Q-Q, et al. Per- and perfluoroalkyl substances alternatives, mixtures and liver function in adults: A community-based population study in China. Environ Int. 2022;163:107179. 10.1016/j.envint.2022.107179. [PubMed: 35325771]

202. Jiang L, Hong Y, Xie G, Zhang J, Zhang H, Cai Z. Comprehensive multi-omics approaches reveal the hepatotoxic mechanism of perfluorohexanoic acid (PFHxA) in mice. Sci Total Environ. 2021;790:148160. 10.1016/j.scitotenv.2021.148160. [PubMed: 34380288]

203. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001;414(6865):799–806. 10.1038/414799a. [PubMed: 11742412]

204. Guasch-Ferré M, Zheng Y, Ruiz-Canela M, Hruby A, Martínez-González MA, Clish CB, et al. Plasma acylcarnitines and risk of cardiovascular disease: effect of Mediterranean diet interventions. Am J Clin Nutr. 2016;103(6):1408–16. 10.3945/ajcn.116.130492. [PubMed: 27099249]

205. Zhao S, Feng X-F, Huang T, Luo H-H, Chen J-X, Zeng J, et al. The Association Between Acylcarnitine Metabolites and Cardiovascular Disease in Chinese Patients With Type 2 Diabetes Mellitus. Front Endocrinol (Lausanne). 2020;11:212-. 10.3389/fendo.2020.00212. [PubMed: 32431666]

206. Scinicariello F, Buser MC, Balluz L, Gehle K, Murray HE, Abadin HG, et al. Perfluoroalkyl acids, hyperuricemia and gout in adults: Analyses of NHANES 2009–2014. Chemosphere. 2020;259:127446. 10.1016/j.chemosphere.2020.127446. [PubMed: 32590180]

207. Zeng XW, Lodge CJ, Dharmage SC, Bloom MS, Yu Y, Yang M, et al. Isomers of per- and polyfluoroalkyl substances and uric acid in adults: Isomers of C8 Health Project in China. Environ Int. 2019;133(Pt A):105160. 10.1016/j.envint.2019.105160. [PubMed: 31518937]

208. Wan HT, Wong AY-M, Feng S, Wong CK-C. Effects of In Utero Exposure to Perfluorooctane Sulfonate on Placental Functions. Environ Sci Technol. 2020;54(24):16050–61. 10.1021/acs.est.0c06569. [PubMed: 33258594]

209. Manta-Vogli PD, Schulpis KH, Dotsikas Y, Loukas YL. The significant role of amino acids during pregnancy: nutritional support. J Matern Fetal Neonatal Med. 2020;33(2):334–40. 10.1080/14767058.2018.1489795. [PubMed: 29909700]

210. Cetin I, Ronzoni S, Marconi AM, Perugino G, Corbetta C, Battaglia FC, et al. Maternal concentrations and fetal-maternal concentration differences of plasma amino acids in normal and intrauterine growth-restricted pregnancies. Am J Obstet Gynecol. 1996;174(5):1575–83. 10.1016/S0002-9378(96)70609-9. [PubMed: 9065132]

211. Smith SM, Dickman ED, Power SC, Lancman J. Retinoids and their receptors in vertebrate embryogenesis. J Nutr. 1998;128(2 Suppl):467s–s470. 10.1093/jn/128.2.467S. [PubMed: 9478050]

212. Bastos Maia S, Rolland Souza AS, Costa Caminha MdF, Lins da Silva S, Callou Cruz RdSBL, Carvalho Dos Santos C, et al. Vitamin A and Pregnancy: A Narrative Review. Nutrients. 2019;11(3):681. 10.3390/nu11030681. [PubMed: 30909386]

213. Cassani B, Villablanca EJ, De Calisto J, Wang S, Mora JR. Vitamin A and immune regulation: role of retinoic acid in gut-associated dendritic cell education, immune protection and tolerance. Mol Aspects Med. 2012;33(1):63–76. 10.1016/jmam.2011.11.001. [PubMed: 22120429]

214. Gutierrez-Mazariegos J, Theodosiou M, Campo-Paysaa F, Schubert M. Vitamin A: a multifunctional tool for development. Semin Cell Dev Biol. 2011;22(6):603–10. 10.1016/j.semcdb.2011.06.001. [PubMed: 21693195]

215. Shin JS, Choi MY, Longtine MS, Nelson DM. Vitamin D effects on pregnancy and the placenta. Placenta. 2010;31(12):1027–34. 10.1016/j.placenta.2010.08.015. [PubMed: 20863562]

216. Weisman Y, Harell A, Edelstein S, David M, Spirer Z, Golander A. 1 alpha, 25-Dihydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 in vitro synthesis by human decidua and placenta. Nature. 1979;281(5729):317–9. 10.1038/281317a0. [PubMed: 551281]

217. Peechakara SV, Pittas AG. Vitamin D as a potential modifier of diabetes risk. Nat Clin Pract Endocrinol Metab. 2008;4(4):182–3. 10.1038/ncpendmet0762. [PubMed: 18283325]

218. Bainbridge SA, von Versen-Höynck F, Roberts JM. Uric acid inhibits placental system A amino acid uptake. Placenta. 2009;30(2):195–200. 10.1016/jplacenta.2008.10.015. [PubMed: 19058847]

219. Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, et al. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. Hypertension. 2005;46(6):1263–9. 10.1161/01.Hyp.0000188703.27002.14. [PubMed: 16246973]

220. Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in preeclampsia. Placenta. 2008;29 Suppl A(Suppl A):S67–S72. 10.1016/j.placenta.2007.11.001. [PubMed: 18093648]

221. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension. 2003;41(6):1287–93. 10.1161/01.Hyp.0000072820.07472.3b. [PubMed: 12743010]

222. Michaliszyn SF, Sjaarda LA, Mihalik SJ, Lee S, Bacha F, Chace DH, et al. Metabolomic profiling of amino acids and β-cell function relative to insulin sensitivity in youth. J Clin Endocrinol Metab. 2012;97(11):E2119–24. 10.1210/jc.2012-2170. [PubMed: 22977272]

223. Butte NF, Liu Y, Zakeri IF, Mohney RP, Mehta N, Voruganti VS, et al. Global metabolomic profiling targeting childhood obesity in the Hispanic population. Am J Clin Nutr. 2015;102(2):256–67. 10.3945/ajcn.115.111872. [PubMed: 26085512]

224. Lee A, Jang HB, Ra M, Choi Y, Lee HJ, Park JY, et al. Prediction of future risk of insulin resistance and metabolic syndrome based on Korean boy's metabolite profiling. Obes Res Clin Pract. 2015;9(4):336–45. 10.1016/j.orcp.2014.10.220. [PubMed: 25465494]

225. Hellmuth C, Kirchberg FF, Lass N, Harder U, Peissner W, Koletzko B, et al. Tyrosine Is Associated with Insulin Resistance in Longitudinal Metabolomic Profiling of Obese Children. J Diabetes Res. 2016;2016:2108909. 10.1155/2016/2108909. [PubMed: 26881241]

226. Perng W, Gillman MW, Fleisch AF, Michalek RD, Watkins SM, Isganaitis E, et al. Metabolomic profiles and childhood obesity. Obesity (Silver Spring). 2014;22(12):2570–8. 10.1002/oby.20901. [PubMed: 25251340]

227. Jin R, Banton S, Tran VT, Konomi JV, Li S, Jones DP, et al. Amino Acid Metabolism is Altered in Adolescents with Nonalcoholic Fatty Liver Disease—An Untargeted, High Resolution Metabolomics Study. J Pediatr. 2016;172:14–9.e5. 10.1016/jjpeds2016.01.026. [PubMed: 26858195]

228. Guasch-Ferré M, Hruby A, Toledo E, Clish CB, Martínez-González MA, Salas-Salvadó J, et al. Metabolomics in Prediabetes and Diabetes: A Systematic Review and Meta-analysis. Diabetes Care. 2016;39(5):833–46. 10.2337/dc15-2251. [PubMed: 27208380]

229. Rayne S, Forest K. Perfluoroalkyl sulfonic and carboxylic acids: A critical review of physicochemical properties, levels and patterns in waters and wastewaters, and treatment methods. J Environ Sci Health A. 2009;44(12):1145–99. 10.1080/10934520903139811.

230. Huang MC, Dzierlenga AL, Robinson VG, Waidyanatha S, DeVito MJ, Eifrid MA, et al. Toxicokinetics of perfluorobutane sulfonate (PFBS), perfluorohexane-1-sulphonic acid (PFHxS), and perfluorooctane sulfonic acid (PFOS) in male and female Hsd: Sprague Dawley SD rats after intravenous and gavage administration. Toxicol Rep. 2019;6:645–55. 10.1016/j.toxrep.2019.06.016. [PubMed: 31334035]

231. Li F, Duan J, Tian S, Ji H, Zhu Y, Wei Z, et al. Short-chain per- and polyfluoroalkyl substances in aquatic systems: occurrence, impacts and treatment. Chem Eng J. 2020;380:122506. 10.1016/j.cej.2019.122506.

232. Wolf CJ, Takacs ML, Schmid JE, Lau C, Abbott BD. Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. Toxicol Sci. 2008;106(1):162–71. 10.1093/toxsci/kfn166. [PubMed: 18713766]

233. Sampson JN, Boca SM, Shu XO, Stolzenberg-Solomon RZ, Matthews CE, Hsing AW, et al. Metabolomics in epidemiology: sources of variability in metabolite measurements and implications. Cancer Epidemiol Biomarkers Prev. 2013;22(4):631–40. 10.1158/1055-9965.EPI-12-1109. [PubMed: 23396963]

234. Kudo N, Kawashima Y. Fish oil-feeding prevents perfluorooctanoic acid-induced fatty liver in mice. Toxicol Appl Pharmacol. 1997;145(2):285–93. 10.1006/taap.1997.8186. [PubMed: 9266801]

235. Lin Y, Capozzi SL, Lin L, Rodenburg LA. Source apportionment of perfluoroalkyl substances in Great Lakes fish. Environ Pollut. 2021;290:118047. 10.1016/j.envpol.2021.118047. [PubMed: 34467881]

236. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006;296(15):1885–99. 10.1001/jama.296.15.1885. [PubMed: 17047219]

237. Hoa NTQ, Lieu TT, Anh HQ, Huong NTA, Nghia NT, Chuc NT, et al. Perfluoroalkyl substances (PFAS) in freshwater fish from urban lakes in Hanoi, Vietnam: concentrations, tissue distribution, and implication for risk assessment. Environ Sci Pollut Res Int. 2022. 10.1007/s11356-022-19532-0.

238. Seshasayee SM, Rifas-Shiman SL, Chavarro JE, Carwile JL, Lin PD, Calafat AM, et al. Dietary patterns and PFAS plasma concentrations in childhood: Project Viva, USA. Environ Int. 2021;151:106415. 10.1016/j.envint.2021.106415. [PubMed: 33706127]

239. Valvi D, Christiani DC, Coull B, Højlund K, Nielsen F, Audouze K, et al. Gene–environment interactions in the associations of PFAS exposure with insulin sensitivity and beta-cell function in a Faroese cohort followed from birth to adulthood. Environ Res. 2023:115600. 10.1016/jenvres.2023.115600. [PubMed: 36868448]

240. Simes RJ. An Improved Bonferroni Procedure for Multiple Tests of Significance. Biometrika. 1986;73(3):751–4. 10.2307/2336545.

241. Whitlock MC. Combining probability from independent tests: the weighted Z-method is superior to Fisher's approach. J Evol Biol. 2005;18(5):1368–73. 10.1111/j.1420-9101.2005.00917.x. [PubMed: 16135132]

242. Zhang Y, Beesoon S, Zhu L, Martin JW. Biomonitoring of Per-fluoroalkyl Acids in Human Urine and Estimates of Biological Half-Life. Environ Sci Technol. 2013;47(18):10619–27. 10.1021/es401905e. [PubMed: 23980546]

243. Glynn A, Berger U, Bignert A, Ullah S, Aune M, Lignell S, et al. Perfluorinated Alkyl Acids in Blood Serum from Primiparous Women in Sweden: Serial Sampling during Pregnancy and Nursing, And Temporal Trends 1996–2010. Environ Sci Technol. 2012;46(16):9071–9. 10.1021/es301168c. [PubMed: 22770559]

244. Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect. 2010;118(2):222–8. 10.1289/ehp.0901252. [PubMed: 20123620]

245. Gomis MI, Vestergren R, Nilsson H, Cousins IT. Contribution of Direct and Indirect Exposure to Human Serum Concentrations of Perfluorooctanoic Acid in an Occupationally Exposed Group of Ski Waxers. Environ Sci Technol. 2016;50(13):7037–46. 10.1021/acs.est.6b01477. [PubMed: 27304840]

246. Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, et al. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med. 2018;75(1):46–51. 10.1136/oemed-2017-104651. [PubMed: 29133598]

247. Li Y, Xu Y, Scott K, Lindh C, Jakobsson K, Fletcher T. Half-lives of PFOA, PFPeS, PFHxS, PFHpS and PFOS after end of exposure to contaminated drinking water. Environ Epidemiol. 2019;3:237. 10.1097/01.Ee9.0000608476.06577.16.

