Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Ecotoxicol Environ Saf. Author manuscript; available in PMC 2026 March 30.

Published in final edited form as:

Ecotoxicol Environ Saf. 2026 March 01; 312: 119955. doi:10.1016/j.ecoenv.2026.119955.

Per- and polyfluoroalkyl substances: A novel risk factor for cardiovascular disease

Wu Chen[a], **Chenyu Qiu**[a], **Zhenchun Yang**[a], **Hannah Nash**[a], **Roksana Karim**[a,b,*], **Zhanghua Chen**[a,**]

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

[b]Atherosclerosis Research Unit, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Abstract

Cardiovascular diseases (CVDs) are the major contributor to global mortality. Exposure to per- and polyfluoroalkyl substances (PFAS), synthetic chemicals that are persistent in the environment and the human body, has emerged as a novel risk factor for CVDs. In this review, we conducted a structured literature search in PubMed and Web of Science to identify original research articles published up to February 14, 2025. We summarized the epidemiological findings for the impact of PFAS exposure on CVDs and the pathologic precursors of CVDs including hypertension, atherosclerosis, and arterial stiffness. Although inconclusive, current evidence suggests a potential association between PFAS exposure, primarily legacy congeners such as perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexanesulfonic acid (PFHxS), with increased incidence, prevalence, and mortality of various CVDs, including ischemic heart disease and stroke, as well as elevated blood pressure, aggravated atherosclerosis, and arterial stiffening. Sex, age, socioeconomic status, and underlying health conditions may influence susceptibility to the cardiovascular effects of PFAS exposure; however, current evidence remains inconclusive. Future work is needed to assess the safety of a broader range of PFAS compounds, particularly the emerging ones. The majority of the existing studies evaluating the association between PFAS exposure and CVDs are cross-sectional. Experimental and longitudinal studies are warranted to establish the causal relationship between PFAS exposure and CVDs, as well as to elucidate the underlying biological mechanisms.

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

*Correspondence to: 1845 N. Soto St., SSB #318D, Los Angeles, CA 90033, USA. rkarim@usc.edu (R. Karim). **Correspondence to: 1845 N. Soto St., SSB #230F, Los Angeles, CA 90033, USA. zhanghuc@usc.edu (Z. Chen).

CRediT authorship contribution statement

Wu Chen: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Chenyu Qiu:** Writing – review & editing. **Zhenchun Yang:** Writing – review & editing. **Hannah Nash:** Writing – review & editing. **Roksana Karim:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Zhanghua Chen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Keywords

PFAS; Cardiovascular disease; Blood pressure; Atherosclerosis; Arterial stiffness

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally (Roth et al., 2020). The etiology of CVDs involves a complex interplay between genetic predisposition and environmental exposures (Bhatnagar, 2017; Sing et al., 2003). Beyond traditional CVD risk factors such as socioeconomic status, poor dietary habits, physical inactivity, and smoking (Mozaffarian et al., 2008; Schultz et al., 2018), there has been increasing concern over the adverse effect of environmental chemicals, particularly per- and polyfluoroalkyl substances (PFAS), on cardiovascular health (Schlezinger and Gokce, 2024; Wen et al., 2023).

PFAS are highly fluorinated aliphatic substances used extensively in industrial and commercial applications because of their chemical and thermal stability, as well as their hydrophobic and oleophobic properties (Buck et al., 2011). Due to their widespread use, environmental persistence, and ability to undergo long-range transport, PFAS have been broadly detected in the environment, wildlife, and humans (Buck et al., 2011). Humans are exposed to PFAS through multiple pathways including drinking water, air, dust, consumer products, and food (Sunderland et al., 2019). Once PFAS enter the human body, they exhibit unique toxicokinetic properties, including strong protein binding, limited biotransformation, and long biological half-lives, resulting in bioaccumulation and prolonged internal exposure (Li et al., 2018). Such sustained internal exposure may disrupt multiple physiological systems and contribute to adverse health outcomes. The metabolic, reproductive, and developmental effects of PFAS have been relatively well recognized (Blake and Fenton, 2020; Gao et al., 2021; Liu et al., 2023; Qi et al., 2020); however, the relationship between PFAS exposure and CVDs is an emerging field of study.

Recent reviews of epidemiological and toxicological evidence suggest that exposure to legacy PFAS, such as perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexanesulfonic acid (PFHxS), and perfluorooctanesulfonic acid (PFOS), may be associated with increased risk of CVDs and related conditions, such as hypertension and dyslipidemia (Schlezinger and Gokce, 2024; Wen et al., 2023). Meta-analyses have reported inconsistent findings, with no significant associations observed for stroke in some analyses (Chang et al., 2024), but positive associations between PFAS exposure and hypertension in others. However, these syntheses were based on a limited number of studies (n = 13–15) and focused on a small subset of legacy PFAS (Pan et al., 2023; Xiao et al., 2023; Yang et al., 2023). Epidemiological research on PFAS and cardiovascular health has expanded rapidly in recent years, particularly with respect to emerging PFAS compounds and mixtures, but has not been comprehensively synthesized. Additionally, susceptibility to PFAS-related cardiovascular effects may vary across populations due to differences in age, sex, socioeconomic status, and health conditions. However, population-level susceptibility, defined here by these demographic and health-related factors, has not been adequately addressed in previous reviews. This narrative review provides an up-to-date summary of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

epidemiological findings on both legacy and emerging PFAS in relation to cardiovascular outcomes and identifies potentially susceptible subgroups to guide targeted CVD prevention.

CVDs evolve gradually and often remain asymptomatic for extended periods (Francula-Zaninovic and Nola, 2018). Atherosclerosis is the leading cause of CVDs (Frostegård, 2013). Monitoring atherosclerosis and related conditions, such as elevated blood pressure and arterial stiffening, is essential for evaluating cardiovascular health, predicting CVD risk, and implementing preventive measures (Francula-Zaninovic and Nola, 2018). Beyond CVD morbidity and mortality, this narrative review summarizes epidemiological evidence regarding the effects of PFAS exposure on blood pressure, atherosclerosis, and arterial stiffness, to comprehensively assess potential cardiovascular impacts and to identify gaps requiring future research.

2. Methods

We employed a structured approach to identify epidemiological studies evaluating the association between PFAS exposure and cardiovascular outcomes, with an emphasis on CVD morbidity and mortality, blood pressure, atherosclerosis, and arterial stiffness. We searched the PubMed and Web of Science for original research articles using the following search query: TS= (“perfluo*” OR “polyfluo*” OR “fluoroalkyl” OR “ fluorocarbon” OR “PFAS” OR “PFASs” OR “PFC” OR “PFCs” OR “PFOS” OR “PFOA” OR “PFNA” OR “PFHxS” OR “PFDA”) AND TS= (“ischemic heart disease*” OR “coronary artery disease*” OR “stroke” OR “myocardial infarction” OR “heart attack” OR “cardiovascular” OR “heart disease*” OR “atherosclerosis” OR “carotid intima-media thickness” OR “CIMT” OR “intima-media thickness” OR “IMT” OR “gray scale median” OR “grey scale median” OR “GSM” OR “intima-media gray scale median” OR “intima-media grey scale median” OR “IM-GSM” OR “blood pressure” OR “hypertension” OR “artery stiffness” OR “arterial stiffness” OR “pulse wave velocity” OR “PWV”). Our initial search retrieved 929 records from PubMed and 1136 records from Web of Science published up to November 30, 2023. A subsequent search conducted on February 14, 2025, identified an additional 134 records from PubMed and 148 records from Web of Science published after November 30, 2023. After excluding 832 duplicates, 1515 records were screened by title and abstract for eligibility, resulting in 96 records selected for full-text screening. Following the second screening on full texts, 7 additional records were excluded. A total of 89 articles met the inclusion criteria and were included in this review: (1) original research; (2) written in English; (3) involved human subjects; (4) assessed exposure to at least one PFAS compound; (5) examined at least one cardiovascular outcome, including CVD morbidity and mortality, blood pressure, atherosclerosis, and arterial stiffness; and (6) reported associations between PFAS exposure and cardiovascular outcomes. Fig. 1 shows the flowchart of screening process.

For each of the 89 articles, key information regarding the study author and year, study design, location, population, PFAS assessment, and main findings were extracted and summarized in tables. Population-level susceptibility was evaluated by synthesizing subgroup-specific results from studies that conducted stratified analyses. Evidence of susceptibility was inferred when multiple studies reported stronger associations between

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

PFAS exposure and cardiovascular outcomes in the same subgroups. The Newcastle-Ottawa Scale was used to assess the quality of cohort and case-control studies (Wells et al., 2009), and the modified Newcastle-Ottawa Scale was used to assess the quality of cross-sectional studies (Modesti et al., 2016).

3. Results

3.1. Literature characteristics

Among the 89 included studies, most focused on blood pressure or hypertension (n = 51), followed by CVD morbidity and mortality (n = 32), while fewer studies examined atherosclerosis (n = 14) or arterial stiffness (n = 3). The most frequently assessed chemicals were legacy PFAS, including PFOA (n = 72), PFOS (n = 65), PFHxS (n = 57), and PFNA (n = 57). Most studies used serum, plasma, or whole blood samples for exposure assessment (n = 76), with median concentrations ranging from 0.68–38.9 ng/mL for PFOA, 1.57–27.55 ng/mL for PFOS, 0.18–6.5 ng/mL for PFHxS, and 0.13–2.14 ng/mL for PFNA (ranges were summarized using median concentrations only to improve comparability across studies; detailed concentrations are provided in Table S1). In contrast, several studies defined PFAS exposure categories based on participants' residential or occupational history (n = 8), or modeled PFAS exposure as estimated cumulative metrics (n = 5). The evidence base was dominated by cross-sectional studies (n = 57), with fewer longitudinal studies (n = 31) and only one ecological study. Geographically, the literature was concentrated in a small number of countries, particularly the United States (U.S., n = 48), China (n = 13), Italy (n = 7), and Sweden (n = 6). Most studies examined the association between PFAS exposure and cardiovascular outcomes among general adult populations (n = 42), followed by clinical populations (n = 13), children and adolescents (n = 11), occupationally exposed populations (n = 9), mother-child cohorts (n = 9), and environmentally exposed communities (n = 6). The quality assessment yielded a mean score of 8.4, indicating moderate to high methodological quality (detailed quality assessment is provided in Table S2).