248. Brede E, Wilhelm M, Göen T, Müller J, Rauchfuss K, Kraft M, et al. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. Int J Hyg Environ Health. 2010;213(3):217–23. 10.1016/jijheh.2010.03.007. [PubMed: 20488749]

249. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect. 2007;115(9):1298–305. 10.1289/ehp.10009. [PubMed: 17805419]

250. Worley RR, Moore SM, Tierney BC, Ye X, Calafat AM, Campbell S, et al. Per- and polyfluoroalkyl substances in human serum and urine samples from a residentially exposed community. Environ Int. 2017;106:135–43. 10.1016/j.envint.2017.06.007. [PubMed: 28645013]

251. Spliethoff HM, Tao L, Shaver SM, Aldous KM, Pass KA, Kannan K, et al. Use of newborn screening program blood spots for exposure assessment: declining levels of perluorinated compounds in New York State infants. Environ Sci Technol. 2008;42(14):5361–7. 10.1021/es8006244. [PubMed: 18754394]

252. Shi Y, Vestergren R, Xu L, Zhou Z, Li C, Liang Y, et al. Human Exposure and Elimination Kinetics of Chlorinated Polyfluoroalkyl Ether Sulfonic Acids (Cl-PFESAs). Environ Sci Technol. 2016;50(5):2396–404. 10.1021/acs.est.5b05849. [PubMed: 26866980]

253. Olsen GW, Chang S-C, Noker PE, Gorman GS, Ehresman DJ, Lieder PH, et al. A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans. Toxicology. 2009;256(1):65–74. 10.1016/j.tox.2008.11.008. [PubMed: 19059455]

254. Chang S-C, Das K, Ehresman DJ, Ellefson ME, Gorman GS, Hart JA, et al. Comparative Pharmacokinetics of Perfluorobutyrate in Rats, Mice, Monkeys, and Humans and Relevance to Human Exposure via Drinking Water. Toxicol Sci. 2008;104(1):40–53. 10.1093/toxsci/kfn057. [PubMed: 18353799]

255. Donat-Vargas C, Bergdahl IA, Tornevi A, Wennberg M, Sommar J, Kiviranta H, et al. Perfluoroalkyl substances and risk of type II diabetes: A prospective nested case-control study. Environ Int. 2019;123:390–8. 10.1016/j.envint.2018.12.026. [PubMed: 30622063]

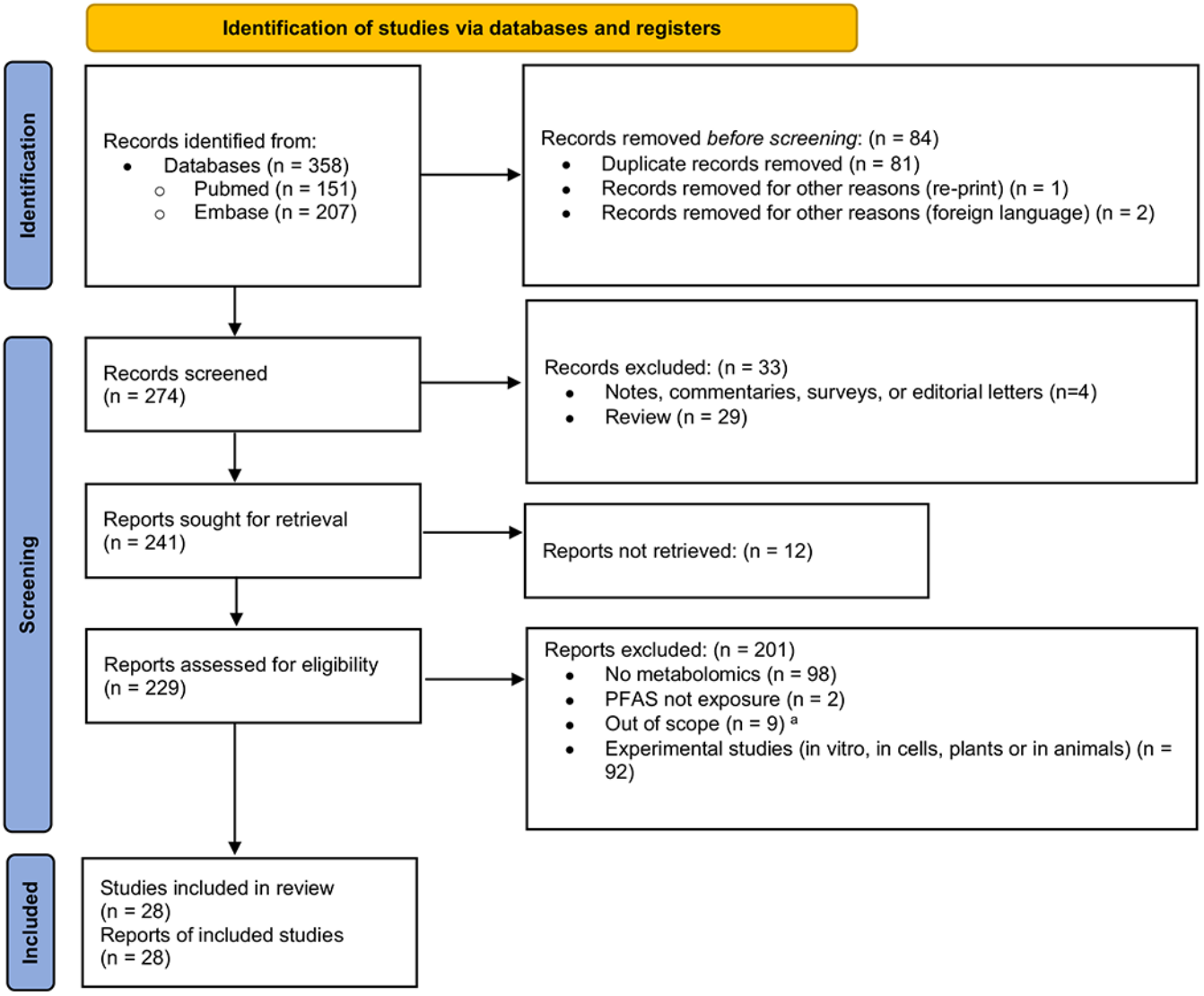

Fig. 1.

PRISMA 2020 flow diagram for PFAS exposures and metabolomics in humans summarizing eligible studies through July 19, 2022

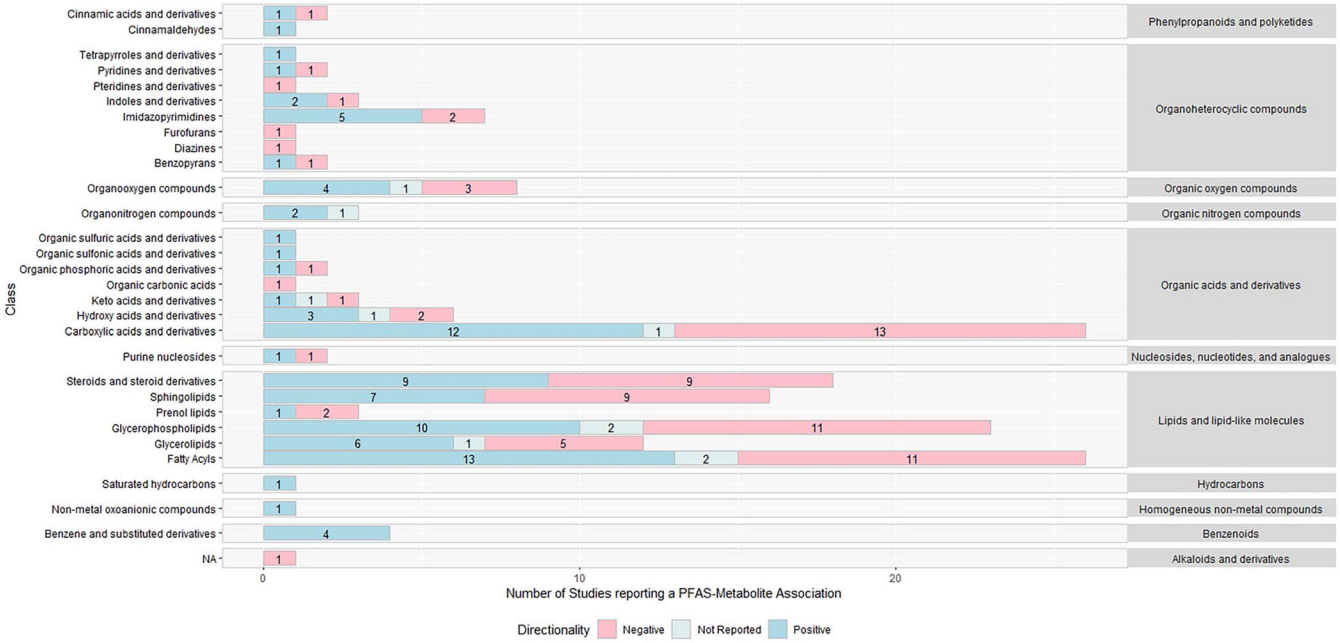

Fig. 2.

Summary of the number of studies reporting targeted and untargeted PFAS-metabolite associations by directionality and metabolite class

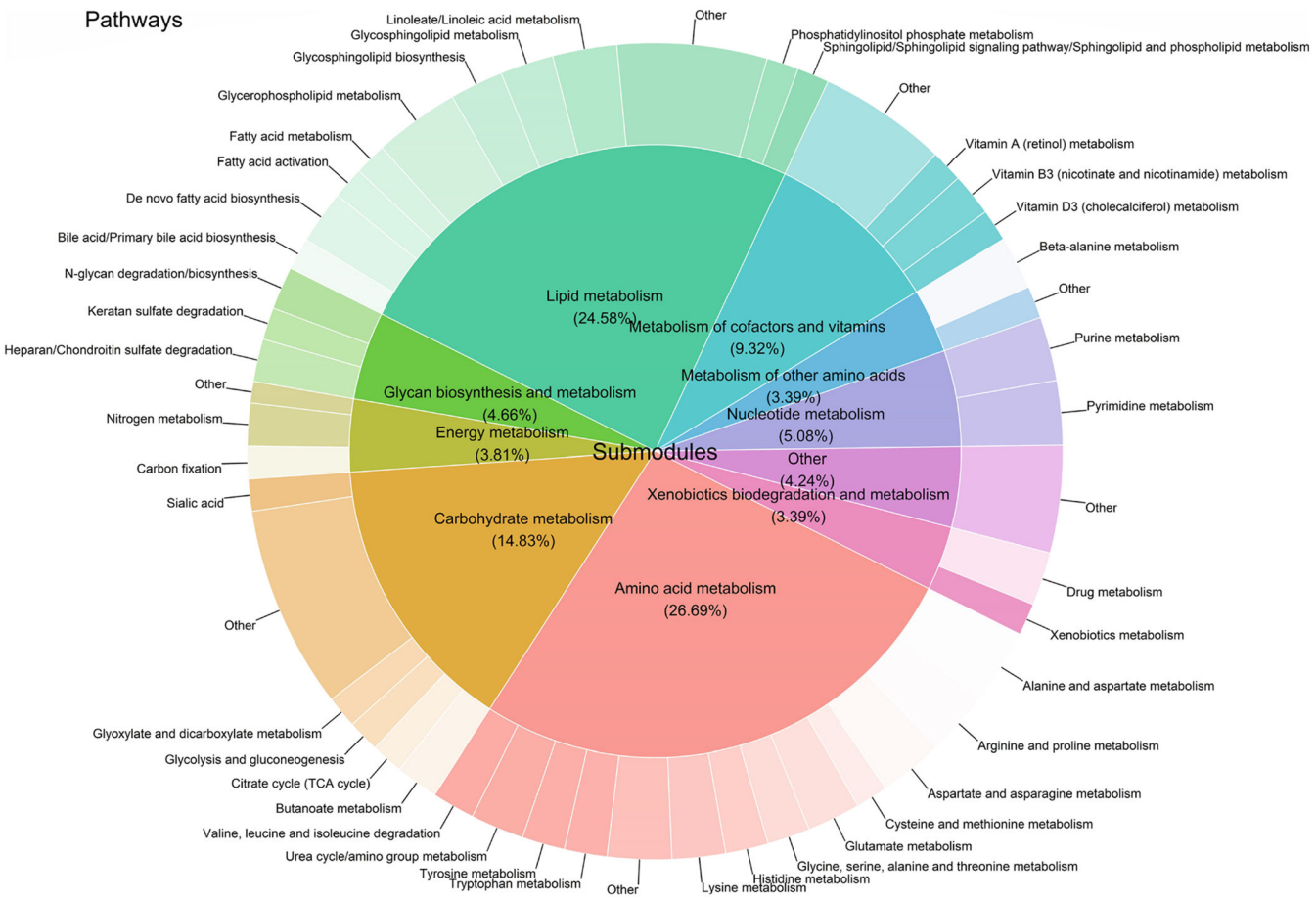

Fig. 3.

Summary of PFAS-related targeted and untargeted pathway associations reported across studies[a]

[a]Classifications based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. Pathways that were associated with PFAS in less than 3 studies where counted as “Other”. Other: includes lipid metabolism (ether lipid metabolism, n=1, 0.42%; NA, n=1, 0.42%; phytanic and peroximal oxidation, n=0.42%; prostaglandin formation from dihomo gama-linoleic acid, n=1, 0.42%; saturated fatty acids beta-oxidation, n=1, 0.43%; carnitine shuttle, n=2, 0.85%; squalene and cholesterol biosynthesis, n=1, 0.42%; steroid hormone biosynthesis, n=1, 0.42%; arachidonic acid metabolism, n-1, 0.42%; alpha-linolenic acid, n=1, 0.42%; omega-3 fatty acid metabolism, n=2, 0.85%; omega-6 fatty acid metabolism, n=2, 0.85%), amino acid metabolism (NA, n=2, 0.85%; valine, leucine, and isoleucine biosynthesis, n=1, 0.42%; valine, leucine, and isoleucine metabolism, n=1, 0.42%; phenylalanine, tyrosine, and tryptophan biosynthesis, n=1, 0.42%; alanine, aspartate metabolism, and glutamate metabolism, n=1, 0.42%), metabolism of other amino acids (glutathione metabolism, n=2, 0.85%; selenoamino acid metabolism, n=1, 0.42%), carbohydrate metabolism (ascorbate and aldarate metabolism, n=2, 0.85%; inositol metabolism, n=1, 0.42%; propanoate metabolism, n=2, 0.85%; pentose phosphate pathway, n=2, 0.85%; pyruvate metabolism, n=1, 0.42%; pentose and glucoronate interconversions, n=1, 0.42%; C5-branched dibasic acid metabolism, n=1, 0.42%; hexose phosphorylation,

n=1, 0.42%; galactose metabolism, n=2, 0.85%; fructose and mannose metabolism, n=2, 0.85%; aminosugars metabolism, n=2, 0.85%; hyaluronan metabolism, n=1, 0.42%; starch and sucrose metabolism, n=1, 0.42%), energy metabolism (electron transport chain, n=1, 0.42%; mitochondrial metabolism, n=1, 0.42%), metabolism of cofactors and vitamins (nicotinate and nicotinamide metabolism, n=2, 0.85%; vitamin B1 metabolism, n=1, 0.42%; vitamin B2 metabolism, n=1, 0.42%; vitamin B6 metabolism, n=1, 0.42%; vitamin B9 metabolism, n=2, 0.85%; vitamin E metabolism, n=1, 0.42%; porphyrin metabolism, n=1, 0.42%; lipoate metabolism , n=1, 0.42%; biopterin metabolism, n=1, 0.42%; ubiquinone biosynthesis, n=1, 0.42%), biosynthesis of other secondary metabolites (caffeine metabolism, n=1, 0.42%; metabolism of alkaloids and their derivatives, n=1, 0.42%), metabolism of terpenoids and polyketides (limonene an pinene degradation, n=1, 0.42%), translation (aminoacyl-tRNA biosynthesis, n=1, 0.42%), structure-based classification (eicosanoid metabolism, n=1, 0.42%), NA (dynorphin metabolism, n=1, 0.42%; kynurenine metabolism, n=1, 0.42%; microbiome metabolism, n=1, 0.42%; bioamines and neurotransmitter metabolism, n=1, 0.42%)

Fig. 4.

Top Reactome pathways involved in PFAS-metabolite associations across studies[a]

[a]Main Reactome pathways for PFAS-metabolite associations with positive (A), negative (B), and all directionalities (C) including positive, negative, and unknown (not reported) directionality. A specific pathway was shown if it was found across more than 25% of the studies and with an FDR<0.05. Reactome entities ratios are denoted by the bubble sizes. Combined *p*-values were calculated [240, 241] for top pathways across studies and shown in the *x*-axis. Studies were included if they reported any PFAS-metabolite

association with an available metabolite KEGG ID recognizable by Reactome (n=26). Abbreviations: glucose-dependent insulinotropic polypeptide (GIP), amino acids (AAs), high-density lipoprotein (HDL), ATP-binding cassette (ABC), diacylglycerol (DAG), triacylglycerol (TAG), phospholipase C (PLC), Fcgamma receptor (FCGR), cardiolipin (CL), phospholipase A2 (PLA2), coat protein complex I (COPI), endoplasmic reticulum (ER), phosphatidylcholine (PC), and solute-carrier gene (SLC).

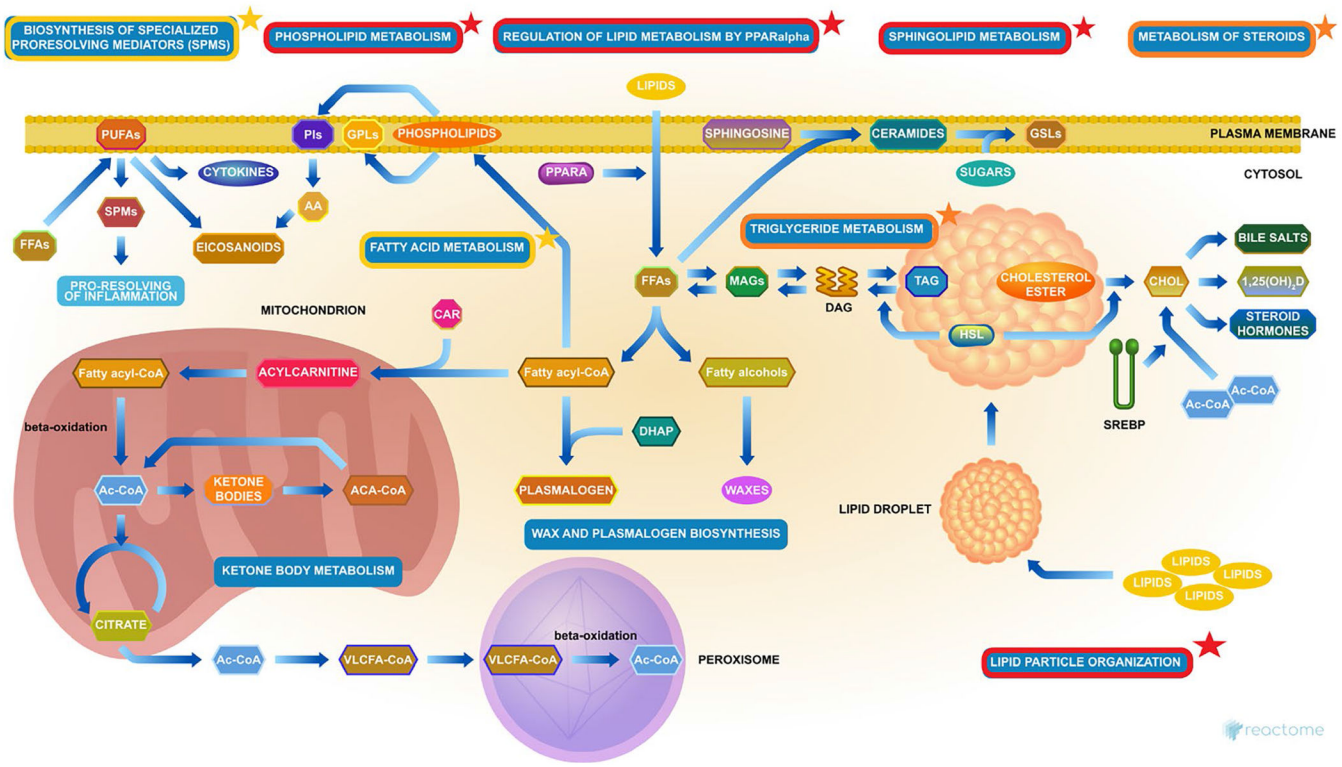

Fig. 5.

Main Reactome pathways involved in lipid metabolism across studies[a]

[a]Highlighted pathways represent more consistently reported lipid pathways across studies as follows: red asterisk represents statistically significant pathways in at least 3 studies (FDR<0.05), orange asterisk represents a pathway present in at least 5 studies with at least one study being statistically significant (FDR<0.05), and a yellow asterisk represents a pathway present in at least 5 studies but not reaching statistical significance (FDR>0.05). This visualization is based on results from Table S9 indicating Reactome pathways related to metabolites with any directionality with respect to PFAS. Studies were included if they reported any PFAS-metabolite association with an available metabolite KEGG ID recognizable by Reactome.

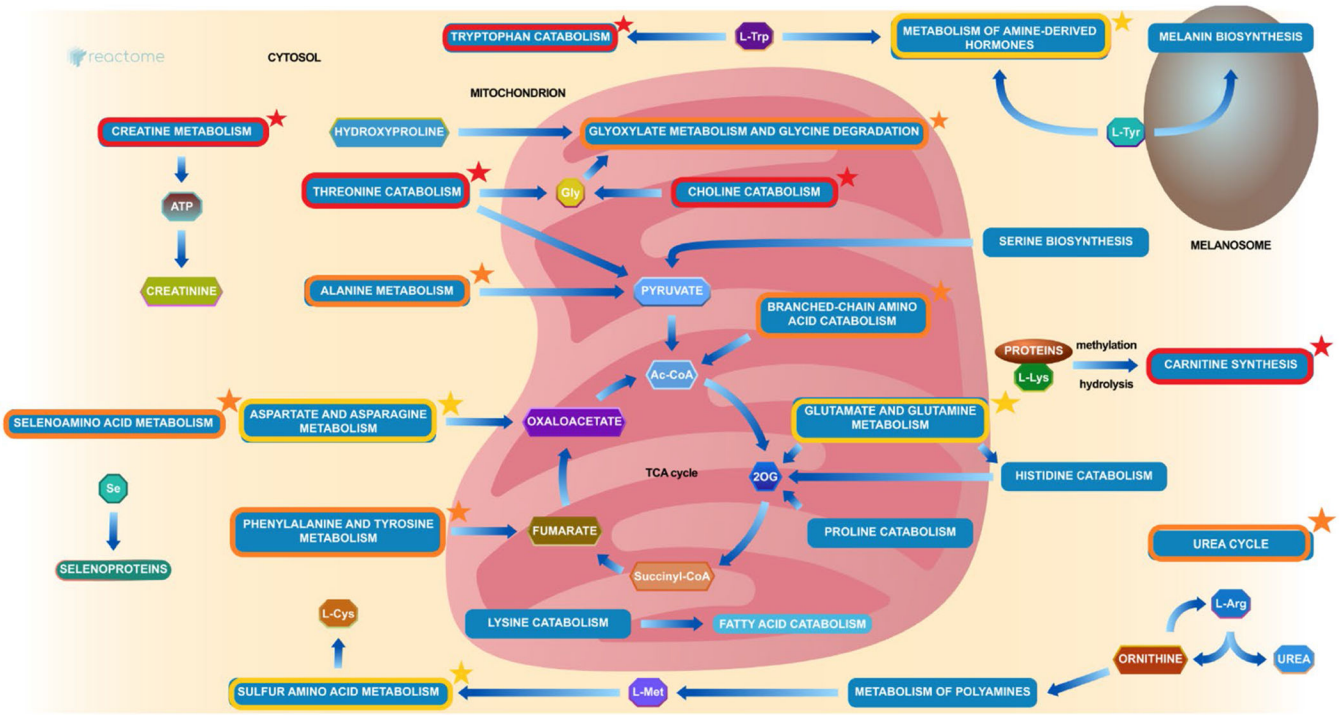

Fig. 6.

Main Reactome pathways involved in amino acid metabolism across studies[a]

[a] Highlighted pathways represent more consistently reported amino acid pathways across studies as follows: red asterisk represents statistically significant pathways in at least 3 studies (FDR<0.05), orange asterisk represents a pathway present in at least 5 studies with at least one study being statistically significant (FDR<0.05), and a yellow asterisk represents a pathway present in at least 5 studies but not reaching statistical significance (FDR>0.05). This visualization is based on results from Table S9 indicating Reactome pathways related to metabolites with any directionality with respect to PFAS. Studies were included if they reported any PFAS-metabolite association with an available metabolite KEGG ID recognizable by Reactome.

Table 1

Summary of PFAS and their characteristics included in metabolomic studies in humans

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
Perfluorotetradecanoic acid (PFTeDA/PFTDA)	McGlinchey et al. 2020	Median (IQR): 0.32 (0.1–0.75) ng/mL	$C_{14}HF_{27}O_2$	14	Carboxylate	Long	–
Perfluorotridecanoic acid (PFTrDA)	Lee et al. 2021	Median: 0.38 ng/mL	$C_{13}HF_{25}O_2$	13	Carboxylate	Long	–
	McGlinchey et al. 2020	Median (IQR): 0.11 (0.06–0.20) ng/mL					
Perfluorododecanoic acid (PFDoA/PFDoDA)	Li et al. 2020	Median (IQR): 0.00 (0.00–0.00) ng/mL[a]	$C_{12}HF_{23}O_2$	12	Carboxylate	Long	–
	McGlinchey et al. 2020	Median (IQR): 0.08 (0.06–0.12) ng/mL					
Perfluorododecane sulfonate (PFDoDS)	McGlinchey et al. 2020	Median (IQR): 0.12 (0.11–0.2) ng/mL	$C_{13}F_{25}O_3S^-$	12	Sulfonate	Long	–
Perfluoroundecanoic acid (PFUnA/PFUnDA/PFUdA)	Huang et al. 2019	Mean (SD): 0.5 (0.5) ug/L	$C_{11}HF_{21}O_2$	11	Carboxylate	Long	4.5–12 years [242]
	Lee et al. 2021	Median: 0.53 ng/mL					
	Li et al. 2020	Median (IQR): 0.00 (0.00–0.00) ng/mL[a]					
	Li et al. 2021	In mothers: Mean (95% CI): 0.97 (0.76–1.17) ng/mL In fetus: Mean (95% CI): 0.70 (0.31–1.09) ng/mL					
	Matta et al. 2022	OMA: Median (IQR): 0.13 (0.10–0.19) ng/m[b] noOMA: Median (IQR): 0.15 (0.10–0.19) ng/mL[b] Control: Median (IQR): 0.13 (0.10–0.17) ng/mL					
	McGlinchey et al. 2020	Median (IQR): 0.27 (0.23–0.34) ng/mL					
	Salihovic et al. 2019	Median (IQR): 0.29 (0.26–0.40) ng/mL					
	Schillemans et al. 2021	T2D cases: Median (IQR): 0.16 (<LOQ–0.23) ng/mL [c] Controls: Median (IQR): 0.18 (<LOQ–0.26) ng/mL[c]					
	Sinisalu et al. 2020	Cord blood: Median (min–max): <LLQ (<LLQ–0.48) ng/mL[d]					