3.2. PFAS and CVD morbidity and mortality

Thirty-two studies have examined the association between PFAS exposure and CVD morbidity and mortality across diverse populations and reported mixed results (details in Table 1, Table S3, and Table S4). Exposure to PFAS has been linked to elevated risks of CVDs including angina, coronary heart disease, myocardial infarction, stroke, and heart failure in epidemiological studies with ecological (Mastrantonio et al., 2018), cross-sectional (Anderson-Mahoney et al., 2008; Arredondo Eve et al., 2024; Feng et al., 2022; Huang et al., 2018; Inoue et al., 2020; Li et al., 2023; Mao et al., 2024; Panikkar et al., 2019; Shankar et al., 2012; Ward-Caviness et al., 2022; Wei et al., 2024; Xiao et al., 2024), or longitudinal designs (Biggeri et al., 2024; Law et al., 2023; Mattsson et al., 2015; Simpson et al., 2013; Wen et al., 2022; Winquist Steenland, 2014; Zhu et al., 2024). However, evidence was inconsistent regarding the specific PFAS associated with higher CVD risk. Several studies have assessed PFAS mixtures, accounting for the complex correlations among PFAS congeners, and reported positive associations between PFAS mixtures and CVD risk (Feng et al., 2022; Wei et al., 2024; Wen et al., 2022). For example, a longitudinal analysis of 11,747 adults in the National Health and Nutrition Examination Survey (NHANES) 1999–

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2014 clustered participants by baseline PFAS mixture exposure and found that those in the high-exposure group had significantly higher CVD-related mortality during follow-up compared with the low-exposure group (Wen et al., 2022).

In contrast, several studies did not find any significant associations between PFAS exposure and morbidity or mortality of CVDs either among general or occupational populations (Christensen et al., 2016; Duan et al., 2024; Dunder et al., 2023; Lazarevic et al., 2023; Nilsson et al., 2022; Sakr et al., 2009), and negative associations were noted in some studies (Gilliland and Mandel, 1993; Honda-Kohmo et al., 2019; Hutcheson et al., 2020; Li et al., 2023; Mao et al., 2024; Raleigh et al., 2014; Schillemans et al., 2022; Steenland and Woskie, 2012). For example, a cross-sectional study found that higher serum PFHxS and PFOS concentrations were associated with a lower stroke risk among 3921 adults with diabetes, whereas PFOA was negatively associated with stroke in 44,285 non-diabetic participants; PFNA showed no association (Hutcheson et al., 2020).

Some studies suggest that PFAS exposure may differentially affect cardiovascular health across age, sex, race/ethnicity, socioeconomic status, lifestyle, and clinical subgroups (Anderson-Mahoney et al., 2008; Dunder et al., 2023; Feng et al., 2022; Honda-Kohmo et al., 2019; Huang et al., 2018; Hutcheson et al., 2020; Inoue et al., 2020; Mao et al., 2024; Wen et al., 2022; Xiao et al., 2024); however, the results are inconsistent. Several studies have demonstrated that males may be more susceptible to PFAS-related CVD risk (Feng et al., 2022; Huang et al., 2018; Li et al., 2023; Mao et al., 2024; Xiao et al., 2024). For example, a cross-sectional study of 7904 NHANES participants (2003–2012) reported that higher serum PFOS concentrations were associated with higher risks of heart attack and stroke, and higher PFNA levels were associated with higher risks of coronary heart disease, heart attack, and stroke among males but not females (Feng et al., 2022). However, a longitudinal study among 11,747 NHANES participants (1999–2014) found the positive association between PFOS exposure and all-cause mortality was stronger among females than males (Wen et al., 2022). Diabetes was identified as an effect modifier of the associations between PFAS exposure and CVDs (Huang et al., 2018; Hutcheson et al., 2020; Wen et al., 2022). A cross-sectional analysis of NHANES 1999–2014 found that higher serum PFOS, PFOA, PFNA, and total PFAS concentrations were associated with higher total CVD prevalence among individuals without diabetes, but not among diabetic patients (Huang et al., 2018), which is consistent with another NHANES research (Wen et al., 2022). Additionally, a cross-sectional study of 3921 diabetic and 44,285 non-diabetic U.S. adults found negative associations between serum PFHxS and PFOS and stroke risk among diabetic patients only (Hutcheson et al., 2020).

3.3. PFAS and blood pressure

Most epidemiological studies investigating PFAS exposure in relation to cardiovascular outcomes have focused on blood pressure and hypertension risk (details in Table 1, Table S3, and Table S5). Twenty-three studies, including 21 cross-sectional ones, have demonstrated positive associations between PFAS exposure and systolic and diastolic blood pressure, as well as hypertension among general adults and those with chronic health conditions (Bao et al., 2017; Batzella et al., 2022; Chung et al., 2024; Davidson Boland, 2023; Ding et al.,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2022; Leary et al., 2020; J. Li et al., 2024; Liao et al., 2020; Lin et al., 2023; P.D. Lin et al., 2020; Maranhao Neto et al., 2022; Mi et al., 2020; Min et al., 2012; Pitter et al., 2020; Ward-Caviness et al., 2022; Winquist Steenland, 2014; B. Wu et al., 2024; M. Wu et al., 2024; Yang et al., 2018; Ye et al., 2021; You et al., 2022; Yu et al., 2021; Zare Jeddi et al., 2021). A U.S. longitudinal study followed 1058 midlife women without hypertension for 18 years and reported that those in the highest tertile of baseline PFAS mixtures had a higher risk of developing hypertension than those in the lowest tertile (Ding et al., 2022). Besides legacy PFAS, two recent reports from China have linked emerging PFAS compounds detected in serum, such as 6:2 chlorinated polyfluorinated ether sulfonic acid (6:2 Cl-PFESA) and 8:2 Cl-PFESA, to increased risks of elevated blood pressure and hypertension (Mi et al., 2020; Yu et al., 2021). In addition to PFAS congeners, different PFAS isomers may elicit diverse effects on blood pressure (Bao et al., 2017; Ye et al., 2021), complicating the identification of key PFAS. Among children and adolescents, positive associations of PFAS exposure with blood pressure and hypertension risk were reported in four cross-sectional studies (Averina et al., 2021; Khalil et al., 2018; Liu et al., 2024; Ma et al., 2019) and three longitudinal studies (Fleury et al., 2024; Warembourg et al., 2019; M. Zhang et al., 2023). Additionally, PFAS exposure during pregnancy, a critical period significantly affecting long-term maternal and child health, has been associated with higher blood pressure in children (Du et al., 2024; Fleury et al., 2024; Lejeune et al., 2025; Li et al., 2021; Wang et al., 2023; Xu et al., 2023; M. Zhang et al., 2023) and in mothers after delivery (Mitro et al., 2020). For example, a longitudinal study in China of 129 mother-child pairs found that maternal plasma PFAS mixture levels across all three trimesters were associated with higher diastolic blood pressure and mean arterial pressure in children at age 4 years, with PFHxS contributing the most (Du et al., 2024).

Due to substantial heterogeneity across studies, no definitive conclusions can be drawn regarding the association between PFAS exposure and blood pressure. Several studies have reported null associations with blood pressure or hypertension among general adults (Aker et al., 2023; Anderson-Mahoney et al., 2008; Lazarevic et al., 2023; Yu et al., 2021; Zheng et al., 2023), children and adolescents (Canova et al., 2021; Geiger et al., 2014; Lin et al., 2013; Zheng et al., 2023), and firefighters (Nilsson et al., 2022). Similarly, two studies of prenatal PFAS exposure found no significant associations with childhood blood pressure (Braun et al., 2022; Manzano-Salgado et al., 2017). In addition, several studies have reported negative associations between PFAS exposure and blood pressure or hypertension (Boafo et al., 2023; Christensen et al., 2016; Donat-Vargas et al., 2019; Fleury et al., 2024; Gump et al., 2023; Lin et al., 2023; P.D. Lin et al., 2020; Maranhao Neto et al., 2022; M. Wu et al., 2024; Xu et al., 2023; Ye et al., 2021; M. Zhang et al., 2023; Zhang et al., 2022). For example, a longitudinal study in China followed 1080 participants free of hypertension, CVDs, diabetes, and cancer at baseline, with blood pressure measured at baseline and 5-year follow-up. Compared with the lowest quartile, the highest quartile of baseline serum PFOS concentrations was negatively associated with incident hypertension and change in systolic blood pressure, whereas no significant association was observed for PFOA (Zhang et al., 2022).

Several studies have examined the effect modification by sex on the associations of PFAS exposure with blood pressure and hypertension, with inconsistent findings (Aker et al., 2023;

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bao et al., 2017; Braun et al., 2022; Canova et al., 2021; Christensen et al., 2016; Ding et al., 2022; Du et al., 2024; Fleury et al., 2024; Lejeune et al., 2025; Li et al., 2021; Liao et al., 2020; P.D. Lin et al., 2020; Ma et al., 2019; Manzano-Salgado et al., 2017; Mi et al., 2020; Pitter et al., 2020; Wang et al., 2023; Winquist Steenland, 2014; B. Wu et al., 2024; M. Wu et al., 2024; Xu et al., 2023; Zhang et al., 2022). Specifically, many studies observed stronger positive associations in females (Bao et al., 2017; Fleury et al., 2024; Lejeune et al., 2025; Mi et al., 2020; Xu et al., 2023). For example, a cross-sectional study of 1612 Chinese adults found that multiple PFAS isomers, including total-PFOS, n-PFOS, total-Br-PFOS, 1m-PFOS, 6m-PFOS, 3 + 4 +5m-PFOS, 6m-PFOA, PFNA, perfluorobutanoic acid (PFBA), and perfluorohexanoic acid (PFHxA), were positively associated hypertension in females, whereas only PFBA showed a significant positive association in males (Bao et al., 2017). However, other studies observed stronger negative associations in females (Canova et al., 2021; M. Wu et al., 2024; Zhang et al., 2022), or did not identify significant modification by sex (Aker et al., 2023; Li et al., 2021; Manzano-Salgado et al., 2017). Additionally, several studies have reported stronger positive associations between PFAS exposure and blood pressure and hypertension in males (Du et al., 2024; P.D. Lin et al., 2020; Ma et al., 2019; Pitter et al., 2020; Wang et al., 2023; B Wu et al., 2024). For example, a cross-sectional study of 10,794 Chinese adults observed positive associations between serum PFNA, perfluorodecanoic acid (PFDA), perfluoroheptanesulfonic acid (PFHpS), and PFOS concentrations and hypertension in males, but not in females (B. Wu et al., 2024). In addition to sex, the associations between PFAS exposure and blood pressure may vary by age group (Anderson-Mahoney et al., 2008; Mitro et al., 2020; Winquist Steenland, 2014) and pubertal stage (Lejeune et al., 2025). For example, a U.S. longitudinal study of 761 women measured plasma PFAS concentrations in early pregnancy and assessed blood pressure at 3 years after delivery. The association between pregnancy PFOS concentrations and post-delivery systolic blood pressure was stronger among females aged ≥ 35 years at pregnancy than those < 35 years (Mitro et al., 2020). Socioeconomic and health factors, such as race/ethnicity, obesity status, and medication use, may also modify the associations between PFAS exposure and blood pressure (J. Li et al., 2024; M. Wu et al., 2024).