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
		3 months Median (min–max): <LLQ (<LLQ–0.53) ng/mL[d]					
	Stratakis et al. 2020	Median (IQR): 0.20 (0.13, 0.30) ng/mL					
	You et al. 2022	Mean (SD): 6.70 (9.60) ng/mL					
Perfluorodecanoic acid (PFDA/PFDeA)	Huang et al. 2019	Mean (SD): 0.3 (0.3) ug/L	$C_{10}HF_{19}O_2$	10	Carboxylate	Long	4.5–12 years [242]
	Lee et al. 2021	Median: 0.69 ng/mL					
	Li et al. 2020	Median (IQR): 0.00 (0.00–0.00) ng/mL[a]					
	Li et al. 2021	In mothers: Mean (95% CI): 0.87 (0.70–1.04) ng/mL In fetus: Mean (95% CI): 0.37 (0.29–0.44) ng/mL					
	Matta et al. 2022	OMA: Median (IQR): 0.21 (0.18–0.32) ng/mL[b] noOMA: Median (IQR): 0.22 (0.18–0.33) ng/mL[b] Control: Median (IQR): 0.19 (0.17–0.25) ng/mL					
	McGlinchey et al. 2020	Median (IQR): 0.19 (0.14–0.25) ng/mL					
	Schillemans et al. 2021	T2D cases: Median (IQR): 0.21 (<LOQ–0.29) ng/mL[c] Controls: Median (IQR): 0.23 (0.17–0.30) ng/mL[c]					
	You et al. 2022	Mean (SD): 1.70 (2.60) ng/mL					
Pefluorodecane sulfonic acid (PFDS)	McGlinchey et al. 2020	Median (IQR): 0.06 (0.05–0.08) ng/mL	$C_{10}HF_{21}O_3S$	10	Sulfonate	Long	6.6 years [243]
Perfluorononanoic acid (PFNA)	Chang et al. 2022	Median (min-max): 0.27 (<LOD–2.27) ng/mL	$C_9HF_{17}O_2$	9	Carboxylate	Long	2.5–4.3 years [242]
	Huang et al. 2019	Mean (SD): 1.0 (0.5) ug/L					
	Kingsley et al. 2019	Mean (SD): 0.90 (0.70) ng/mL					
	Lee et al. 2021	Median: 1.33 ng/mL					
	Li et al. 2020	Median (IQR): 0.00 (0.00–0.00) ng/mL[a]					
	Li et al. 2021	In mothers: Mean (95% CI): 0.90 (0.71–1.08) ng/mL					

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
		In fetus: Mean (95% CI): 0.73 (0.28–1.18) ng/mL					
	Maitre et al. 2018	Primary cohort: Median (IQR): 0.77 (0.56–1.05) ng/g lipid[e] Replication cohort: Median (IQR): 0.60 (0.46–0.78) ng/g lipid[e]					
	Matta et al. 2022	OMA: Median (IQR): 0.49 (0.41–0.65) ng/mL[b] noOMA: Median (IQR): 0.48 (0.37–0.67) ng/mL[b] Control: Median (IQR): 0.46 (0.31–0.52) ng/mL					
	McGlinchey et al. 2020	Median (IQR): 0.39 (0.28–0.54) ng/mL					
	Mitro et al. 2021	Median (IQR): 0.60 (0.40–0.80) ng/mL					
	Salihovic et al. 2019	Median (IQR): 0.71 (0.53–0.97) ng/mL					
	Schillemans et al. 2021	T2D cases: Median (IQR): 0.55 (0.40–0.76) ng/mL[c] Controls: Median (IQR): 0.53 (0.42–0.78) ng/mL[c]					
	Sen et al. 2022	Median (min–max): 0.37 (0.09–1.08) ng/mL					
	Sinisalu et al. 2021 [f]	Median (min–max): 0.84 (LOD–O.31) ng/mL					
	Stratakis et al. 2020	Median (IQR): 0.72 (0.47–1.11) ng/mL					
	You et al. 2022	Mean (SD): 2.1 (3.1) ng/mL					
	Yu et al. 2022	Mean (SD): 1.02 (0.89) ng/mL					
Perfluorononane sulfonate (PFNS)	McGlinchey et al. 2020	Median (IQR): 0.03 (0.00–0.06) ng/mL	$C_9F_{19}O_3S^-$	9	Sulfonate	Long	–
Perfluorooctanoic acid (PFOA)[g]	Alderete et al. 2019	Geometric mean (SD): 2.78 (1.29) ng/mL	$C_8HF_{15}O_2$	8	Carboxylate	Long	1.8–22 years 9,242–251]
	Chang et al. 2022	Median (min–max): 0.72 (<LOD–4.42) ng/mL					
	Chen et al. 2020	Geometric mean (95% CI): 2.26 (1.61–3.18) ug/L					
	Huang et al. 2019	Mean (SD): 2.5 (2.6) ug/L					
	Ji et al. 2021	Median (IQR): 39.6(27.5–48.9) ng/g creatinine[h]					
	Jin et al. 2020	Median (IQR): 3.42 (1.65) ng/mL [i]					
	Kingsley et al. 2019	Mean (SD): 2.6 (1.0) ng/mL					

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
	Lee et al. 2021	Median: 2.99 ng/mL					
	Li et al. 2020	Median (IQR): 0.40 (0.25–0.60) ng/mL [a]					
	Li et al. 2021	In mothers: Mean (95% CI): 2.66 (2.03–3.29) ng/mL In fetus: Mean (95% CI): 3.84 (2.38–5.29) ng/mL					
	Lu et al. 2019	Median (min–max): 164.6 (2.00–7214) ng/mL [j]					
	Maitre et al. 2018	Primary cohort: Median (IQR): 2.68 (1.69–3.67) ng/g lipid [e] Replication cohort: Median (IQR): 1.66 (1.28–2.32) ng/g lipid [e]					
	Matta et al. 2022	OMA: Median (IQR): 1.22 (0.81–1.58) ng/mL [b] noOMA: Median (IQR): 1.21(0.81–1.58) ng/mL [b] Control: Median (IQR): 1.10 (0.77–1.69) ng/mL					
	McGlinchey et al. 2020	Median (IQR): 1.02 (0.68–1.41) ng/mL					
	Mitro et al. 2021	Median (IQR): 5.0 (3.6–6.8) ng/mL					
	Salihovic et al. 2019	Median (IQR): 3.33 (2.55–4.39) ng/mL					
	Schillemans et al. 2021	T2D cases: Median (IQR): 2.8 (2.15–3.6) ng/mL [c] Controls: Median (IQR): 3.0 (2.3–4.2) ng/mL [c]					
	Sen et al. 2022	Median (min–max): 1.89 (0.49–6.36) ng/mL					
	Sinisalu et al. 2020	Cord blood: Median (min–max): 2.32 (1.31–4.80) ng/mL [d] 3 months: Median (min–max): 4.34 (1.23–9.17) ng/mL [d]					
	Sinisalu et al. 2021 [f]	Median (min–max): 0.66 (0.36–3.6) ng/mL					
	Stratakis et al. 2020	Median (IQR): 2.38 (1.45, 3.45) ng/mL					
	Wang et al. 2017	Median (IQR): 7.56 (6.09–10.7) nM					
	You et al. 2022	Mean (SD): 20.1 (24.0) ng/mL					
	Yu et al. 2022	n-PFOA: Mean (SD): 2.07 (0.85) ng/mL					

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
Perfluorooctane sulfonic acid (PFOS)[k]	Alderete et al. 2019	Geometric mean (SD): 12.22 (1.91) ng/mL	$C_8HF_{17}O_3S$	8	Sulfonate	Long	2.9–8.2 years [9, 89, 242, 243, 246, 247, 249–251]
	Chang et al. 2022	Median (min–max): 2.10 (<LOD–12.40) ng/mL					
	Chen et al. 2020	Geometric mean (95% CI): 4.29 (1.61–11.5) ug/L					
	Hu et al. 2019	Median (IQR): 33.9 (16.1–61.0) ng/mL					
	Huang et al. 2019	Mean (SD): 6.5 (4.6) ug/L					
	Ji et al. 2021	Median (IQR): 67.6 (41.0–96.5) ng/g creatinine [h]					
	Jin et al. 2020	Median (IQR): 5.59 (4.46) ng/mL[i]					
	Kingsley et al. 2019	Mean (SD): 4.4 (3.2) ng/mL					
	Lee et al. 2021	Median: 3.79 ng/mL					
	Li et al. 2020	Median (IQR): 33.9 (16.1–61.0) ng/mL[a]					
	Li et al. 2021	In mothers: Mean (95% CI): 5.36 (4.59–6.14) ng/mL In fetus: Mean (95% CI): 2.53 (2.21–2.85) ng/mL					
	Lu et al. 2019	Median (min–max): 909.3 (9.60–43,299) ng/mL[j]					
	Maitre et al. 2018	Primary cohort: Median (IQR): 6 (3.94–8.15) ng/g lipid[e] Replication cohort: Median (IQR): 5.3 (4.15–7.18) ng/g lipid[e]					
	Matta et al. 2022	OMA: Median (IQR): 2.45 (1.65–3.44) ng/mL[b] noOMA: Median (IQR): 2.09 (1.56–3.38) ng/mL[b] Control: Median (IQR): 1.87 (1.24–2.32) ng/mL					
	McGlinchey et al. 2020	Median (IQR): 1.38 (0.97–1.86) ng/mL					
	Mitro et al. 2021	Median (IQR): 26.6 (17.3–40.3) ng/mL					
	Salihovic et al. 2019	Median (IQR): 13.35 (10.13–17.79) ng/mL					
	Schillemans et al. 2021	T2D cases: Median (IQR): 19 (15–25) ng/mL[c]					

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PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
		Controls: Median (IQR): 20 (16–27) ng/mL[c]					
	Sen et al. 2022	Br-PFOS: Median (min–max): 2.13 (0.63–9.71) ng/mL L-PFOS: Median (min–max): 2.50 (0.74–11.8) ng/mL					
	Sinisalu et al. 2020	Cord blood: Median (min–max): 2.21 (0.27–8.17) ng/mL[d] 3 months: Median (min–max): 2.93 (0.27–7.66) ng/mL[d]					
	Sinisalu et al. 2021 [f]	Median (min–max): 0.45 (LOQ–1.80) ng/mL					
	Stratakis et al. 2020	Median (IQR): 6.74 (4.43, 10.4) ng/mL					
	Wang et al. 2017	Median (IQR): 12.8 (10.5–15.6) nM					
	You et al. 2022	Mean (SD): 9.1 (9.0) ng/mL					
	Yu et al. 2022	n-PFOS: Mean (SD): 2 (1.31) ng/mL Sm-PFOS: Mean (SD): 0.77 (0.41) ng/mL					
Perfluorooctanesulfonamide (PFOSA)	Li et al. 2020	PFOSA Median (IQR): 0.00 (0.00–0.04) ng/mL[a] MePFOSAAcOH Median (IQR): 0.00 (0.00–0.00) ng/mL[a] EtPFOSAAcOH Median (IQR): 0.28 (0.12–0.53) ng/mL[a]	$C_8H_2F_{17}NO_2S$	8	Sulfonamide	Long	1.7 years [251]
	McGlinchey et al. 2020	Median (IQR): 0.01 (0.002–0.01) ng/mL					
Chlorinated polyfluorinated ether sulfonic acids (Cl-PFESAs)[a]	Li et al. 2021	6:2 Cl-PFESA In mothers: Mean (95% CI): 2.58 (2.24–2.92) ng/mL In fetus: Mean (95% CI): 1.16 (1.00–1.31) ng/mL 8:2 Cl-PFESA In mothers: Mean (95% CI): 0.25 (0.21–0.30) ng/mL In fetus: Mean (95% CI): 0.21 (0.17–0.25) ng/mL	–	8	Sulfonate	Long	15.3 years [252]
	Lu et al. 2019	Median (min–max): 8.90 (<LOD–43.4) ng/mL[j]					
	Sinisalu et al. 2021 [f]	Median (min–max): 0.19 (0.07–1.82) ng/mL					
Perfluoroheptane sulfonic acid (PFHpS)	Li et al. 2021	In mothers: Mean (95% CI): 0.22 (0.19–0.25) ng/mL	$C_7HF_{15}O_3S$	7	Sulfonate	Long	1.54.7 years [9, 247]

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
		In fetus: Mean (95% CI): 0.16 (0.14–0.18) ng/mL					
	Matta et al. 2022	OMA: Median (IQR): 0.05 (0.05–0.12) ng/mL[b] noOMA: Median (IQR): 0.05 (0.05–0.13) ng/mL[b] Control: Median (IQR): 0.05 (0.05–0.07) ng/mL					
	McGlinchey et al. 2020	Median (IQR): 0.06 (0.05–0.07) ng/mL					
Perfluorooctane sulfonamide acetic acids (EtFOSAA, MeFOSAA) [m]	Hu et al. 2019	EtFOSAA-AcOH: Median (IQR): 0.28 (0.12–0.53) ng/mL	–	–	Sulfonamide	Long	–
	Mitro et al. 2021	EtFOSAA: Median (IQR): 1.2 (0.6–2.1) ng/mL MeFOSAA: Median (IQR): 1.0 (0.5–1.7) ng/mL					
Perfluoroheptanoic acid (PFHpA)	Lee et al. 2021	Median: 0.30 ng/mL	$C_7HF_{13}O_2$	7	Carboxylate	Short	62 days–1.5 years [9, 242]
	Li et. al 2020	Median (IQR): 0.00 (0.00–0.00) ng/mL[a]					
	McGlinchey et al. 2020	Median (IQR): 0.12 (0.04–0.19) ng/mL					
	Salihovic et al. 2019	Median (IQR): 0.07 (0.05–0.11) ng/mL					
	Sinisalu et al. 2020	Cord blood: Median (min–max): <LLQ (<LLQ–0.5) ng/mL 3 months Median (min–max): <LLQ (<LLQ–1.09) ng/mL					
Potassium perfluoro-4-ethyl-cyclohexanesulfonate (PFECHS)	McGlinchey et al. 2020	Median (IQR): 0.06 (0.06–0.06) ng/mL	–	–	Sulfonate	–	–
Perfluorohexane sulfonic acid (PFHxS)	Alderete et al. 2019	Geometric mean (SD): 1.65 (2) ng/mL	$C_6HF_{13}O_3S$	6	Sulfonate	Long	2.9–35 years [9, 242, 246, 247, 250, 251]
	Chang et al. 2022	Median (min–max): 1.09 (<LOD–4.80) ng/mL					
	Chen et al. 2020	Geometric mean (95% CI): 1.37 (0.32–5.79) ug/L					
	Huang et al. 2019	Mean (SD): 0.7 (0.9) ug/L					

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
	Jin et al. 2020	Median (IQR): 1.53 (3.17) ng/mL [i]					
	Kingsley et al. 2019	Mean (SD): 2.1 (2.7) ng/mL					
	Lee et al. 2021	Median: 0.93 ng/mL					
	Li et al. 2020	Median (IQR): 2.29 (1.02–3.68) ng/mL[a]					
	Li et al. 2021	In mothers: Mean (95% CI): 1.42(1.24–1.61) ng/mL In fetus: Mean (95% CI): 1.46 (1.19–1.73) ng/mL					
	Lu et al. 2019	Median (min–max): 785.2 (<LOD–1,226) ng/mL[j]					
	Maitre et al. 2018	Primary cohort: Median (IQR): 0.87 (0.69–1.14) ng/g lipid[e] Replication cohort: Median (IQR): 0.44 (0.34–0.57) ng/g lipid[e]					
	McGlinchey et al. 2020	Median (IQR): 0.33 (0.27–0.43) ng/mL					
	Mitro et al. 2021	Median (IQR): 2.3 (1.50–3.8) ng/mL					
	Salihovic et al. 2019	Median (IQR): 2.08 (1.61–3.45) ng/mL					
	Schillemans et al. 2021	T2D cases: Median (IQR): 0.99 (0.69–1.40) ng/mL[c] Controls: Median (IQR): 1.10 (0.76–1.40) ng/mL[c]					
	Sen et al. 2022	Median (min–max): 0.60 (0.16–10.6) ng/mL					
	Sinisalu et al. 2020	Cord blood: Median (min–max): 0.55 (0.31–1.03) ng/mL 3 months: Median (min–max): 0.70 (0.31–1.62) ng/mL					
	Sinisalu et al. 2021[f]	Median (min–max): 0.09 (LOQ–2.1) ng/mL					
	Stratakis et al. 2020	Median (IQR): 0.59 (0.34, 0.93) ng/mL					
	Yu et al. 2022	Mean (SD): 0.91 (1.32) ng/mL					
Perfluoropentanoic acid (PFPeA)	McGlinchey et al. 2020	Median (IQR): 0.15 (0.13–0.21) ng/mL	$C_5HF_9O_2$	5	Carboxylate	Short	–
Perfluoropentane sulfonic acid (PFPeS)	McGlinchey et al. 2020	Median (IQR): 0.04 (0.04–0.06) ng/mL	$C_5HF_{11}O_3S$	5	Sulfonate	Short	0.6–1 year [9, 247]
Perfluorobutane sulfonic acid (PFBS)	Lu et al. 2019	Median (min–max): 76.4 (0.80–2449) ng/mL [j]	$C_4HF_9O_3S$	4	Sulfonate	Short	26–44 days [9, 253]

PFAS name	Studied in relation to metabolomics	Available descriptive statistics (when included in analytic dataset)	Chemical formula	Number of carbons	Functional group	Chain length	Half-life ($T_{1/2}$)
	McGlinchey et al. 2020	Median (IQR): 0.0059 (0.003–0.064) ng/mL					
Perfluorobutyric acid or perfluorobutanoic acid (PFBA)	Lu et al. 2019 McGlinchey et al. 2020	Median (min–max): 17.4 (<LOD–189.6) ng/mL[j] Median (IQR): 0.37 (0.29–0.43) ng/mL	$C_4HF_7O_2$	4	Carboxylate	Short	74 days [254]

[a] Descriptive data reported in Hu et al. in the Child Health and Development Studies (CHDS) cohort [112]

[b] In patients with endometriosis with endometrioma (OMA) and in patients with endometriosis and no endometrioma (noOMA)

[c] Descriptive data reported in Donat-Vargas et al. in type 2 diabetes cases and controls from the Västerbotten Intervention Programme (VIP) cohort [255]

[d] In patients with celiac disease

[e] In blood from pregnant women

[f] Study reporting 14 chemicals evaluated but for only 5 chemicals descriptive information was provided

[g] Includes n-PFOA and Sb-PFOA

[h] In urine from COVID-19 patients

[i] In children with NAFLD

[j] In occupational workers

[k] Includes n-PFOS, Br-PFOS, L-PFOS, and Sm-PFOS

[l] Includes 6:2 Cl-PFESA and 8:2 Cl-PFESA

[m] Includes EtPFOSAAcOH

Table 2

Summary of studies examining PFAS and untargeted metabolomics in humans[a]

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
Maitre et al. 2018 [102]	*N* = 750. Birth cohort (INMA, Spanish cohort, from two locations)	Cross-sectional and longitudinal associations (prospective)	Prenatal (2004–2008)	Multiple exposures: 35 chemicals quantified in first-trimester blood samples (organochlorine pesticides, PCBs, **PFAS-PFHxS, PFNA, PFOA, PFOS**), in cord blood (mercury), and twice in urine at 12 and 32 weeks of pregnancy (metals, phthalates, bisphenol A)	1H nuclear magnetic resonance (NMR)	PFHxS was correlated with ↓pregnanolone-3G, ↓acetone, and ↑succinate; PFOA with ↑3-hydroxybutyrate/3-aminoisobutyrate, ↓alanine, ↓glycine; but significantly in the population of 1 location only (stratified analysis) and with respect to trimester 3. PFAS did not show consistent associations with the urine metabolome during pregnancy	NA	FDR-adjusted to 5%: (*q*-value	Confounders: Time of the day of sampling (nonpersistent analysis only), gestational week, age, and BMI (endogenous and exogenous factors affecting metabolism including diet and smoking)
McGlinchey et al. 2020 [30]	*N* = 264 (dyads). Mother-children pairs (EDIA cohort), in Finland	Prospective	Prenatal (2013–2014)	Detected PFAS: PFBA, PFBS, PFDA, PFDoDA, PFDoDS, PFDS, PFECHS, PFHpA, PFHpS, PFHxS, PFNA, PFNS, PFOA, L-PFOS, PFOSA, PFPeA, PFPeS, PFTDA, PFTrDA, PFUnDA	UHPLC-QTOFMS	High prenatal PFAS exposure associates with decreased postnatal serum ↓phospholipids. In mothers: total PFAS, as well as several individual PFAS levels were positively associated with maternal polar metabolite cluster (amino acids, saturated free fatty acids, and cholesterol). In cord serum: PFOS, PFOA, and total PFAS exposure inversely associated with ↓lipids, particularly for clusters CLC2 (sphingomyelins (SMs), abundant phosphatidylcholines (PCs); SM(38:1), SM(42:2), PC(34:2), PC(36:4)), CLC3 (lysophosphatidylcholines (LPCs); LPC(18:0), LPC(18:1), LPC(20:4)), and CLC4 (PUFA-containing phosphatidylcholines PCs; PC(36:5), PC(40:7), PE(38:6)); PFOS and PFDA exposure was associated with ↑CMC4 cluster (amino acids;	NA	NA (not for-omics)	Age and BMI (in linear regression analyses only). Effect modification by HLA gene

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						serine, methionine, aspartic acid, phenylalanine). In univariate analyses, 39 molecular lipids, mainly decreased ↓LPCs, ↓SMs and ↓PCs and 10 polar metabolites (increased ↑amino acids), differed between higher and lower quartiles of total maternal PFAS exposure. Regression analysis showed that PFNA, PFOS, and PFDA were the top predictors of cord serum LPC (20:4) (from CLC3) while PFNA, PFPeA, and PFOA were the linear predictors of SM (d38:1). PFHxS, followed by PFDA, PFOS, and PFNA, identified as a top predictors of cord serum methionine. Interaction effect between HLA risk and PFAS exposure on lipids			
Chang et al. 2022 [119]	*N* = 313. Pregnant African-American women at 8–14 weeks of gestation in Atlanta, GA	Cross-sectional	Prenatal (2014–18)	PFHxS, PFOS, PFOA, PFNA in serum	LC-HRMS. HILIC with (+) ESI and reverse phase (C18) chromatography with (−) ESI	Unique significant features associated with PFAS: 5000. 10 overlapping metabolites associated with both PFAS and fetal growth endpoints: level 1 confidence- PFNA with ↑glycine, ↑taurine, ↑uric acid; PFOA with ↑uric acid, and ↓ferulic acid; level 2 confidence- PFOS and PFHxS with ↑2-hexyl-3-phenyl-2-propenal; unsaturated fatty acid C18:1 (PFOA and PFNA with↓elaidic acid, oleic acid, or vaccenic acid); PFNA with ↑androgenic hormone conjugates (PFNA and ↑DHEA-S, ↑testosterone sulfate, or androsterone sulfate); ↑parent bile acid (PFNA and PFOA with ↑CDCA, DCA, HDCA, or isoursodeoxycholic acid); and ↓bile acid-glycine conjugate (PFOS and PFOA with ↓chenodeoxycholylglycine, deoxycholylglycine, or ursodeoxycholylglycine)	21 pathways identified related to amino acid, lipid and fatty acid, bile acid, uric acid, and androgenic hormone metabolism. ≥2 PFAS/birth weight/SGA birth: linoleate metabolism, arginine and proline metabolism, histidine metabolism, nitrogen metabolism, alanine and aspartate metabolism, pyrimidine metabolism, tryptophan metabolism, and vitamin B3 metabolism. ≥2 PFAS and birth weight: de novo fatty acid biosynthesis, fatty acid activation, purine metabolism, and vitamin	FDR-adjusted using Benjamini–Hochberg method	Confounders in linear regression: maternal age, education, parity, BMI, tobacco use, marijuana use, and infan's sex

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
							D3 (cholecalciferol) metabolism. ≥2 PFAS and SGA: glutamate metabolism, lysine metabolism, methionine and cysteine metabolism, aspartate and asparagine metabolism, glycan pathways (keratan sulfate degradation, glycosphingolipid metabolism, and glycosphingolipid biosynthesis-ganglioseries), glycerophospholipid metabolism, and butanoate metabolism		
Sinisalu et al. 2021 [124]	*N* = 104. Chinese infants	Cross-sectional	Prenatal (2018)	Total PFAS and individual PFAS; 16 PFAS (14 detected) in cord plasma including 6:2 Cl-PFESA, PFOS, PFHxS, PFNA, PFOA (detected in > 50% for multivariable analyses)	UHPLC-qTOF/MS, dual ESI in negative mode	In adjusted analyses, PFAS was associated with ↑bile acids (HCA, GHCA, GCDCA, TaMCA), ↑TGs, ↑↓PCs, ↑lysophosphatidylethanolamines (total PFAS and lysoPE 18:1), ↑ceramides, ↑↓sphingomyelins, ↑C18:2, ↑C16:1, ↑palmitic acid, ↑oleic acid, ↓lysophosphatidylcholines, and ↑phosphatidylserine. Overall, PFOS, PFOA, PFNA, and PFHxS associated with ↑TG with saturated fatty acids and ↓phospholipids (i.e., LPC, PC and lysoPE)	NA	NA	maternal age, delivery type and birth weight
Abrahamsson et al. 2021 [110]	*N* = 590. Matched maternal and cord blood samples (total 295 pairs) enrolled at UCSF, in California	Cross-sectional	Prenatal (2014–2017)	Exogenous chemicals (including **PFAS-detected PFHxS, PFOS, PFDA, PFUnA, PFNA)**	LC-QTOF/MS in ESI+and ESI− and in soft ionization (MS) and fragmentation (MS/MS) modes	In mothers: PFAS (alkyl acids: PFUnA, PFNA, PFDA) showed to correlate with certain fatty acids (PFDA with↑stearic acid, ↑4-oxopentanoic acid, ↑beta-hydroxyisovaleric acid, ↑nonanoic acid, ↓oleic acid; PFNA with ↑beta-hydroxyisovaleric acid, ↑nonanoic acid; PFUnA with ↑nonanoic acid), PFOS with ↑chrysanthemic acid. In cord blood: PFOS and↑FA 18:2 + 2O, PFDA	NA	FDR-adjusted using Benjamini–Hochberg method	NA

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						with↑hexadecanedioic acid, ↑4-oxopentanoic acid, ↑stearic acid, ↑beta-hydroxyisovaleric acid, PFUnA with ↑stearic acid, PFNA with ↑stearic acid, ↑beta-hydroxyisovaleric acid			
Hu et al. 2019 [112]	*N* = 397. Child Health and Development Studies (CHDS) in California: leveraged matched case–control (breast cancer) population based on birth year and trimester of maternal blood draw (white, non-obese,~25 y.o.)	Cross-sectional within matched case–control	Perinatal (1959–1967)	PFOS, its precursor EtFOSAA, and EtFOSAA-to-PFOS ratio	High-resolution C18 LC coupled with MS with positive ESI	34 features had an association with PFOS, and 49 with EtFOSAA. 63 features were commonly associated with EtFOSAA, PFOS and the ratio. EtFOSAA/PFOS ratio associated with ↓β-alanine, ↓creatinine, ↓pipecolate, ↓lysine, ↓arginine, ↓creatine, ↓adrenochrome, ↑homocysteine, ↑betaine, ↑phosphoserine, ↑N6,N6-dimethyl-L-lysine, ↑citrulline. EtFOSAA associated with ↑homocysteine, ↑betaine, ↑phosphoserine, ↑citrulline, ↓creatinine, ↓arginine, ↓creatine, ↑5beta-Cholestan-3-one, ↑aminobutanal, ↑mercaptopurine, ↓phosphoglycolate, ↑trihydroxyvitamin D3, ↑tyramine, ↓ureidoisobutyrate. However, PFOS associated with↑lysine, ↑targinine, ↑creatine, ↑adrenochrome, ↓betaine, ↓phosphoserine, ↓N6,N6-dimethyl-L-lysine, ↑aminoisobutyric acid, ↑clupanodonyl carnitine, ↑glutamate, ↑carnitine, ↑hexadecenoyl carnitine, ↓N1-methyl-4-pyridone-5-carboxamide, ↑peptide 2-(3-carboxy-3-aminopropyl)-L-histidine,↓linoelaidyl carnitine, ↓histidine, ↑tetracosapentaenoyl carnitine	All PFOS, EtFOSAA, and their ratio were associated with enriched pathways for glycine, serine,alanine, and threonine metabolism, and urea cycle/amino group metabolism. PFOS was strongly associated with carnitine shuttle, lysine metabolism, and BCAA metabolism (valine, leucine, and isoleucine degradation) and moderately associated with β-alanine, vitamin B3, and butanoate metabolism. Other mild associations were found between EtFOSAA with enriched pathways for bile acid biosynthesis, alanine and aspartate metabolism, and between EtFOSAA/PFOS ratio and pyrimidine metabolism, lysine metabolism, alanine and aspartate metabolism, and aspartate and asparagine metabolism	FDR-adjusted using Benjamini–Hochberg method	Confounders: total cholesterol, age and p,p'-DDE level