3.4. PFAS and atherosclerosis

Research on atherosclerosis, a key pathologic process in CVDs, may help clarify the causal role of PFAS exposure in CVD onset and progression (Frostegård, 2013). Fourteen studies have investigated the impact of PFAS exposure on atherosclerosis (details in Table 1, Table S3, and Table S6). Notably, ten of these studies have reported positive associations between PFAS exposure and atherosclerosis markers, particularly carotid intima-media thickness (CIMT), the gold standard for assessing atherosclerosis, in both adults and children (De Toni et al., 2020; Gump et al., 2023; Liberda et al., 2019; Lin et al., 2013, 2016, 2022; Lind et al., 2017, 2018; Osorio-Yáñez et al., 2021; Yang et al., 2024). For example, in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study in Sweden, 1016 participants were enrolled at age 70 and followed at ages 75 (n = 826) and 80 (n = 602). Plasma PFAS concentrations and atherosclerosis markers were measured at all three time points. Changes in perfluoroheptanoic acid (PFHpA), PFHxS, PFOS, PFOA, PFNA, PFDA, perfluorooctanesulfonamide (PFOSA), and PFUnDA were positively associated with 10-year changes in CIMT (Lind et al., 2018). On the contrary, two U.S. cross-sectional

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

studies did not observe significant associations between atherosclerosis markers and serum PFAS concentrations among male firefighters (Khalil et al., 2020) or the general population (Koskela et al., 2022). Additionally, a cross-sectional study in China of 957 mother-child pairs found negative associations between maternal plasma PFAS concentrations in the first trimester and CIMT in children at age 4 years (Wang et al., 2023).

Females may be more susceptible to the impact of PFAS exposure on atherosclerosis. In a cross-sectional analysis of the PIVUS study, plasma PFOSA concentrations were associated with higher CIMT, PFNA was associated with higher gray-scale median of the intima-media complex (IM-GSM), and PFUnDA was associated with increased plaque prevalence in females, but not in males (Lind et al., 2017).

3.5. PFAS and arterial stiffness

Three studies have investigated the associations between PFAS exposure and arterial stiffness (details in Table 1, Table S3, and Table S7), an important early indicator of CVDs (Cecelja and Chowienczyk, 2012). All of them were cross-sectional studies with relatively small sample sizes, conducted in the U.S., and reported no significant associations between PFAS exposure and pulse wave velocity (PWV), a gold standard measure for arterial stiffness (Gump et al., 2023; Koshy et al., 2017; Van Bortel et al., 2012; Wittkopp et al., 2022). In a study of 291 children aged 9–11 years, serum PFAS, whether individual congeners (PFOS, PFOA, PFNA, PFHxS, and PFDA) or mixtures, were not associated with carotid-femoral PWV (Gump et al., 2023). A study of 123 children in New York City exposed to chemical contaminants from the World Trade Center disaster and 185 socio-demographically matched controls found that serum PFOA and PFNA concentrations were positively associated with brachial artery distensibility, whereas no associations were observed with PWV or augmentation index (Koshy et al., 2017). Additionally, a study of 94 adult outpatients with no known CVDs reported that PFAS mixtures were negatively associated with brachial artery reactivity testing values, with PFHpA contributing the most, while no associations were found with PWV (Wittkopp et al., 2022).

4. Discussion

4.1. Potential biological mechanisms

While the exact mechanisms linking PFAS exposure to greater cardiovascular risks remain uncertain, oxidative stress and inflammation emerge as a candidate. PFAS can disrupt signaling pathways of key transcription factors that regulate oxidative stress and inflammatory responses, such as nuclear factor kappa B (NF-κB), nuclear factor erythroid 2-related factor 2 (NRF2), and aryl hydrocarbon receptor (AHR) (Chen et al., 2022; Dale et al., 2022; Ehrlich et al., 2023; Houck et al., 2021; Tang et al., 2023; Zhang et al., 2021; Zhu et al., 2015). This disruption leads to increased generation of reactive oxidative species (ROS), reduced total antioxidant capacity, altered activity of key antioxidant enzymes, lipid peroxidation, DNA damage, mitochondrial destabilization, and elevated release of inflammatory mediators (Bonato et al., 2020; Chen et al., 2023; C.Y. Lin et al., 2020; Ojo et al., 2021; Omoike et al., 2021; Palaniyandi et al., 2023; Taibl et al., 2022; Tan et al., 2023; Wielsøe et al., 2015; L. Zhang et al., 2023). For example, a recent meta-analysis found

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

that PFAS were positively associated with albumin, an important circulating antioxidant (Roche et al., 2008), as well as γ-glutamyl-transpeptidase and uric acid, both predictive biomarkers of systemic oxidative stress and CVD risk (Chen et al., 2023; Koenig and Seneff, 2015; Ndrepepa and Kastrati, 2016; Saito et al., 2021). PFAS-induced oxidative stress and inflammation may cause cardiovascular impairment. Because demographic, socioeconomic, and health factors can influence oxidative stress and inflammatory status, for example, aging and chronic conditions such as obesity, diabetes, and hypertension are associated with elevated chronic inflammation, susceptibility to PFAS-related cardiovascular effects may vary across these factors (Ferrucci and Fabbri, 2018; Khanna et al., 2022; Tsalamandris et al., 2019).

PFAS-induced disruption of lipid, fatty acid, amino acid, and glucose metabolism may contribute to conditions such as obesity, dyslipidemia, insulin resistance, and diabetes, thereby increasing CVD risk (Cardenas et al., 2017; Chen et al., 2020; Goodrich et al., 2021; Guo et al., 2022; Kannel and McGee, 1979; Liu et al., 2023; Prince et al., 2023; Qi et al., 2020; Van Gaal et al., 2006; Yusuf et al., 2004). PFAS may exert its metabolic impacts by interacting with peroxisome proliferator-activated receptors (PPARs), key regulators of lipid and glucose metabolism and homeostasis. The interaction is underpinned by the structural similarity between PFAS and natural fatty acid agonists of PPARs (Behr et al., 2020; Houck et al., 2021; Pederick et al., 2024; Rosen et al., 2017). Additional nuclear receptors, such as the constitutive androstane receptor (CAR) and the pregnane-X receptor (PXR), have also been identified as targets of PFAS. These xenobiotic sensors regulate the metabolism and elimination of foreign compounds and also participate in fatty acid, lipid, and glucose metabolism (Houck et al., 2021; Lai et al., 2020; Wada et al., 2009). Variations in susceptibility across subpopulations may be partly attributed to differences in metabolic status, as PFAS may exert adverse effects through overlapping metabolic pathways (Barzilai et al., 2012).

PFAS may increase CVD risk through their endocrine-disrupting properties. PFAS can alter the homeostasis of endogenous hormones, including sex hormones and thyroid hormones (Coperchini et al., 2020; He et al., 2023; L. Li et al., 2024; Lopez-Espinosa et al., 2016; Wang et al., 2021). For example, a meta-analysis of 11 studies with 7714 participants reported that PFHxS exposure was significantly associated with higher levels of estradiol in females, and PFOA and PFOS were negatively associated with testosterone levels in males (L. Li et al., 2024). PFAS may disrupt sex hormone homeostasis by interfering with sex hormone receptors, including the estrogen receptor (ER) and androgen receptor (AR), as well as by affecting the hypothalamic-pituitary-gonadal (HPG) axis (Azhagiya Singam et al., 2020; Kjeldsen and Bonefeld-Jørgensen, 2013; Rodríguez-Carrillo et al., 2023; Shi et al., 2018; Vinggaard et al., 2021). Sex hormones play a crucial role in the pathogenesis of CVDs and contribute considerably to the sex disparity in CVD risk (Arnold et al., 2017; Hodis et al., 2016; Rexrode et al., 2003). Additionally, the effects of PFAS exposure on sex hormones differ by sex (He et al., 2023; L. Li et al., 2024; Lopez-Espinosa et al., 2016; Rodríguez-Carrillo et al., 2023), potentially contributing to the diverse cardiovascular impacts of PFAS exposure among different sex groups.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Importantly, these biological pathways are not independent but may interact and reinforce one another. Oxidative stress and inflammation are intrinsic to metabolic dysfunction and disruption of endocrine homeostasis (Abtin et al., 2025; Liu et al., 2025; Wei et al., 2023). Meanwhile, metabolic disturbances, such as dyslipidemia and insulin resistance, can amplify oxidative and inflammatory responses (Jukema et al., 2019; Shimobayashi et al., 2018). In parallel, endocrine disruption, such as alterations in sex hormone and thyroid hormone signaling, may modulate metabolic regulation as well as oxidative and inflammatory processes (Chainy and Sahoo, 2020; Mullur et al., 2014). Collectively, these interconnected mechanisms provide a plausible biological framework through which PFAS exposure may contribute to cardiovascular impairment and help explain the heightened susceptibility observed in certain populations.

4.2. Sources of inconsistency and limitations

Epidemiological evidence on the relationship between PFAS exposure and cardiovascular health is inconsistent. The discrepancies may partly reflect differences in study design and PFAS exposure assessment. Most existing studies are cross-sectional, making them susceptible to reverse causality and residual confounding (Savitz and Wellenius, 2023). Even among the 31 longitudinal studies, many relied on a single PFAS measurement to approximate long-term exposure (Braun et al., 2022; Ding et al., 2022; Duan et al., 2024; Dunder et al., 2023; Lejeune et al., 2025; Manzano-Salgado et al., 2017; Mitro et al., 2020; Schillemans et al., 2022; Wang et al., 2023; Warembourg et al., 2019; Wen et al., 2022; Xu et al., 2023; Zhang et al., 2022; Zhu et al., 2024). However, PFAS body burdens fluctuate over time due to continuous exposure and elimination through metabolism and excretion. Relying on a single-time-point measurement may introduce bias when evaluating associations with cardiovascular outcomes assessed at a later time. Additionally, several studies have used exposure models to estimate cumulative exposure to PFAS (Raleigh et al., 2014; Sakr et al., 2009; Simpson et al., 2013; Steenland and Woskie, 2012; Winquist and Steenland, 2014); however, these estimates carry substantial uncertainty due to limited or imprecise information on key parameters such as PFAS sources, residential histories, and time-activity patterns (Winquist et al., 2013). Studies classifying PFAS exposure solely by residential or occupational history may be particularly prone to exposure misclassification when individual-level exposure variability is not adequately captured (Anderson-Mahoney et al., 2008; Biggeri et al., 2024; Davidson and Boland, 2023; Gilliland and Mandel, 1993; Law et al., 2023; Mastrantonio et al., 2018; Panikkar et al., 2019; Ward-Caviness et al., 2022).