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
Alderete et al. 2019 [29]	*N* = 40. High-risk overweight/obese population, Hispanic children (Los Angeles area), 3 year follow up	Cross-sectional within a prospective cohort	Childhood (2001–2011)	PFOA, PFOS, PFHxS in plasma	HRM, LC–MS, HILIC with ESI source operated in positive mode	PFOA and PFHxS concentrations and ↑glucose. Identified 149, 298, and 17 metabolite features associated with plasma concentrations of PFOA, PFOS, and PFHxS, respectively. The integrated analysis identified a cluster of children with increased 2-h glucose levels over follow up, characterized by increased PFAS levels and altered metabolite patterns: ↑palmitic acid, ↑hydroperoxylinoleic acid, ↑tyrosine, ↑phenylalanine, ↑arginine, and decreased plasma levels of ↓sphingomyelin, ↓linoleic acid, and ↓aspartate	Pathway enrichment analysis showed significant alterations (24 pathways) in association to PFASs exposure: lipids (glycosphingolipid metabolism, glycoshingolipid biosynthesis-ganglioseries, glycoshingolipid biosynthesis-globoseries, de novo fatty acid biosynthesis, fatty acid metabolism, linoleate metabolism), amino acids (aspartate and asparagine metabolism, tyrosine metabolism, arginine, and proline metabolism, alanine and aspartate metabolism, glycine, serine, alanine and threonine metabolism, histidine metabolism, selenoamino acid metabolism, beta-alanine metabolism, glutathione metabolism, glutamate metabolism), aminosugars metabolism, vitamins and cofactors pathways (vitamin B3 (nicotinate and nicotinamide) metabolism, vitamin B9 (folate) metabolism), nitrogen metabolism, urea cycle/amino group metabolism, pyrimidine	FDR-adjusted <20%) using Benjamini–Hochberg method	Confounders: age, sex, and social position

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
							metabolism, sialic acid metabolism, drug metabolism-cytochrome P450		
Jin et al. 2020 [116]	*N* = 74. Patients with nonalcoholic fatty liver disease (NAFLD), ages 7–19 y.o., 71% male, 51% Hispanic, 85% obese, in Atlanta, GA	Cross-sectional	Childhood (2007–2015)	PFOA, PFOS, PFHxS	LC and high-resolution MS, in plasma	Overall, PFOA associated with 348 metabolite features; PFOS with 349; and PFHxS with 662 features. For higher risk population (NASH), increased PFAS levels altered plasma metabolite levels ↑phosphoethanolamine, ↑tyrosine, ↑phenylalanine, ↑aspartate and ↑creatine, and ↓betaine	Overall, 21 metabolic pathways including tyrosine metabolism, aspartate and asparagine metabolism, xenobiotics metabolism, glycine, serine, alanine and threonine metabolism, urea cycle/amino group metabolism, glycerophospholipid metabolism, arginine and proline metabolism, lysine metabolism, valine, leucine and isoleucine degradation, butanoate metabolism, phosphatidylinositol phosphate metabolism, drug metabolism-other enzymes, ascorbate and aldarate metabolism, citrate cycle (TCA cycle), nicotinate and nicotinamide metabolism, alanine and aspartate metabolism, caffeine metabolism, glutamate metabolism, vitamin B6 metabolism, glyoxylate and dicarboxylate metabolism, carbon fixation	FDR-adjusted using Benjamini–Hochberg method	Confounders: age, sex, ethnicity, z-BMI Effect modifiers: sex, ethnicity, liver histologic features

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
Kingsley et al. 2019 [121]	*N* = 114 8-year-old children from Cincinnati, OH (HOME cohort)	Cross-sectional	Childhood (2011–2014)	PFOA, PFOS, PFNA and PFHxS (in serum)	LC and high-resolution MS, in serum: HILIC with ESI in positive mode and reversed-phase chromatography (RPC) with ESI operated in negative mode (C18-negative)	PFAS concentrations were associated with certain enriched metabolic features primarily ↑lipids and ↑dietary factors. In the C18-negative mode, 17, 63, 47, and 29 m/z features were associated with serum PFOA, PFOS, PFNA, and PFHxS. In the HILIC-positive mode, 18, 253, 76, and 39 m/z features were associated with serum PFOA, PFOS, PFNA, and PFHxS	Pathways associated with all four PFAS included lipid metabolism, amino acids metabolism-arginine and proline metabolism, aspartate and asparagine metabolism, butanoate metabolism, beta-alanine metabolism, glutamate metabolism, glycine, serine, alanine and threonine metabolism, glycerophospholipid metabolism, glycosphingolipid metabolism, glyoxylate and dicarboxylate metabolism, histidine metabolism, linoleate metabolism, methionine and cysteine metabolism, tyrosine metabolism, urea cycle/amino group metabolism, vitamin B1 (thiamin) metabolism, vitamin B3 (nicotinate and nicotinamide) metabolism	FDR-adjusted using Benjamini–Hochberg method	Confounders: child age, sex, and race
Yu et al. 2022 [106]	*N* = 152. Adolescent girls in the Growing Up Healthy Study in New York City	Cross-sectional	Adolescence (2005–2017)	n-PFOS, n-PFOA, Sm-PFOS, PFHxS, PFNA in plasma	Reverse-phase and hydrophilic LC-HRMS in negative and positive modes	In positive mode, ↑betaine (n-PFOS), ↓LPE(18:0) (n-PFOS), ↓LPC(16:0) (n-PFOS, n-PFOA), ↑LPG(18:1) (n-PFOS), ↓LPC(18:0) (n-PFOS), ↓SM(d18:2/14:0) (n-PFOS), ↓PE(20:4/P-18:0) (Sm-PFOS), ↓GPE(16:0/22:6) (n-PFOA), ↓SM(d18:1/24:1) (Sm-PFOS); in negative mode, ↑hippuric acid (n-PFOS), ↑gamma-glutamyl leucine (n-PFOS), ↑N(2)-phenylacetyl glutamine (n-PFOS), ↓dihomolinolenic	NA	FDR-adjusted using Benjamini–Hochberg method	NA

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						acid (n-PFOS), ↓11,14-trans-eicosadienoic acid (n-PFOS), ↓dehydroepiandrosterone sulfate (n-PFOA), ↓androsterone sulfate (n-PFOA), ↑glycocholic acid (n-PFOS), ↑taurodeoxycholate (n-PFOS, n-PFOA), ↑LPE(20:4) (n-PFOS), ↑LPC(18:2) (n-PFOS), and ↑GPC(P-18:0/20:4) (n-PFOS)			
Chen et al. 2020 [118]	*N* = 102. Young adults (17–22 y.o.), 82% overweight or obese, 60% Hispanic (Meta-AIR study), in California	Cross-sectional	Early adulthood (2017)	PFOA, PFOS and PFHxS in plasma	LC and high-resolution MS, HILIC with positive ESI and C18 hydrophobic RPC with negative ESI (plasma). MS/MS (serum)	In fasting plasma, 231 metabolomic (HILIC positive) and 239 metabolomic features (C18 negative). Using 30-min postglucose challenge plasma samples, 372 metabolomic (HILIC positive) features and 518 metabolomic (C18 negative) features. All marginal significant associations with at least one PFAS. 19 metabolites identified linked to pathway analyses (proline, glutamine (PFOS, PFHxS), methionine, citrulline (PFOA), mannose/galactose (PFOA, PFOS, PFHxS), lysoPC(18:0) (PFOA, PFOS), sphingosine (PFOS), lactate (PFOS, PFHxS), oxovalerate/ ketoisovalerate (PFOS, PFHxS), hydroxymethylglutarate (PFOA, PFOS, PFHxS), glucose (PFHxS), fatty acids including octanoate (PFOS, PFHxS), palmitate (PFOA, PFOS), linolenic acid (PFOA, PFHxS), linoleic acid (PFOA, PFOS), oleic acid (PFOA, PFOS), stearic acid (PFOA, PFOS), homolinoleic acid (PFOA, PFOS), arachidonic acid (PFOA, PFOS))	Pathways with dysregulated metabolism of lipids (glycerophospholipid, glycosphingolipid, fatty acids), amino acids such as arginine, proline, and tryptophan, as well as hexoses	NA for -omics data	Confounders: age, sex, parental education, race/ethnicity, cigarette and e-cigarette smoking status in the past week, physical activity levels and dietary covariates, (body fat) Effect modifiers: obesity
Lu et al. 2019 [17]	*N* = 92 (40 occupational workers and 52 controls in China)	Cross-sectional within case–control	Adulthood (2017)	Σ6PFASs (PFBA, PFOA, PFBS, PFHxS, PFOS, and 6:2 Cl-PFESA)	LC–MS, and GC–MS, in plasma	14 metabolites: ↑3-hydroxyoctanoic acid, ↓azelaic acid, ↑sebacic acid, ↑gamma-CEHC, ↑acylcarnitines (C18:1-CN, C18:2-CN), ↑pyroglutamic acid, ↑ornithine, ↓methionine sulfoxide,	Pathways involved included lipid metabolism, amino acids metabolism, purine metabolism, inositol metabolism, retinol metabolism,	NA	Confounders: Age, BMI, gender, smoking, and drinking status

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						↑DL-2-aminooctanoic acid, ↑hypoxanthine, ↓myo-inositol, ↓glycerophosphocholine, ↓piperine	metabolism of alkaloids and their derivatives		
Schillemans et al. 2021 [113]	*N* = 374. 187 matched pairs (based on age, sex and date of blood draw), nested within the Vasterbotten Intervention Programme cohort who donated blood samples (Swedish population)	Nested case–control (cross-sectional metabolomics design)	Adulthood (baseline: 1990–2003: follow-up: 2000–2013)	PFOS, PFOA, PFHxS, PFDA, PFNA, PFUnA	LC-qTOF-MS on reverse phase and HILIC columns in both positive and negative ionization modes	PFAS levels (particularly long-chain) correlated with 171 metabolite features. In partial correlations (adjusted), PFAS was associated with ↑5 glycerophospholipids (PFOS (1), PFDA (5), PFNA (1), PFUnDA (3), long-chain PFAS (5)), ↓2 glycerophospholipids (PFDA (2), PFUnDA (2), PFNA (1), long-chain PFAS (2)), ↑1 fatty acid (PFDA, PFNA, PFUnDA, long-chain PFAS), ↑3 diacylglycerols (PFOS (1), PFDA (3), PFNA (3), long-chain PFAS (3)), ↓1 diacylglycerol (PFDA, PFNA, long-chain PFAS), ↓gammabutyrobetaine (PFHxS, PFDA, long-chain PFAS), ↑ 3,4,5-trimethoxycinnamic acid (PFNA, PFUnDA, long-chain PFAS), ↑docosahexaenoic acid (PFHxS, PFDA, PFNA, PFUnDA, long-chain PFAS)	NA	FDR-adjusted	Confounders: sex, age, sample year, marital status, education, smoking status, physical activity, and case–control status
Li et al. 2020 [31]	*N* = 397. Leveraged matched case–control population (based on birth year and trimester of maternal blood draw) of women (white, non-obese, ~ 25 y.o.) from the Child Health and Development Studies (CHDS) cohort in California	Cross-sectional within matched case–control	Adulthood (1960s)	Mixed exposures (39 chemicals) including **PFAS (PFOA,PFHxS, PFOS, PFOSA, PFHpA, PFNA, PFUdA, PFDeA, PFDoA, MePFOS-AAcOH, EtP-FOSAAcOH**), DDT, and PCBs (from serum)	High-resolution LC–MS using C18 column in positive ESI mode	Metabolite communities showed strong associations with DDT, PFAS communities (and lipids)	Common metabolite communities associated with PCB, PFAS and lipids include: linoleate metabolism, fatty acid metabolism, omega-3 fatty acid metabolism, de novo fatty acid biosynthesis, xenobiotics metabolism, tryptophan metabolism, purine metabolism, sialic acid metabolism, bile acid bionsynthesis, vitamin E metabolism, TCA cycle, lysine	NA	NA

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
							metabolism, methionine and cysteine metabolism, valine, leucine and isoleucine metabolism, electron transport chain, glycerophospholipid metabolism, glycosphingolipid metabolism, chondroitin sulfate degradation, N-glycan degradation, heparan sulfate degradation, pentose phosphate pathway, beta-alanine metabolism, alanine and aspartate metabolism, glyoxylate and dicarboxylate metabolism, arginine and proline metabolism, urea cycle/amino group metabolism, aspartate and asparagine metabolism, drug metabolism-cytochrome P450		
Wang et al. 2017 [123]	*N* = 181. Chinese male adult population	Cross-sectional	Adulthood (NA)	PFOA, PFOS, Total PFCs (PFOA, PFOS, PFDA, PFHxS, PFNA, PFUnA)	LC/obitrap-MS in negative ion mode, in serum	High exposure PFAS levels associated with ↓D-glucurono-6,3-lactone (PFOA, PFOS, PFAS), ↓α-carboxyethyl hydroxychromanol (PFOA), ↓arachidonic acid (PFOA), ↓hypoxanthine (PFOA, PFOS, PFAS), ↓oxoglutaric acid (PFOA, PFOS, PFAS), ↓pyroglutamic acid (PFOA, PFOS, PFAS), ↓tetrahydrobiopterin (PFOA, PFOS, PFAS), ↓xanthine (PFOA, PFOS, PFAS), ↑deoxyarabinohexonic acid (PFOA, PFOS, PFAS), and ↑hydroxybutyric acid (PFOS, PFAS)	NA/Pathway analyses not conducted (metabolite findings implied that PFAS exposure may play a role in lipid metabolism, oxidative stress, α-tocopherol metabolism, xenobiotic detoxification, antioxidation, nitric oxide (NO) signal pathways, glutathione (GSH) cycle, Krebs cycle, and purine metabolism)	NA	Confounders: age, BMI, smoking and drinking status

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
Salihovic et al. 2019 [117]	*N* = 965. Swedish population (aged 70 years, 50% women)	Cross-sectional	Late adulthood (2001–2004)	PFOS, PFHpA, PFOA, PFNA, PFUnDA, PFHxS	UPLC-QTOF-MS operated in positive electrospray mode, in plasma	15 metabolites were found to be associated with levels of PFASs, except PFHxS. PFNA and PFUnDA were associated with multiple glycerophosphocholines (↑phosphatidylcholines (P-36:4, 40:6, 38:5, 38:6, 36:5), ↑lysophosphatidylcholines (20:5/0:0, 0:0/20:5)), ↑dicarboxylic acid (C12H14O5). PFUnDA was also related to fatty acids (↑docosapentaenoic acid (DPA), ↑docosahexaenoic acid (DHA)), ↓L-proline, ↑lysophosphatidylcholines (P-16:0/0:0, 0:0/18:0). PFOA was only related to ↑dicarboxylic acid (C12H14O5), PFHpA only to ↑uric acid, and PFOS were associated with ↑dicarboxylic acid (C12H14O5) and ↓monoacylglycerol (16:1)	Human metabolic pathways were significantly enriched in lipids and fatty acids: glycerophospholipid metabolism (significant), linoleic acid metabolism (significant), and α-linoleic acid metabolism (not significant)	Bonferroni FDR-adjusted	Confounders: sex, smoking, exercise habits, education, energy, and alcohol intake
You et al. 2022 [105]	*N* = 496. Cohort with 5 major chronic diseases (71 obese, 81 hyperuricemia 83 hypertensive, 74 diabetic, 104 dyslipidemia patients, and 83 controls) in China	Cross-sectional	Adulthood (2018–2019)	Multiple chemicals including individual PFAS and ΣPFAS (PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFHxS and PFOS), ΣPFCA (PFOA, PFNA, PFDA, PFUnDA and PFDoDA), and ΣPFSA (PFHxS and PFOS). Only **PFOA, PFNA, PFDA, PFUnDA and PFOS** used solely in the matabolomics analyses	LC-HRMS method	240 endogenous metabolite markers were significantly associated with at least one PFAS. At least 2 or more PFAS groups (total PFAS, PFCA, or PFSA) correlated with↑↓amino acids (↑creatine, ↑creatinine, ↑pyroglutamic acid, ↑3-methyl-L-histidine, ↑benzoic acid, ↓glutamic acid, ↓pipecolic acid), ↑peptides (prolyl-isoleucine, Phe-Pro), ↑↓xenobiotics (↑1,7-dimethylxanthine, ↑caffeine, ↓3,7-dimethyluric acid), ↑uric acid, ↑↓sterol lipids (↑DHEA-S, ↓ST 28:1;O;S), ↑↑↓bile acids, ↑cholesterol, ↑↑↓carnitines, ↑↑↓fatty acids, ↑glycerides (MGs, DGs, TGs), ↑↑↓phosphatidylcholines (PCs), ↑phosphatidylethanolamine (PEs), ↑↑↓lysophospholipids, ↑glycerophospholipids, ↑↑↓ceramides, ↓tocopherol, and ↑↑↓sphingolipids	NA	NA. FDR-adjusted only in analyses comparing hyperuricemia vs. controls	Gender, age, BMI, sampling time, location, education level, cigarette smoking and alcohol drinking history

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
Bessonneau et al. 2021 [109]	*N* = 143. 69 California women firefighters (FF) and 74 office workers (OW) enrolled in the Women Firefighters Biomonitoring Collaborative (WFBC) study	Cross-sectional	Adulthood (2014–2015)	Exposome data matrix of 620 unique chemicals which matched to 300 chemical formulas, including **PFHxS and PFOS**	LC-HRMS in negative ESI mode	In firefighters only, PFHxS was associated with microbial-derived secondary bile acid ↑sulfolithocholylglycine; PFOS was correlated with one inflammatory signaling molecule ↓15d PGD2, and ↑calcitriol (vitamin D)	NA	FDR-adjusted, threshold of 0.1	NA for -omics data
Huang et al. 2019 [107]	*N* = 57. Males in the CISTPFP study in China	Cross-sectional	Adulthood (2009–2010)	Arsenic, PAE, and 11 PFC (PFOA, PFOS, PFBA, PFBS, PFDA, PFHpA, PFHxA, PFHxS, PFNA, PFUnA, and PFDoA) in blood. Only **PFOA, PFOS, PFHxS, PFUnA, PFDA, PFNA** were detected and included in analyses	UPLC/MS/MS with heated ESI in positive and negative ion mode	PFHxS, PFUnA, total PFCs associated with ↑pivaloylcarnitine and PFHxS also with ↑glycerophosphocholine. (Eicosatetraenoate, carnitines, and tocotrienol possible mediators of the positive association between PFHxS and sperm concentration)	NA	FDR-adjusted	Age, body mass index (BMI), abstinence time, smoking, and alcohol drinking status
Li et al. 2021 [122]	*N* = 84. Pregnant women in Beijing, China	Cross-sectional	Adulthood and prenatal (2015–2016)	PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFHpS, PFOS, 6:2 Cl-PFESA, 8:2 Cl-PFESA measured in maternal and cord serum	HPLC-QTOF-MS	279 metabolites in mothers and 338 meteabolites in fetus associated with PFAS. Shorter legacy PFAS (PFOA and PFHxS) associated with more metabolites than novel PFAS (6:2 Cl-PFESA and 8:2 Cl-PFESA). PFAS-related metabolites in **maternal serum** included steroid hormones (6:2 Cl-PFESA/8:2 Cl-PFESA and ↑pregnenolone; PFOA and ↓cortisol 21-sulfate), ↓anahormones (PFNA and ↓5α-pregnane-3,20-dione), ↓fatty acids (PFHpS and ↓16-hydroxypalmitate; PFHxS and ↓linoleate; PFDA and ↓decanoic acid), and ↓terpenoids (PFUnDA	Pathways in maternal serum and pathways in cord serum found to be associated with PFAS exposure: steroid hormone biosynthesis, arachidonic acid metabolism, α-linolenic acid metabolism, linoleic acid metabolism, and retinol metabolism	FDR-adjusted to 20%: q-value (pFDR) using Bayesian posterior probability	Confounders: age, weight, gravidity, parity, and residence of the pregnant women, as well as the length, weight, and gender of the fetuses

Author/year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						and ↓canthaxanthin). PFAS-related metabolites in **cord serum** included ↑fatty acids (PFDA and ↑docosahexaenoic acid; PFOA, PFNA, PFUnDA and ↑octadecenoic acid; PFHxS and ↑8-[(1R,2R)-3-oxo-2-{(Z)-pent-2-enyl}cyclopentyl]octanoate; PFHpS and ↑arachidonate; PFOS and ↑glycolithocholate)			
Chen et al. 2021 [103]	*N* = 120. 9–80 y.o. in Wuxi City, China	Cross-sectional	Childhood/ Adolescence/ Adulthood (NA)	Multiple contaminants including 66 PFCs (**PFOA and PFOS** in metabolomics analyses)	UPLC-Q-Orbitrap HRMS	In untargeted analyses, PFOA and PFOS associated with ↑ total lysophosphatidylcholine (LPC); PFHxS with ↑total lysophosphatidylcholine (LPC) and ↑total sphingomyelin (SM); PFDA with ↑total triglycerides (TG): and PFUnA with total ↑TG, ↑SM, and ↑LPC	NA	NA	Age, BMI, and health status

[a] See Table S2 for a complete summary of all significant metabolites and pathways altered by PFAS across studies. Table ordered by age or developmental stages. If multiple age stages are studied, these studies are included at the end. ↑ (upregulated metabolite), ↓ (downregulated metabolite), ↑↑↓ (both upregulated and downregulated metabolite across PFAS subtypes but with overall more upregulation), and ↑↓↓ (both upregulated and downregulated metabolite across PFAS subtypes but with overall more downregulation)

Table 3

Summary of studies examining PFAS and targeted metabolomics in humans

Author/ year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
Stratakis et al. 2020 [115]	*N* = 1,105. Mother-children pairs (multicenter study, European HELIX cohort), 6–10 year follow-up	Prospective	Prenatal (1999–2010)	PFOS, PFNA, PFOA, PFHxS, and PFUnDA (in plasma from pregnant mothers around mid-2000s)	LC ESI–MS/MS, in child serum (circa 2014)	Network of children at high vs low risk for liver injury involved particularly metabolites: 5 amino acids (PFNA, PFUnDA with ↑leucine, ↑valine, ↑isoleucine, ↑tryptophan, ↑phenylalanine), 1 ↑↓biogenic amine (acetylornithine (↓PFHxS, ↑PFNA, ↑PFUnDA)), 18 glycerophospholipids (PC ae C36:3 (↓PFHxS, ↑PFNA, ↑PFUnDA), PC aa C34:1 (↓PFHxS, ↑PFNA, ↑PFUnDA), PC aa C40:6 (↑PFHxS, ↑PFOS, ↑PFOA), PC aa C36:6 (↑PFOA, ↑PFHxS, ↑PFOS), PC aa C38:0 (↑PFOA, ↑PFHxS, ↑PFOS), PC aa C38:6 (↑PFOA, ↑PFHxS, ↑PFOS), PC ae C38:0 (↑PFHxS, ↑PFOS), PC aa C36:5 (↑PFHxS), PC aa C36:3 (↓PFHxS, ↑PFNA, ↑PFUnDA), PC aa C32:0 (↓PFHxS, ↑PFNA, ↑PFUnDA), PC ae C34:1 (↓PFHxS, ↑PFNA, ↑PFUnDA), PC ae C36:5 (↑PFNA, ↑PFUnDA), PC ae C36:4 (↑PFNA, ↑PFUnDA), PC ae C38:4 (↑PFNA, ↑PFUnDA), PC ae C38:5 (↑PFNA, ↑PFUnDA), LysoPC a C20:3 (↓PFHxS, ↑PFNA, ↑PFUnDA), LysoPC a C18:1 (↓PFHxS, ↑PFNA, ↑PFUnDA), LysoPC a C20:4 (↓PFHxS, ↑PFNA, ↑PFUnDA)), 3 sphingomyelins (↑SM C18:0 (PFOS, PFNA, PFUnDA), ↑SM C18:1 (PFNA, PFUnDA), ↑↓SM (OH) C22:1 (↓PFHxS, ↑PFNA, ↑PFUnDA)), 1 ↑hexose (PFNA, PFUnDA)	Protein and amino acid pathways (protein digestion and absorption; aminoacyl-tRNA biosynthesis; valine, leucine, and isoleucine biosynthesis; valine, leucine, and isoleucine degradation; phenylalanine, tyrosine and tryptophan biosynthesis) and lipid metabolism pathways (glycerophos-pholipid metabolism, ether lipid metabolism, and sphingolipid signaling pathway)	NA	NA for -omics data
Lee et al. 2021 [125]	*N* = 290. 8–10 y.o. Taiwanese children from the Taiwan Birth Panel Study (TBPS, *N* = 214) and Taiwan Early-Life Cohort (TEC, *N* = 76	Cross-sectional	Childhood (2013–2014)	13 PFAS from which 8 were detected > 10% (PFOS, PFTrDA, PFDA, PFOA, PFUnDA, PFHpA, PFNA, PFHxS)	UPLC-MS/MS	PFTrDA and PFDA exposures (high vs low level) were associated with serum lipid profiles (PLS-DA), and PFOS was marginally associated. In multiple linear regression (tertile 3 vs 1), PFOS associated with ↑lysoPC(18:2/0:0),↓PC(16:1/16:1), ↓PC(16:1/16:0), ↓PC(16:1/18:2), ↓PC(16:0/18:1), ↓PC(16:0/20:3), ↓PC(18:0/22:4), ↓PC(18:0/20:3), ↑PC(20:4/20:4), ↑P-PC (P-16:0/18:2, P-16:0/18:1, P-36:4, P-36:2,	NA	NA	Gender, age, BMI, household income (in multivariable linear regression analyses)