Another contributor to inconsistent findings is heterogeneity in study populations and exposure contexts. Most evidence comes from studies conducted in a small number of countries, with limited data available from other regions. This may introduce discrepancies and limit the generalizability of current findings, given regional differences in population characteristics and PFAS exposure scenarios (Ackerman Grunfeld et al., 2024). In addition, studies have focused on diverse populations, such as the general population, environmentally exposed communities, children and adolescents, clinical populations, and occupational populations. Individuals across diverse demographic, socioeconomic, and health backgrounds may exhibit distinct exposure profiles and differential susceptibility

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

to PFAS-related cardiovascular effects (Anderson-Mahoney et al., 2008; Bao et al., 2017; Braun et al., 2022; Canova et al., 2021; Dunder et al., 2023; Feng et al., 2022; Honda-Kohmo et al., 2019; Huang et al., 2018; Hutcheson et al., 2020; Inoue et al., 2020; Lejeune et al., 2025; J. Li et al., 2024; Liao et al., 2020; Lind et al., 2017; Ma et al., 2019; Mi et al., 2020; Pitter et al., 2020; Wen et al., 2022; Winquist Steenland, 2014; M. Wu et al., 2024; Xiao et al., 2024; Zhang et al., 2022). Additionally, null or negative associations between PFAS and CVDs in occupational studies may be partly attributed to healthy-worker effects (Li and Sung, 1999).

The wide range of PFAS assessed may also contribute to discrepancies. Thousands of PFAS compounds are currently in use, and the number continues to grow over time (Wang et al., 2017). Different PFAS compounds, and even different isomers of the same compound, vary in chemical structure and physicochemical properties, potentially leading to distinct health impacts (Fenton et al., 2021). However, studies examining cardiovascular effects have primarily focused on a small subset of PFAS compounds, particularly legacy PFAS such as PFOA, PFOS, PFHxS, and PFNA. The health impacts of other PFAS compounds, especially those promoted as “safe” alternatives are unknown, although growing evidence has raised concerns about their safety to humans and the environment (Wang et al., 2019). Additionally, co-exposure to PFAS mixtures and potential nonlinear exposure-response relationships may further contribute to the inconsistent findings and complicate efforts to elucidate the impact of PFAS on cardiovascular health (Feng et al., 2022; Liao et al., 2020; Wei et al., 2024; Yang et al., 2024).

5. Future research directions

Growing concerns have emerged regarding the cardiometabolic effects of PFAS exposure. Although evidence remains inconclusive, studies suggest potential links between exposure to PFAS, especially PFOA, PFOS, PFNA, and PFHxS, and increased incidence, prevalence, and mortality of various CVDs, such as ischemic heart disease and stroke, as well as elevated blood pressure, aggravated atherosclerosis, and arterial stiffening. Given the long-term progression of CVDs (Karmali and Lloyd-Jones, 2013) and the dynamic nature of PFAS body burdens, longitudinal studies with extended follow-up periods and repeated exposure and health measurements are essential to clarify temporal relationships and strengthen causal inference. As evidence on population susceptibility remains limited, future research should examine how demographic, socioeconomic, and health factors modify the cardiovascular effects of PFAS exposure, with particular attention to high-risk groups such as postmenopausal women (Hodis et al., 2016) and ethnic minorities (He et al., 2021). The continuous introduction of new PFAS compounds highlight the need to evaluate the safety of emerging PFAS compounds and mixtures. Finally, mechanistic studies in human and experimental models are warranted to elucidate biological pathways, generate causal evidence, and identify potential intervention targets. In summary, future studies are required to solidify the relationship between PFAS exposure and CVDs and explore the feasibility of incorporating PFAS, a modifiable environmental factor, into CVD prevention strategies.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

This work was supported by the National Institute of Environmental Health Sciences (R01ES033705 and R01ES032247), and the American Heart Association Postdoctoral Fellowship (25POST1376733).

Data availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2026.119955.

References

Abtin S, Ziveh T, Rezaee-Tavirani M, 2025. The complicated relationship between inflammation and metabolic dysfunction. J. Diabetes Metab. Disord 24, 237. [PubMed: 41116875]

Ackerman Grunfeld D, Gilbert D, Hou J, Jones AM, Lee MJ, Kibbey TC, et al. , 2024. Underestimated burden of per-and polyfluoroalkyl substances in global surface waters and groundwaters. Nat. Geosci 17, 340–346.

Aker A, Ayotte P, Caron-Beaudoin É, Ricard S, Gaudreau É, Lemire M, 2023. Cardiometabolic health and per and polyfluoroalkyl substances in an Inuit population. Environ. Int 181, 108283. [PubMed: 37883911]

Anderson-Mahoney P, Kotlerman J, Takhar H, Gray D, Dahlgren J, 2008. Self-reported health effects among community residents exposed to perfluorooctanoate. N. Solut 18, 129–143.

Arnold AP, Cassis LA, Eghbali M, Reue K, Sandberg K, 2017. Sex Hormones and sex chromosomes cause sex differences in the development of cardiovascular diseases. Arterioscler. Thromb. Vasc. Biol 37, 746–756. [PubMed: 28279969]

Arredondo Eve A, Tunc E, Mehta D, Yoo JY, Yilmaz HE, Emren SV, et al. , 2024. PFAS and their association with the increased risk of cardiovascular disease in postmenopausal women. Toxicol. Sci 200, 312–323. [PubMed: 38758093]

Averina M, Brox J, Huber S, Furberg AS, 2021. Exposure to perfluoroalkyl substances (PFAS) and dyslipidemia, hypertension and obesity in adolescents. The Fit Futures study. Environ. Res 195, 110740. [PubMed: 33460636]

Azhagiya Singam ER, Tachachartvanich P, Fourches D, Soshilov A, Hsieh JCY, La Merrill MA, et al. , 2020. Structure-based virtual screening of perfluoroalkyl and polyfluoroalkyl substances (PFASs) as endocrine disruptors of androgen receptor activity using molecular docking and machine learning. Environ. Res 190, 109920. [PubMed: 32795691]

Bao WW, Qian ZM, Geiger SD, Liu E, Liu Y, Wang SQ, et al. , 2017. Gender-specific associations between serum isomers of perfluoroalkyl substances and blood pressure among Chinese: isomers of C8 Health Project in China. Sci. Total Environ 607-608, 1304–1312. [PubMed: 28738507]

Barzilai N, Huffman DM, Muzumdar RH, Bartke A, 2012. The critical role of metabolic pathways in aging. Diabetes 61, 1315–1322. [PubMed: 22618766]

Batzella E, Girardi P, Russo F, Pitter G, Da Re F, Fletcher T, et al. , 2022. Perfluoroalkyl substance mixtures and cardio-metabolic outcomes in highly exposed male workers in the Veneto Region: a mixture-based approach. Environ. Res 212, 113225. [PubMed: 35390304]

Behr AC, Plinsch C, Braeuning A, Buhrke T, 2020. Activation of human nuclear receptors by perfluoroalkylated substances (PFAS). Toxicol. Vitr 62, 104700.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bhatnagar A., 2017. Environmental Determinants of Cardiovascular Disease. Circ. Res 121, 162–180. [PubMed: 28684622]

Biggeri A, Stoppa G, Facciolo L, Fin G, Mancini S, Manno V, et al. , 2024. All-cause, cardiovascular disease and cancer mortality in the population of a large Italian area contaminated by perfluoroalkyl and polyfluoroalkyl substances (1980-2018). Environ. Health 23, 42. [PubMed: 38627679]

Blake BE, Fenton SE, 2020. Early life exposure to per- and polyfluoroalkyl substances (PFAS) and latent health outcomes: A review including the placenta as a target tissue and possible driver of peri- and postnatal effects. Toxicology 443, 152565. [PubMed: 32861749]

Boafo YS, Mostafa S, Obeng-Gyasi E, 2023. Association of combined metals and PFAS with cardiovascular disease risk. Toxics 11.

Bonato M, Corrà F, Bellio M, Guidolin L, Tallandini L, Irato P, et al. , 2020. PFAS environmental pollution and antioxidant responses: an overview of the impact on human field. Int. J. Environ. Res. Public Health 17.

Braun JM, Papandonatos GD, Li N, Sears CG, Buckley JP, Cecil KM, et al. , 2022. Physical activity modifies the relation between gestational perfluorooctanoic acid exposure and adolescent cardiometabolic risk. Environ. Res 214, 114021. [PubMed: 35952751]

Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, et al. , 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr. Environ. Assess. Manag 7, 513–541. [PubMed: 21793199]

Canova C, Di Nisio A, Barbieri G, Russo F, Fletcher T, Batzella E, et al. , 2021. PFAS Concentrations and Cardiometabolic Traits in Highly Exposed Children and Adolescents. Int. J. Environ. Res. Public Health 18.

Cardenas A, Gold DR, Hauser R, Kleinman KP, Hivert MF, Calafat AM, et al. , 2017. Plasma Concentrations of Per- and Polyfluoroalkyl Substances at Baseline and Associations with Glycemic Indicators and Diabetes Incidence among High-Risk Adults in the Diabetes Prevention Program Trial. Environ. Health Perspect 125, 107001. [PubMed: 28974480]

Cecelja M, Chowienczyk P, 2012. Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis. 1.