Author/ year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						P-16:1/22:5), ↑SM (32:1), ↑SM (33:1), ↑SM (34:1), ↑SM (38:1), ↑SM (40:2), ↑SM (40:1), ↑SM (41:2), ↑SM (41:1), ↑SM (42:2): PFTrDA associated with ↓PC(16:0/20:3), ↓PC(16:1/16:0), ↓PC(16:1/18:2), ↓PC(38:4), ↓lysoPC(18:2/0:0), ↓lysoPC(0:0/18:2), ↑PC(18:2/18:2), ↑PC(16:0/22:6), ↓PC(18:0/20:3), ↑PC(20:4/20:4), ↓PC(18:0/22:4), ↑P-PC(P-16:1/22:5), ↑SM(38:1): and PFDA associated with ↓PC(16:0/18:1), ↓PC(16:1/16:1), ↓PC(16:1/18:2), ↑PC(20:4/20:4), ↑PC(18:2/18:2), ↓SM (32:1), ↑SM(34:2), ↑SM(36:2), ↑SM(38:1), ↑SM(40:1), ↑SM(42:3)			
Chen et al. 2020 [118]	*N* = 102. Young adults (17–22 y.o.), 82% overweight or obese, 60% Hispanic (Meta-AIR study), in California	Cross-sectional	Early adulthood (2017)	PFOA, PFOS and PFHxS in plasma	LC and high-resolution MS, HILIC with positive ESI and C18 hydrophobic RPC with negative ESI (plasma). MS/MS (serum)	In serum, non-stratified analyses: PFOA, PFOS, and PFHxS associated with ↑glycerol, and PFOA also associated with grouped ↑short-chain non-OH/DC acylcarnitines. PFHxS associated with ↑acylcarnitine C16:1-OH/C14:1-DC. Interaction between PFHxS and obesity on 3-hydroxybutyrylcarnitine (C4-OH)	NA	NA for -omics data	Confounders: age, sex, parental education, race/ethnicity, cigarette and e-cigarette smoking status in the past week, physical activity levels, and dietary covariates, (body fat) Effect modifiers: obesity
Mitro et al. 2021 [111]	*N* = 691. Participants at higher risk for diabetes (BMI > 24, > 25 y.o., with impaired glucose tolerance and a fasting plasma glucose of 5.3–6.9 mmol/L) enrolled in the Diabetes Prevention	Cross-sectional	Adulthood (1996–1999)	Total PFOS, n-PFOS, Sm-PFOS, total PFOA, n-PFOA, Sb-PFOA, PFNA, PFHxS, EtFOSAA, MeFOSAA, in plasma	HILIC coupled to MS in positive ion mode (for amino acids and amines); C8 chromatography coupled to MS in positive ion mode (lipids); amide chromatography coupled to MS using negative ion mode electrospray	38 metabolites significantly associated with any PFAS. 4 DAGs and 18 TAGs were associated with at least one PFAS. 4 plasmalogens (3↑ and 1↓) and 4 sphingomyelins were significantly associated with at least one PFAS. All PFOS were associated with 3 ↑PC plasmalogens (C36:1 PC plasmalogen, C36:4 PC plasmalogen, C34:1 PC plasmalogen-A), ↑C16:1 sphingomyelin (SM), and ↑C18:2 SM). All PFOA were associated with 3 ↑phosphatidylethanolamines (C36:3 PE, C38:4 PE, C36:4 PE) and 4 ↑triacylglycerols (C54:2 TAG, C52:1 TAG, C50:1 TAG, C50:3 TAG). Sb-PFOA was inversely associated	NA/Pathway analyses not conducted (metabolite findings implied that PFAS concentrations were associated with amino acid, glycerolipid, and glycerophospholipid pathways)	FDR-adjusted using Benjamini–Hochberg method	Confounders: Age, sex, race/ethnicity, use of anti-hyperlipidemic or triglyceride-lowering medication income, years of education, marital status, smoking, family history of diabetes (BMI, waist circumference, parity,

Author/ year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
	Program (DPP cohort), in the US				ionization (for organic acids)	with ↓C34:4 PC plasmalogen. PFNA was significantly associated with ↑C54:6 triacylglycerol, EtFOSAA was significantly associated with ↑C18:2 SM. Sb-PFOA was associated with ↑leucine. Total PFOA, n-PFOA, Sb-PFOA associated with ↓glycine. Total PFOS, total PFOA, n-PFOA, Sb-PFOA, and EtFOSAA, associated with total ↑BCAAs. Total PFOS, n-PFOS, Sm-PFOS, total PFOA, n-PFOA, and EtFOSAA associated with total ↑sphingolipids (C16:1 SM, C18:1 SM, C18:2 SM, and C22:1 SM) and total ↑glycerophospholipids (including total phosphatidylethanolamines and total plasmalogens). Total PFOA and Sb-PFOA was associated with ↑glycerolipids (diacylglycerols and triacylglycerols)			menopausal status, other PFAS)
Sen et al. 2022 [108]	*N* = 105. NAFLD (70% female) patients undergoing a laparoscopic bariatric surgery. Northen European population	Cross-sectional	Adulthood (NA)	Environmental contaminants including **PFAS (PFHxS PFNA, PFOA,2 PFOS isomers)**	Hepatic polar metabolites (GC × GC–TOFMS), hepatic molecular lipids (UHPLC-QTOFMS), hepatic acylcarnitines (UHPLC-QQQMS), hepatic BAs (UHPLC-QQQMS)	In females, serum concentrations of PFAS associated with glyco- and tauro-conjugated primary, and secondary↑BAs (PFNA with TCA (taurocholic acid), GCDCA (glycochenodeoxycholic acid), TCDCA (taurochenodeoxycholic acid), GUDCA (glycoursodeoxycholic acid); PFOA with TCDCA, GHCA (glycohyocholic acid), GUDCA, CA (cholic acid), DCA (deoxycholic acid); PFOS with CA and DCA. Furthermore, PFAS alters and ↑lipid metabolism (↑Cers and ↑HexCers (PFNA, PFOA, and PFOS with ↑HexCer d18:1/18:0, PFOA an PFOS with ↑HexCer d18:1/24:0, PFOS with ↑Cer d18:0/16:0 and Cer d18:0/18:0), ↑ether phospholipids (O-PCs (PFOA and PFOS with↑O-PC 40:4, O-PC 40:5, O-PC 44:5; phosphatidylcholines (PFNA with↓LysoPC d20:4)), ↑TGs (PFNA with TG 52:0, TG 54:1, TG 55:2; PFOA with TG 55:3, TG 55:2, TG 54:1, TG 53:2, TG 52:2, TG d18:1/18:1/18:1, TG(d16:0/18:1/2 0:1) + TG(d18:0/18:1/18:1); PFOS and TG 55:3, TG 55:2, TG 54:1, TG 53:2, TG 53:1, TG 52:3, TG 52:2, TG 52:0, TG 51:2, TG 51:1, TG 50:1, TG 50:0, TG d18:1/18:1/18:1, TG (d16:0/18:1/20:1) + TG(d18:0/18:1/18:1) and ↑DGs	In both sexes, primary bile acid biosynthesis, glycerophospholipid metabolism, along with alanine, aspartate and glutamate metabolism were over-represented comparing high vs low PFAS level. Sphingolipid metabolism pathways were over-represented in highly exposed females	FDR-adjusted	NA

Author/ year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						(PFOA with DG 36:3, DG 36:2; PFOS with DG 36:2, DG 34:1)) and polar metabolites (PFNA and ↑alanine, ↓cholesterol; PFOA with ↓malic acid; PFOS with ↓ aspartic acid, cholesterol, serine, threonine). Inverse associations were observed in males: PFNA was associated with ↓THCA, cholesterol, PFOA with ↓GUDCA, TG 55:5, TG 60:4, and PFOS associated with ↓DCA, TG 60:3, DG 32:1, phosphatidylethanolamine PE 42:0, LysoPC d18:0, HexCer d18:1/16:0, Cerd18:1/26:1 +Cer d18:2/26:0, Cer d18:0/24:1, citric acid			
Matta et al. 2022 [104]	*N* = 87. 18–45 y.o. women in France with endometriosis and controls	Cross-sectional	Adulthood (2018–2019)	Persistent organic pollutants, including **14 PFAS (PFAS retained for analyses: PFHpS, PFOS, PFOA, PFNA, PFDA,PFUnA)**	Small molecules measured by LC–MS/MS and lipids by flow injection analysis (FIA)-MS/MS with ESI source	PFAS associated with↓ratio of diacylhosphatidylcholines and cyl-alkylphosphatidylcholines to choline, ↓ratio of hydroxylated sphingomyelins to non-hydroxylated sphingomyelins (Ratio. SMOHs.to.SMNonOHs). PFOS, PFOA associated with ↓HexCer d18:1/24:0. PFOA associated with tetradecenoylcarnitine (C14:1), PFOS with TG 16:0 (40.6) and TG 16:0 (40.8), PFDA with TG 16:0 (40.8) and TG 18:1 (35.3), PFNA with TG 18:1 (35.3) and ↑HexCer d18:1/24:0	NA	NA	NA
Ji et al. 2021 [120]	*N* = 160. 80 COVID-19 patients and 80 symptom-free controls were recruited from Shanxi and Shandong provinces in China	Cross-sectional	Adulthood (2020)	PFOA, PFOS, and total 12 PFAS (PFOS, PFOA, PFBS, PFHxA, PFHpA, PFHxS, PFNA, PFDA, PFUnA, PFDoA, PFTrDA, and PFTeDA) in urine and serum	LC–MS/MS	In COVID patients, 49 metabolites associated with PFOA, PFOS, and ↗ (12) PFASs, including mitochondrial metabolism metabolites. In adjusted analyses in COVID patients total PFAS, PFOA, PFOS were associated with mitochondrial metabolism metabolites (↑2-aminobutyric acid, ↑2-hydroxyglutarate, ↑3-hydroxyisobutyric acid, ↑acetoacetic acid, ↑aconitic acid, ↑butyrylcarnitine, ↑glycolic acid, ↓hydroxypropionic acid, ↑itaconic acid, ↑L-acetylcarnitine, ↑pyruvic acid, ↑succinic acid, ↑tiglylglycine), kynurenine metabolism metabolites (↑3-hydroxyanthranilic acid, ↑hydroxykynurenine, ↑L-kynurenine), and eicosanoids metabolism metabolites (↑8-isoprostane, ↑11-dTxB2, ↑PGF2alpha, ↑tetranor-PGEM, ↑TXB2). PFOA additionally associated with ↑3-methyladipic acid, ↑quinolinic	PFAS associated with mitochondrial metabolism, kynurenine metabolism, eicosanoid metabolism, glycolysis and gluconeogenesis metabolism, niacin metabolism, purine and pyrimidine metabolism, microbiome metabolism, sphingolipid and phospholipid metabolism, amino acid metabolism, bioamines and neurotransmitter	FDR-adjusted, threshold of 0.2	Adjusted for age, gender, body mass index (BMI), diabetes, cardiovascular diseases (CVDs), and urine albumin-to-creatinine ratio (UACR) in random effects model

Author/ year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
						acid. PFOA and total PFAS were also associated with ↑N-formylkynurenine	metabolism in COVID patients		
Sinisalu et al. 2020 [114]	*N* = 66. Newborns in Finland in the Type 1 Diabetes Prediction and Prevention (DIPP) study (17 progressors to celiac disease and 16 healthy controls) with measured samples at both birth and 3-month follow-up	Prospective	Prenatal and childhood (1999–2005)	7 PFAS compounds detected but 5 detected in > 10% of samples and used for analyses (PFHpA, PFHxS, PFOA, PFOS, and PFUnDA) both at birth and at 3 months of age	UPLC-MS/MS	PFAS exposure may modulate lipid and BA metabolism, and the impact is different in the infants who develop CD later in life, in comparison to HCs.In multivariate correlation analysis, there were associations among PFAS, BAs and molecular lipids that were different in cord blood than at 3 months (from negative to positive correlations) including as cholesterol esters (CEs), lysophosphatidylcholines (LPCs), phosphatidylcholines (PCs), phosphatidylethanolamines (PEs), sphingomyelin (SMs) and triacylglycerols (TGs). More specifically, at baseline in controls (PFHpA associated with ↓GCDCA, ↓TG; PFOS with ↑GCDCA; PFUnDA with ↓LPC,↓PC; total PFAS with ↓GCDCA), at baseline in CD progressors (PFOA, PFOS, total PFAS associated with ↓DCA), at 3 months in controls (PFHpA associated with ↓GUDCA; PFUnDA, PFOA with ↓LPC) and at 3 months in CD progressors (PFOA associated with ↑GCDCA-PFOS with ↑DCA, ↑CDCA, ↑GCDCA; total PFAS with ↑DCA, ↑CDCA, ↑GCDCA; PFUnDA with ↑TG; PFHpA with ↑TG_mfa). In multiblock analyses for lipids: in cord blood, comparing the celiac risk group vs. controls, where PFOA and PFOS contributed the most, there were inverse correlations with ↓CEs and ↓ether-linked PCs (PC(O-34:3), PC(O-36:3,4) and PC(O-38:4,5,6)); and at 3 months, where PFHxS contributed the most to celiac risk group compared to controls, several ↑PCs, ↑SM(d36:2), ↑PC(O-38:4,5) were upregulated	NA	NA	NA
Chen et al. 2021 [103]	*N* = 120. 9–80 y.o. in Wuxi City, China	Cross-sectional	Childhood/ Adolescence/ Adulthood (NA)	Multiple contaminants including 66 PFCs (**PFOA, and PFOS** in	UPLC-Q-Orbitrap HRMS	In targeted adjusted analyses, PFOA, PFOS, PFHxS, PFUnA associated with 18:0 lysophosphoethanolamine (LPE(18:0))	NA	NA	Age, BMI, and health status

Author/ year	Study population	Study design	Window of PFAS exposure (calendar year)	PFAS included in analytic dataset	Metabolomics analytical method	Main findings (metabolites)	Main findings (inferred pathways)	Multiple testing correction	Covariates
				metabolomics analyses)					

[a]See Table S2 for a complete summary of all significant metabolites and pathways altered by PFAS across studies. Table ordered by age or developmental stages. If multiple age stages are studied, these studies are included at the end.↑ (upregulated metabolite), ↓ (downregulated metabolite), ↑↑↓ (both upregulated and downregulated metabolite across PFAS subtypes but with overall more upregulation), and ↑↓↓ (both upregulated and downregulated metabolite across PFAS subtypes but with overall more downregulation)