Chainy GBN, Sahoo DK, 2020. Hormones and oxidative stress: an overview. Free Radic. Res 54, 1–26. [PubMed: 31868060]

Chang MC, Chung SM, Kwak SG, 2024. Exposure to perfluoroalkyl and polyfluoroalkyl substances and risk of stroke in adults: a meta-analysis. Rev. Environ. Health 39, 791–800. [PubMed: 37656598]

Chen H, Qiu W, Yang X, Chen F, Chen J, Tang L, et al. , 2022. Perfluorooctane Sulfonamide (PFOSA) Induces Cardiotoxicity via Aryl Hydrocarbon Receptor Activation in Zebrafish. Environ. Sci. Technol 56, 8438–8448. [PubMed: 35652794]

Chen JC, Baumert BO, Li Y, Li Y, Pan S, Robinson S, et al. , 2023. Associations of per- and polyfluoroalkyl substances, polychlorinated biphenyls, organochlorine pesticides, and polybrominated diphenyl ethers with oxidative stress markers: a systematic review and meta-analysis. Environ. Res 239, 117308. [PubMed: 37813138]

Chen Z, Yang T, Walker DI, Thomas DC, Qiu C, Chatzi L, et al. , 2020. Dysregulated lipid and fatty acid metabolism link perfluoroalkyl substances exposure and impaired glucose metabolism in young adults. Environ. Int 145, 106091. [PubMed: 32892005]

Christensen KY, Raymond M, Thompson BA, Anderson HA, 2016. Perfluoroalkyl substances in older male anglers in Wisconsin. Environ. Int 91, 312–318. [PubMed: 27003842]

Chung SM, Kim KH, Moon JS, Won KC, 2024. Association between mixed exposure to per- and polyfluoroalkyl substances and metabolic syndrome in Korean adults: Data from the Korean National environmental health survey cycle 4. Int J. Hyg. Environ. Health 261, 114427. [PubMed: 39032326]

Coperchini F, Croce L, Ricci G, Magri F, Rotondi M, Imbriani M, et al., 2020. Thyroid Disrupting Effects of Old and New Generation PFAS. Front Endocrinol. (Lausanne) 11, 612320.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Dale K, Yadetie F, Horvli T, Zhang X, Frøysa HG, Karlsen OA, et al. , 2022. Single PFAS and PFAS mixtures affect nuclear receptor- and oxidative stress-related pathways in precision-cut liver slices of Atlantic cod (Gadus morhua). Sci. Total Environ 814, 152732. [PubMed: 34974025]

Davidson LM, Boland MR, 2023. Investigating three classification methods for per/poly-fluoroalkyl substance (pfas) exposure from electronic health records and potential for bias. AMIA Jt Summits Transl. Sci. Proc 2023 52–61.

De Toni L, Radu CM, Sabovic I, Di Nisio A, Dall'Acqua S, Guidolin D, et al. , 2020. Increased cardiovascular risk associated with chemical sensitivity to perfluorooctanoic acid: role of impaired platelet aggregation. Int J. Mol. Sci 21.

Ding N, Karvonen-Gutierrez CA, Mukherjee B, Calafat AM, Harlow SD, Park SK, 2022. Per- and Polyfluoroalkyl Substances and Incident Hypertension in Multi-Racial/Ethnic Women: The Study of Women's Health Across the Nation. Hypertension 79, 1876–1886. [PubMed: 35695012]

Donat-Vargas C, Bergdahl IA, Tornevi A, Wennberg M, Sommar J, Koponen J, et al. , 2019. Associations between repeated measure of plasma perfluoroalkyl substances and cardiometabolic risk factors. Environ. Int 124, 58–65. [PubMed: 30639908]

Du B, Wang Q, Xu Z, Wang H, Li Z, Wu Y, et al. , 2024. Exploring the impact of prenatal perfluoroalkyl and polyfluoroalkyl substances exposure on blood pressure in early childhood: A longitudinal analysis. Ecotoxicol. Environ. Saf 274, 116220. [PubMed: 38513531]

Duan SY, Wu YF, Zhu JM, Wang X, Zhang YH, Gu CM, et al. , 2024. Development of interpretable machine learning models associated with environmental chemicals to predict all-cause and specific-cause mortality: A longitudinal study based on NHANES. Ecotoxicol. Environ. Saf 270, 9.

Dunder L, Salihovic S, Varotsis G, Lind PM, Elmståhl S, Lind L, 2023. Plasma levels of per- and polyfluoroalkyl substances (PFAS) and cardiovascular disease - Results from two independent population-based cohorts and a meta-analysis. Environ. Int 181, 108250. [PubMed: 37832261]

Ehrlich V, Bil W, Vandebriel R, Granum B, Luijten M, Lindeman B, et al. , 2023. Consideration of pathways for immunotoxicity of per- and polyfluoroalkyl substances (PFAS). Environ. Health 22, 19. [PubMed: 36814257]

Feng X, Long G, Zeng G, Zhang Q, Song B, Wu KH, 2022. Association of increased risk of cardiovascular diseases with higher levels of perfluoroalkylated substances in the serum of adults. Environ. Sci. Pollut. Res. Int 29, 89081–89092. [PubMed: 35849234]

Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, et al. , 2021. Per- and polyfluoroalkyl substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. Environ. Toxicol. Chem 40, 606–630. [PubMed: 33017053]

Ferrucci L, Fabbri E, 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol 15, 505–522. [PubMed: 30065258]

Fleury ES, Kuiper JR, Buckley JP, Papandonatos GD, Cecil KM, Chen A, et al. , 2024. Evaluating the association between longitudinal exposure to a PFAS mixture and adolescent cardiometabolic risk in the HOME Study. Environ. Epidemiol 8, e289. [PubMed: 38343730]

Francula-Zaninovic S, Nola IA, 2018. Management of Measurable Variable Cardiovascular Disease' Risk Factors. Curr. Cardiol. Rev 14, 153–163. [PubMed: 29473518]

Frostegård J., 2013. Immunity, atherosclerosis and cardiovascular disease. BMC Med 11, 117. [PubMed: 23635324]

Gao X, Ni W, Zhu S, Wu Y, Cui Y, Ma J, et al. , 2021. Per- and polyfluoroalkyl substances exposure during pregnancy and adverse pregnancy and birth outcomes: A systematic review and meta-analysis. Environ. Res 201, 111632. [PubMed: 34237336]

Geiger SD, Xiao J, Shankar A, 2014. No association between perfluoroalkyl chemicals and hypertension in children. Integr. Blood Press Control 7 1–7. [PubMed: 24520202]

Gilliland FD, Mandel JS, 1993. Mortality among employees of a perfluorooctanoic acid production plant. J. Occup. Med 35, 950–954. [PubMed: 8229349]

Goodrich JA, Alderete TL, Baumert BO, Berhane K, Chen Z, Gilliland FD, et al. , 2021. Exposure to perfluoroalkyl substances and glucose homeostasis in youth. Environ. Health Perspect 129, 97002. [PubMed: 34468161]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Gump BB, Hill DT, Robinson M, Kannan K, Heffernan K, Atallah-Yunes NH, et al. , 2023. Perfluoroalkyl substances (PFAS) and lead (Pb) as "cardiovascular disruptors" in 9-11-year-old children living in Syracuse, New York, United States. Environ. Res 236, 116758. [PubMed: 37532213]

Guo P, Furnary T, Vasiliou V, Yan Q, Nyhan K, Jones DP, et al. , 2022. Non-targeted metabolomics and associations with per- and polyfluoroalkyl substances (PFAS) exposure in humans: A scoping review. Environ. Int 162, 107159. [PubMed: 35231839]

He J, Zhu Z, Bundy JD, Dorans KS, Chen J, Hamm LL, 2021. Trends in Cardiovascular Risk Factors in US Adults by Race and Ethnicity and Socioeconomic Status, 1999–2018. Jama 326, 1286–1298. [PubMed: 34609450]

He Y, Hu C, Zhang Y, Fan X, Gao W, Fang J, et al. , 2023. Association of perfluoroalkyl and polyfluoroalkyl substances with sex hormones in children and adolescents 6-19 Years of age. Environ. Pollut 329, 121707. [PubMed: 37098366]

Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, et al. , 2016. Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. N. Engl. J. Med 374, 1221–1231. [PubMed: 27028912]

Honda-Kohmo K, Hutcheson R, Innes KE, Conway BN, 2019. Perfluoroalkyl substances are inversely associated with coronary heart disease in adults with diabetes. J. Diabetes Complicat 33, 407–412.

Houck KA, Patlewicz G, Richard AM, Williams AJ, Shobair MA, Smeltz M, et al. , 2021. Bioactivity profiling of per- and polyfluoroalkyl substances (PFAS) identifies potential toxicity pathways related to molecular structure. Toxicology 457, 152789. [PubMed: 33887376]

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

Hutcheson R, Innes K, Conway B, 2020. Perfluoroalkyl substances and likelihood of stroke in persons with and without diabetes. Diab Vasc. Dis. Res 17.

Inoue K, Goto A, Sugiyama T, Ramlau-Hansen CH, Liew Z, 2020. The Confounder-Mediator Dilemma: Should We Control for Obesity to Estimate the Effect of Perfluoroalkyl Substances on Health Outcomes? Toxics 8.

Jukema RA, Ahmed TAN, Tardif JC, 2019. Does low-density lipoprotein cholesterol induce inflammation? If so, does it matter? Current insights and future perspectives for novel therapies. BMC Med 17, 197. [PubMed: 31672136]

Kannel WB, McGee DL, 1979. Diabetes and cardiovascular disease. The Framingham study. Jama 241, 2035–2038. [PubMed: 430798]

Karmali KN, Lloyd-Jones DM, 2013. Adding a life-course perspective to cardiovascular-risk communication. Nat. Rev. Cardiol 10, 111–115. [PubMed: 23296067]

Khalil N, Ebert JR, Honda M, Lee M, Nahhas RW, Koskela A, et al. , 2018. Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8-12 year old children: A pilot study. Environ. Res 160, 314–321. [PubMed: 29040951]

Khalil N, Ducatman AM, Sinari S, Billheimer D, Hu C, Littau S, et al. , 2020. Per- and polyfluoroalkyl substance and cardio metabolic markers in firefighters. J. Occup. Environ. Med 62, 1076–1081. [PubMed: 33105404]

Khanna D, Khanna S, Khanna P, Kahar P, Patel BM, 2022. Obesity: a chronic low-grade inflammation and its markers. Cureus 14e22711.

Kjeldsen LS, Bonefeld-Jørgensen EC, 2013. Perfluorinated compounds affect the function of sex hormone receptors. Environ. Sci. Pollut. Res Int 20, 8031–8044. [PubMed: 23764977]

Koenig G, Seneff S, 2015. Gamma-Glutamyltransferase: A Predictive Biomarker of Cellular Antioxidant Inadequacy and Disease Risk. Dis. Markers 2015, 818570. [PubMed: 26543300]

Koshy TT, Attina TM, Ghassabian A, Gilbert J, Burdine LK, Marmor M, et al. , 2017. Serum perfluoroalkyl substances and cardiometabolic consequences in adolescents exposed to the World Trade Center disaster and a matched comparison group. Environ. Int 109, 128–135. [PubMed: 28890218]

Koskela A, Ducatman A, Schousboe JT, Nahhas RW, Khalil N, 2022. Perfluoroalkyl Substances and Abdominal Aortic Calcification. J. Occup. Environ. Med 64, 287–294. [PubMed: 35001069]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Lai TT, Eken Y, Wilson AK, 2020. Binding of Per- and Polyfluoroalkyl Substances to the Human Pregnane X Receptor. Environ. Sci. Technol 54, 15986–15995. [PubMed: 33228354]

Law HD, Armstrong BK, D'Este C, Hosking R, Smurthwaite KS, Trevenar S, et al. , 2023. Relative rates of cancers and deaths in Australian communities with PFAS environmental contamination associated with firefighting foams: A cohort study using linked data. Cancer Epidemiol. 82, 102296. [PubMed: 36508965]

Lazarevic N, Smurthwaite KS, D'Este C, Lucas RM, Armstrong B, Clements AC, et al. , 2023. Liver and cardiometabolic markers and conditions in a cross-sectional study of three Australian communities living with environmental per- and polyfluoroalkyl substances contamination. Environ. Res 226, 115621. [PubMed: 36898423]

Leary DB, Takazawa M, Kannan K, Khalil N, 2020. Perfluoroalkyl Substances and Metabolic Syndrome in Firefighters: A Pilot Study. J. Occup. Environ. Med 62, 52–57. [PubMed: 31658221]

Lejeune N, Rouxel E, Monfort C, Tillaut H, Rouget F, Costet N, et al. , 2025. Associations between prenatal exposure to PFAS and cardiometabolic health in preadolescents. Environ. Res 266, 120607. [PubMed: 39672492]

Li CY, Sung FC, 1999. A review of the healthy worker effect in occupational epidemiology. Occup. Med (Lond.) 49, 225–229. [PubMed: 10474913]

Li H, Chen J, Jingchao L, Yang J, Tan Z, Li L, et al. , 2023. Association of exposure to perfluoroalkyl substances and risk of the acute coronary syndrome: A case-control study in Shijiazhuang Hebei Province. Chemosphere 313, 137464. [PubMed: 36495974]

Li J, Ye S, Zhao Z, Xue Z, Ren S, Guan Y, et al. , 2024. Association of PFDeA exposure with hypertension (NHANES, 2013-2018). Sci. Rep 14, 918. [PubMed: 38195691]

Li L, Guo Y, Ma S, Wen H, Li Y, Qiao J, 2024. Association between exposure to per- and perfluoroalkyl substances (PFAS) and reproductive hormones in human: A systematic review and meta-analysis. Environ. Res 241, 117553. [PubMed: 37931739]

Li N, Liu Y, Papandonatos GD, Calafat AM, Eaton CB, Kelsey KT, et al. , 2021. Gestational and childhood exposure to per- and polyfluoroalkyl substances and cardiometabolic risk at age 12 years. Environ. Int 147.

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

Liao S, Yao W, Cheang I, Tang X, Yin T, Lu X, et al. , 2020. Association between perfluoroalkyl acids and the prevalence of hypertension among US adults. Ecotoxicol. Environ. Saf 196, 110589. [PubMed: 32278136]

Liberda EN, Zuk AM, Tsuji LJS, 2019. Complex contaminant mixtures and their associations with intima-media thickness. BMC Cardiovasc Disord. 19, 289. [PubMed: 31830904]

Lin CY, Lin LY, Wen TW, Lien GW, Chien KL, Hsu SH, et al. , 2013. Association between levels of serum perfluorooctane sulfate and carotid artery intima-media thickness in adolescents and young adults. Int J. Cardiol 168, 3309–3316. [PubMed: 23664439]

Lin CY, Chen PC, Lo SC, Torng PL, Sung FC, Su TC, 2016. The association of carotid intima-media thickness with serum Level of perfluorinated chemicals and endothelium-platelet microparticles in adolescents and young adults. Environ. Int 94, 292–299. [PubMed: 27288966]

Lin CY, Lee HL, Hwang YT, Su TC, 2020. The association between total serum isomers of per- and polyfluoroalkyl substances, lipid profiles, and the DNA oxidative/nitrative stress biomarkers in middle-aged Taiwanese adults. Environ. Res 182, 109064. [PubMed: 31884197]

Lin CY, Lee HL, Chen CW, Wang C, Sung FC, Su TC, 2022. Global DNA methylation mediates the association between serum perfluorooctane sulfonate and carotid intima-media thickness in young and middle-aged Taiwanese populations. Ecotoxicol. Environ. Saf 241, 113782. [PubMed: 35753273]

Lin N, Zhang Y, Su S, Feng Y, Wang B, Li Z, 2023. Exposure characteristics of legacy and novel per- and polyfluoroalkyl substances in blood and association with hypertension among low-exposure population. J. Hazard Mater 459, 132185. [PubMed: 37531760]

Lin PD, Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, et al. , 2020. Per- and polyfluoroalkyl substances and blood pressure in pre-diabetic adults-cross-sectional and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

longitudinal analyses of the diabetes prevention program outcomes study. Environ. Int 137, 105573. [PubMed: 32088543]

Lind PM, Salihovic S, van Bavel B, Lind L, 2017. Circulating levels of perfluoroalkyl substances (PFASs) and carotid artery atherosclerosis. Environ. Res 152, 157–164. [PubMed: 27771570]

Lind PM, Salihovic S, Stubleski J, Kärrman A, Lind L, 2018. Changes in plasma levels of perfluoroalkyl substances (PFASs) are related to increase in carotid intima-media thickness over 10 years - a longitudinal study. Environ. Health 17, 59. [PubMed: 29970113]

Liu B, Zhu L, Wang M, Sun Q, 2023. Associations between Per- and Polyfluoroalkyl Substances Exposures and Blood Lipid Levels among Adults-A Meta-Analysis. Environ. Health Perspect 131, 56001. [PubMed: 37141244]

Liu S, Liu J, Wang Y, Deng F, Deng Z, 2025. Oxidative Stress: Signaling Pathways, Biological Functions, and Disease. MedComm 6 (2020).

Liu SH, Chen Y, Feuerstahler L, Chen A, Starling A, Dabelea D, et al. , 2024. The U.S. PFAS exposure burden calculator for 2017-2018: Application to the HOME Study, with comparison of epidemiological findings from NHANES. Neurotoxicol Teratol. 102, 107321. [PubMed: 38224844]

Lopez-Espinosa MJ, Mondal D, Armstrong BG, Eskenazi B, Fletcher T, 2016. Perfluoroalkyl Substances, Sex Hormones, and Insulin-like Growth Factor-1 at 6-9 Years of Age: A Cross-Sectional Analysis within the C8 Health Project. Environ. Health Perspect 124, 1269–1275. [PubMed: 26794451]

Ma S, Xu C, Ma J, Wang Z, Zhang Y, Shu Y, et al. , 2019. Association between perfluoroalkyl substance concentrations and blood pressure in adolescents. Environ. Pollut 254, 112971. [PubMed: 31394346]

Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, Ballester F, Iñiguez C, Martinez D, et al. , 2017. Prenatal Exposure to Perfluoroalkyl Substances and Cardiometabolic Risk in Children from the Spanish INMA Birth Cohort Study. Environ. Health Perspect 125, 097018. [PubMed: 28934720]

Mao Z, Chen Y, Li H, Lu Q, Zhou K, 2024. TLR4 as a Potential Target of Me-PFOSA-AcOH Leading to Cardiovascular Diseases: Evidence from NHANES 2013-2018 and Molecular Docking. Toxics 12.

Maranhao Neto GA, Polcrova AB, Pospisilova A, Blaha L, Klanova J, Bobak M, et al. , 2022. Associations between Per- and Polyfluoroalkyl Substances (PFAS) and Cardiometabolic Biomarkers in Adults of Czechia: The Kardiovize Study. Int J. Environ. Res Public Health 19.

Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P, 2018. Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. Eur. J. Public Health 28, 180–185. [PubMed: 28541558]

Mattsson K, Rignell-Hydbom A, Holmberg S, Thelin A, Jönsson BA, Lindh CH, et al. , 2015. Levels of perfluoroalkyl substances and risk of coronary heart disease: Findings from a population-based longitudinal study. Environ. Res 142, 148–154. [PubMed: 26142720]

Mi X, Yang YQ, Zeeshan M, Wang ZB, Zeng XY, Zhou Y, et al. , 2020. Serum levels of per- and polyfluoroalkyl substances alternatives and blood pressure by sex status: Isomers of C8 health project in China. Chemosphere 261, 127691. [PubMed: 32717511]

Min JY, Lee KJ, Park JB, Min KB, 2012. Perfluorooctanoic acid exposure is associated with elevated homocysteine and hypertension in US adults. Occup. Environ. Med 69, 658–662. [PubMed: 22652006]

Mitro SD, Sagiv SK, Fleisch AF, Jaacks LM, Williams PL, Rifas-Shiman SL, et al. , 2020. Pregnancy Per- and Polyfluoroalkyl Substance Concentrations and Postpartum Health in Project Viva: A Prospective Cohort. J. Clin. Endocrinol. Metab 105, e3415–e3426. [PubMed: 32620010]

Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. , 2016. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. PLoS One 11, e0147601. [PubMed: 26808317]

Mozaffarian D, Wilson PW, Kannel WB, 2008. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. Circulation 117, 3031–3038. [PubMed: 18541753]

Mullur R, Liu YY, Brent GA, 2014. Thyroid hormone regulation of metabolism. Physiol. Rev 94, 355–382. [PubMed: 24692351]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ndrepepa G, Kastrati A, 2016. Gamma-glutamyl transferase and cardiovascular disease. Ann. Transl. Med 4, 481. [PubMed: 28149843]

Nilsson S, Smurthwaite K, Aylward LL, Kay M, Toms LM, King L, et al. , 2022. Associations between serum perfluoroalkyl acid (PFAA) concentrations and health related biomarkers in firefighters. Environ. Res 215, 114370. [PubMed: 36174755]

Ojo AF, Xia Q, Peng C, Ng JC, 2021. Evaluation of the individual and combined toxicity of perfluoroalkyl substances to human liver cells using biomarkers of oxidative stress. Chemosphere 281, 130808. [PubMed: 34022600]

Omoike OE, Pack RP, Mamudu HM, Liu Y, Strasser S, Zheng S, et al. , 2021. Association between per and polyfluoroalkyl substances and markers of inflammation and oxidative stress. Environ. Res 196, 110361. [PubMed: 33131681]

Osorio-Yáñez C, Sanchez-Guerra M, Cardenas A, Lin PD, Hauser R, Gold DR, et al. , 2021. Per- and polyfluoroalkyl substances and calcifications of the coronary and aortic arteries in adults with prediabetes: Results from the diabetes prevention program outcomes study. Environ. Int 151, 106446. [PubMed: 33631604]

Palaniyandi J, Bruin JE, Kumarathasan P, MacPherson S, Borghese MM, Ashley-Martin J, 2023. Prenatal exposure to perfluoroalkyl substances and inflammatory biomarker concentrations. Environ. Epidemiol 7, e262. [PubMed: 37545803]

Pan K, Xu J, Long X, Yang L, Huang Z, Yu J, 2023. The relationship between perfluoroalkyl substances and hypertension: A systematic review and meta-analysis. Environ. Res 232, 116362. [PubMed: 37295593]

Panikkar B, Lemmond B, Allen L, DiPirro C, Kasper S, 2019. Making the invisible visible: results of a community-led health survey following PFAS contamination of drinking water in Merrimack, New Hampshire. Environ. Health 18, 79. [PubMed: 31470871]

Pederick JL, Frkic RL, McDougal DP, Bruning JB, 2024. A structural basis for the activation of peroxisome proliferator-activated receptor gamma (PPARγ) by perfluorooctanoic acid (PFOA). Chemosphere 354, 141723. [PubMed: 38494006]

Pitter G, Zare Jeddi M, Barbieri G, Gion M, Fabricio ASC, Daprà F, et al. , 2020. Perfluoroalkyl substances are associated with elevated blood pressure and hypertension in highly exposed young adults. Environ. Health 19, 102. [PubMed: 32958007]

Prince N, Begum S, Mínguez-Alarcón L, Génard-Walton M, Huang M, Soeteman DI, et al. , 2023. Plasma concentrations of per- and polyfluoroalkyl substances are associated with perturbations in lipid and amino acid metabolism. Chemosphere 324, 138228. [PubMed: 36878362]

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

Raleigh KK, Alexander BH, Olsen GW, Ramachandran G, Morey SZ, Church TR, et al. , 2014. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. Occup. Environ. Med 71, 500–506. [PubMed: 24832944]

Rexrode KM, Manson JE, Lee IM, Ridker PM, Sluss PM, Cook NR, et al. , 2003. Sex hormone levels and risk of cardiovascular events in postmenopausal women. Circulation 108, 1688–1693. [PubMed: 12975257]

Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E, 2008. The antioxidant properties of serum albumin. FEBS Lett. 582, 1783–1787. [PubMed: 18474236]

Rodríguez-Carrillo A, Remy S, Koppen G, Wauters N, Freire C, Olivas-Martínez A, et al. , 2023. PFAS association with kisspeptin and sex hormones in teenagers of the HBM4EU aligned studies. Environ. Pollut 335, 122214. [PubMed: 37482334]

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

Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. , 2020. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J. Am. Coll. Cardiol 76, 2982–3021. [PubMed: 33309175]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Saito Y, Tanaka A, Node K, Kobayashi Y, 2021. Uric acid and cardiovascular disease: A clinical review. J. Cardiol 78, 51–57. [PubMed: 33388217]

Sakr CJ, Symons JM, Kreckmann KH, Leonard RC, 2009. Ischaemic heart disease mortality study among workers with occupational exposure to ammonium perfluorooctanoate. Occup. Environ. Med 66, 699–703. [PubMed: 19553230]

Savitz DA, Wellenius GA, 2023. Can Cross-Sectional Studies Contribute to Causal Inference? It Depends. Am. J. Epidemiol 192, 514–516. [PubMed: 35231933]

Schillemans T, Donat-Vargas C, Lindh CH, de Faire U, Wolk A, Leander K, et al. , 2022. Per- and Polyfluoroalkyl Substances and Risk of Myocardial Infarction and Stroke: A Nested Case-Control Study in Sweden. Environ. Health Perspect 130, 37007. [PubMed: 35285690]

Schlezinger JJ, Gokce N, 2024. Perfluoroalkyl/polyfluoroalkyl substances: links to cardiovascular disease risk. Circ. Res 134, 1136–1159. [PubMed: 38662859]

Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. , 2018. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. Circulation 137, 2166–2178. [PubMed: 29760227]

Shankar A, Xiao J, Ducatman A, 2012. Perfluorooctanoic acid and cardiovascular disease in US adults. Arch. Intern Med 172, 1397–1403.

Shi G, Guo H, Sheng N, Cui Q, Pan Y, Wang J, et al. , 2018. Two-generational reproductive toxicity assessment of 6:2 chlorinated polyfluorinated ether sulfonate (F-53B, a novel alternative to perfluorooctane sulfonate) in zebrafish. Environ. Pollut 243, 1517–1527. [PubMed: 30292160]

Shimobayashi M, Albert V, Woelnerhanssen B, Frei IC, Weissenberger D, Meyer-Gerspach AC, et al. , 2018. Insulin resistance causes inflammation in adipose tissue. J. Clin. Invest 128, 1538–1550. [PubMed: 29528335]

Simpson C, Winquist A, Lally C, Steenland K, 2013. Relation between perfluorooctanoic acid exposure and strokes in a large cohort living near a chemical plant. Environ. Res 127, 22–28. [PubMed: 24199934]

Sing CF, Stengård JH, Kardia SL, 2003. Genes, environment, and cardiovascular disease. Arterioscler. Thromb. Vasc. Biol 23, 1190–1196. [PubMed: 12730090]

Steenland K, Woskie S, 2012. Cohort mortality study of workers exposed to perfluorooctanoic acid. Am. J. Epidemiol 176, 909–917. [PubMed: 23079607]

Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG, 2019. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. J. Expo. Sci. Environ. Epidemiol 29, 131–147. [PubMed: 30470793]

Taibl KR, Schantz S, Aung MT, Padula A, Geiger S, Smith S, et al. , 2022. Associations of per- and polyfluoroalkyl substances (PFAS) and their mixture with oxidative stress biomarkers during pregnancy. Environ. Int 169, 107541. [PubMed: 36191484]

Tan Y, Taibl KR, Dunlop AL, Barr DB, Panuwet P, Yakimavets V, et al. , 2023. Association between a Mixture of Per- and Polyfluoroalkyl Substances (PFAS) and Inflammatory Biomarkers in the Atlanta African American Maternal-Child Cohort. Environ. Sci. Technol 57, 13419–13428. [PubMed: 37649345]

Tang L, Qiu W, Zhang S, Wang J, Yang X, Xu B, et al. , 2023. Poly- and Perfluoroalkyl Substances Induce Immunotoxicity via the TLR Pathway in Zebrafish: Links to Carbon Chain Length. Environ. Sci. Technol 57, 6139–6149. [PubMed: 37017313]

Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, et al. , 2019. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. Eur. Cardiol 14, 50–59. [PubMed: 31131037]

Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. , 2012. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J. Hypertens 30, 445–448. [PubMed: 22278144]

Van Gaal LF, Mertens IL, De Block CE, 2006. Mechanisms linking obesity with cardiovascular disease. Nature 444, 875–880. [PubMed: 17167476]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Vinggaard AM, Bonefeld-Jørgensen EC, Jensen TK, Fernandez MF, Rosenmai AK, Taxvig C, et al. , 2021. Receptor-based in vitro activities to assess human exposure to chemical mixtures and related health impacts. Environ. Int 146, 106191. [PubMed: 33068852]

Wada T, Gao J, Xie W, 2009. PXR and CAR in energy metabolism. Trends Endocrinol. Metab 20, 273–279. [PubMed: 19595610]

Wang J, Du B, Wu Y, Li Z, Wang H, Niu Y, et al. , 2023. Maternal plasma perfluoroalkyl substances concentrations in early pregnancy and cardiovascular development in offspring: A prospective cohort study. Environ. Int 173, 107748. [PubMed: 36848830]

Wang Y, Chang W, Wang L, Zhang Y, Zhang Y, Wang M, et al. , 2019. A review of sources, multimedia distribution and health risks of novel fluorinated alternatives. Ecotoxicol. Environ. Saf 182, 109402. [PubMed: 31280095]

Wang Y, Aimuzi R, Nian M, Zhang Y, Luo K, Zhang J, 2021. Perfluoroalkyl substances and sex hormones in postmenopausal women: NHANES 2013–2016. Environ. Int 149, 106408. [PubMed: 33548847]

Wang Z, DeWitt JC, Higgins CP, Cousins IT, 2017. A Never-Ending Story of Per- and Polyfluoroalkyl Substances (PFASs)? Environ. Sci. Technol 51, 2508–2518. [PubMed: 28224793]

Ward-Caviness CK, Moyer J, Weaver A, Devlin R, Diaz-Sanchez D, 2022. Associations between PFAS occurrence and multimorbidity as observed in an electronic health record cohort. Environ. Epidemiol 6, e217. [PubMed: 35975166]

Warembourg C, Maitre L, Tamayo-Uria I, Fossati S, Roumeliotaki T, Aasvang GM, et al. , 2019. Early-Life Environmental Exposures and Blood Pressure in Children. J. Am. Coll. Cardiol 74, 1317–1328. [PubMed: 31488269]

Wei C, Zhang W, Chen J, He Q, Cao L, Zhang P, et al. , 2023. Systematic analysis between inflammation-related index and sex hormones in American adults: cross-sectional research based NHANES 2013-2016. Front Immunol. 14, 1175764. [PubMed: 37304307]

Wei Z, Wei K, Yang M, Ying M, Yin Z, Wang N, et al. , 2024. Kidney function mediates the effects of four per-and polyfluoroalkyl substances (PFAS) on atherosclerotic cardiovascular disease. Ecotoxicol. Environ. Saf 288, 117395. [PubMed: 39608156]

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. 2009. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available: ⟨https://ohri.ca/en/who-we-are/core-facilities-and-platforms/ottawa-methods-centre/newcastle-ottawa-scale⟩.

Wen X, Wang M, Xu X, Li T, 2022. Exposure to per- and polyfluoroalkyl substances and mortality in U.S. adults: a population-based cohort study. Environ. Health Perspect 130, 67007. [PubMed: 35731224]

Wen ZJ, Wei YJ, Zhang YF, Zhang YF, 2023. A review of cardiovascular effects and underlying mechanisms of legacy and emerging per- and polyfluoroalkyl substances (PFAS). Arch. Toxicol 97, 1195–1245. [PubMed: 36947184]

Wielsøe M, Long M, Ghisari M, Bonefeld-Jørgensen EC, 2015. Perfluoroalkylated substances (PFAS) affect oxidative stress biomarkers in vitro. Chemosphere 129, 239–245. [PubMed: 25455676]

Winquist A, Steenland K, 2014. Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. Environ. Health Perspect 122, 1299–1305. [PubMed: 25260175]

Winquist A, Lally C, Shin HM, Steenland K, 2013. Design, methods, and population for a study of PFOA health effects among highly exposed mid-Ohio valley community residents and workers. Environ. Health Perspect 121, 893–899. [PubMed: 23735518]

Wittkopp S, Wu F, Windheim J, Robinson M, Kannan K, Katz SD, et al. , 2022. Vascular endothelium as a target for perfluroalkyl substances (PFAs). Environ. Res 212, 113339. [PubMed: 35447152]

Wu B, Sheng N, Li Z, Wang J, Ji S, Zhao F, et al. , 2024. Positive Associations of Perfluoroalkyl and Polyfluoroalkyl Substances With Hypertension May Be Attenuated by Endogenous Sex Hormones: A Nationally Representative Cross-Sectional Study. Hypertension 81, 1799–1810. [PubMed: 38853753]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Wu M, Zhu Z, Wan R, Xu J, 2024. Exposure to per- and polyfluoroalkyl substance and metabolic syndrome: A nationally representative cross-sectional study from NHANES, 2003-2018. Environ. Pollut 346, 123615. [PubMed: 38402937]

Xiao F, An Z, Lv J, Sun X, Sun H, Liu Y, et al. , 2023. Association between per- and polyfluoroalkyl substances and risk of hypertension: a systematic review and meta-analysis. Front Public Health 11, 1173101. [PubMed: 37655293]

Xiao W, Jian G, Ma F, Li H, Yang X, Zhang H, et al. , 2024. Exposure to specific polyfluoroalkyl chemicals is associated with cardiovascular disease in US adults: a population-based study. Front Cardiovasc Med 11, 1487956. [PubMed: 39850378]

Xu Z, Du B, Wang H, Li Z, Wu Y, Wang Q, et al. , 2023. Perfluoroalkyl substances in umbilical cord blood and blood pressure in offspring: a prospective cohort study. Environ. Health 22, 72. [PubMed: 37858165]

Yang J, Zhang K, Shen C, Tang P, Tu S, Li J, et al. , 2023. The Association of Hypertension with Perfluoroalkyl and Polyfluoroalkyl Substances. Int Heart J. 64, 1079–1087. [PubMed: 37967990]

Yang J, Wang T, Li K, Wäng Y, 2024. Associations between per- and polyfluoroalkyl chemicals and abdominal aortic calcification in middle-aged and older adults. J. Adv. Res

Yang Q, Guo X, Sun P, Chen Y, Zhang W, Gao A, 2018. Association of serum levels of perfluoroalkyl substances (PFASs) with the metabolic syndrome (MetS) in Chinese male adults: A cross-sectional study. Sci. Total Environ 621, 1542–1549. [PubMed: 29054655]

Ye WL, Chen ZX, Xie YQ, Kong ML, Li QQ, Yu S, et al. , 2021. Associations between serum isomers of perfluoroalkyl acids and metabolic syndrome in adults: Isomers of C8 Health Project in China. Environ. Res 196.

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

Yu S, Feng WR, Liang ZMA, Zeng XY, Bloom MS, Hu GC, et al. , 2021. Perfluorooctane sulfonate alternatives and metabolic syndrome in adults: New evidence from the Isomers of C8 Health Project in China. Environ. Pollut 283.

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. , 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364, 937–952. [PubMed: 15364185]

Zare Jeddi M, Dalla Zuanna T, Barbieri G, Fabricio ASC, Daprà F, Fletcher T, et al. , 2021. Associations of Perfluoroalkyl Substances with Prevalence of Metabolic Syndrome in Highly Exposed Young Adult Community Residents-A Cross-Sectional Study in Veneto Region, Italy. Int J. Environ. Res Public Health 18.

Zhang H, Shen L, Fang W, Zhang X, Zhong Y, 2021. Perfluorooctanoic acid-induced immunotoxicity via NF-kappa B pathway in zebrafish (Danio rerio) kidney Fish. Shellfish Immunol 113, 9–19.

Zhang L, Louie A, Rigutto G, Guo H, Zhao Y, Ahn S, et al. , 2023. A systematic evidence map of chronic inflammation and immunosuppression related to per- and polyfluoroalkyl substance (PFAS) exposure. Environ. Res 220, 115188. [PubMed: 36592815]

Zhang M, Aris IM, Lin PD, Rifas-Shiman SL, Brady TM, James-Todd T, et al. , 2023. Prenatal and Childhood Per- and Polyfluoroalkyl Substance (PFAS) Exposures and Blood Pressure Trajectories From Birth to Late Adolescence in a Prospective US Prebirth Cohort. J. Am. Heart Assoc 12, e030760. [PubMed: 37642023]

Zhang Z, Wang F, Zhang Y, Yao J, Bi J, He J, et al. , 2022. Associations of serum PFOA and PFOS levels with incident hypertension risk and change of blood pressure levels. Environ. Res 212, 113293. [PubMed: 35427595]

Zheng H, Yin Z, Luo X, Zhou Y, Zhang F, Guo Z, 2023. Association of per- and polyfluoroalkyl substance exposure with metabolic syndrome and its components in adults and adolescents. Environ. Sci. Pollut. Res Int 30, 112943–112958. [PubMed: 37845597]

Zhu J, Qian W, Wang Y, Gao R, Wang J, Xiao H, 2015. Involvement of mitogen-activated protein kinase and NF-κB signaling pathways in perfluorooctane sulfonic acid-induced inflammatory reaction in BV2 microglial cells. J. Appl. Toxicol 35, 1539–1549. [PubMed: 25677194]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Zhu L, Liu B, Hu Y, Wang M, Furtado JD, Rimm EB, et al. , 2024. Per- and polyfluoroalkyl substances, apolipoproteins and the risk of coronary heart disease in US men and women. Environ. Health 23, 108. [PubMed: 39627728]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

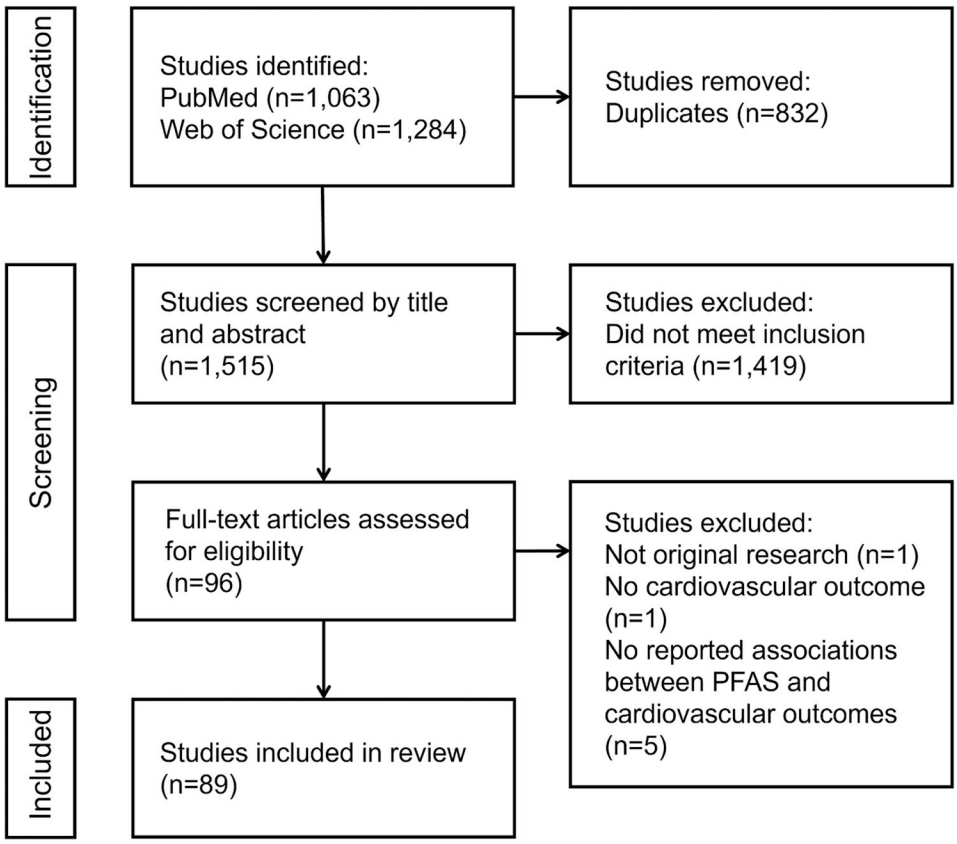

Fig. 1.
Flowchart showing the study selection and screening process.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Number of epidemiological studies reporting associations between PFAS exposure and cardiovascular outcomes[a].

Pollutant	CVD morbidity and mortality				Blood pressure / hypertension				Atherosclerosis				Arterial stiffness			
	Total	↑	↓	→	Total	↑	↓	→	Total	↑	↓	→	Total	↑	↓	→
PFOA	26	10	5	11	42	17	2	23	11	2		9	3	1		2
PFOS	18	8	2	8	40	17	6	18	11	5	1	5	3			3
PFHxS	16	1	3	12	35	9	3	23	9	2	1	6	3			3
PFNA	13	3	1	9	35	7	2	26	10	1		9	3	1		2
PFDA	10	2		8	19	3	1	15	6	3	1	2	3			3
PFUnDA	8	4	1	3	16		1	15	6	2	2	2	2			2
PFHpA	5	2		3	8	4		4	3	1		2	1	1		
MeFOSAA	3	3			5	3		2	2			2				
PFDoA	3	1		2	5	3		2	1			1				
PFBS	2	1		1	4	1		3	1			1	1			1
PFHpS	2			2	5	1		4								
APFO	2		1	1												
PFOSA	1	1			1			1	2	2						
EtFOSAA	1	1			4	2	2	1	1	1						
PFSA	1			1												
6:2 Cl-PFESA					4	2	1	1								
PFHxA					2	2							1			1
8:2 Cl-PFESA					2	2										
PFTrA					2		1	1								
PFBA					1	1										
PFDS					1	1										
PFPA					1	1										
PFTeA					1			1								
PFPeA													1	1		
Total PFAS	8	6	1	1	6	3		3	2	1		1				
PFAS mixture	5	3		2	14	7	1	6	3	1	1	1	1	1		

[a]. Values indicate the number of studies reporting positive (↑), negative (↓), or null (→) associations for each PFAS-outcome pair.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Abbreviations: APFO, ammonium perfluorooctanoate; Cl-PFESA, chlorinated polyfluoroalkyl ether sulfonate; CVD, cardiovascular disease; EtFOSAA, 2-(N-Ethyl-perfluorooctanesulfonamido)acetic acid; MeFOSAA, 2-(N-Methylperfluorooctanesulfonamido)acetic acid; PFAS, per- and polyfluoroalkyl substances; PFBA, perfluorobutanoic acid; PFBS, perfluorobutanesulfonic acid; PFDA, perfluorodecanoic acid; PFDoA, perfluorododecanoic acid; PFDS, perfluorodecanesulfonic acid; PFHpA, perfluoroheptanoic acid; PFHpS, perfluoroheptanesulfonic acid; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PFOSA, perfluorooctane sulfonamide; PFPA, perfluorophosphonic acid; PFPeA, perfluoropentanoic acid; PFTeA, perfluorotetradecanoic acid; PFTrA, perfluorotridecanoic acid; PFUnDA, perfluoroundecanoic acid.