Review Article

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To which extent are per-and poly-fluorinated substances associated to metabolic syndrome?

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Abstract: Exposure to per- and polyfluoroalkyl substances (PFAS), ubiquitous persistent environmental contaminants, has led to substantial global concern due to their potential environmental and human health effects. Several epidemiological studies have assessed the possible association between PFAS exposure and risk of metabolic syndrome (MetS), however, the results are ambiguous. The aim of this study was to assess the current human epidemiologic evidence on the association between exposure to PFAS and MetS. We performed a systematic search strategy using three electronic databases (PubMed, Scopus, and Web of Science) for relevant studies concerning the associations of PFAS with MetS and its clinical relevance from inception until January 2021. We undertook meta-analyses where there were five or more studies with exposure and outcomes assessments that were reasonably comparable. The pooled odd ratios (ORs) were calculated using random effects models and heterogeneity among studies was assessed by I2 index and Q test. A total of 12 cross-sectional studies (10 studies on the general population and two studies in the occupational settings) investigated the association between PFAS exposure and MetS. We pooled data from seven studies on the general population for perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) and five studies for perfluorohexanesulfonate (PFHxS) and perfluorononanoic acid (PFNA). Predominately, most studies reported no statistically significant association between concentrations of PFAS and MetS. In the meta-analysis, the overall measure of effect was not statistically significant, showing no evidence of an association between concentrations of PFOA, PFOS, PFNA, and PFHxS and the risk of MetS. Based on the results of the meta-analysis, current small body of evidence does not support association between PFAS and MetS. However, due to limited number of studies and substantial heterogeneity, results should be interpreted with caution. Further scrutinizing cohort studies are needed to evaluate the association between various and less well-known PFAS substances and their mixture with MetS and its components in both adults and children in different settings.

Keywords: cardiometabolic risk factors; forever chemicals; insulin resistance; metabolic outcome; systematic review.

Introduction

Per- and polyfluoroalkyl substances (PFAS) have become a serious global concern due to their ubiquitous presence in the environmental. PFAS have a carbon backbone with one or more fluorine substitutions and functional end groups which provide specific properties. The extremely strong carbon-fluorine bond, results in high chemical, thermal and biological stability of PFAS. Structurally diverse PFAS are used in a wide variety of commercial products and industrial applications since the 1940s and can be found in everyday household products [1]. Direct exposure to PFAS in humans can occur through eating and drinking contaminated food and water, household dust or via occupational related exposure [2]. Once absorbed, PFAS do not appear to undergo metabolism in the liver or other tissues and can persist in the body by binding to liver and serum proteins. Important routes of elimination include

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urinary and biliary excretion, with urinary excretion generally considered to be predominating for most PFAS compounds [3]. There are substantial differences in PFAS elimination rates between humans, and animals (monkeys, and rodents) with longer half-lives found in humans ranging from 1 to 10 years [4].

In recent years, a growing number of scientific reports have indicated a wide range of potential health effect of PFAS exposure in both humans and animals [5–8]. Certain PFAS are suspected endocrine disruptors and are increasingly linked to metabolic, immune, reproductive and developmental toxicity and carcinogenicity [6, 9–11]. To date, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), exposure has been evidently associated with altered cholesterol levels [7], while the associations are still inconclusive for other adverse health outcomes [5, 7, 12–14].

Metabolic syndrome (MetS) is a cluster of interconnected physiological, biochemical, clinical and metabolic factors [15]. MetS is also known as Insulin Resistance Syndrome, Syndrome X, and the deadly quartet. The constellation of metabolic abnormalities becomes a syndrome if the patient has any three of the following MetS-related traits: abdominal obesity, hypertension, dyslipidemia (elevated triglycerides [TG] and/or reduced high-density lipoprotein cholesterol [HDL-C]), and hyperglycemia [16, 17].

There is ongoing debate and dispute as to whether there is a common underlying aetiology that could trigger this clustering of cardiometabolic risk factors, considering the link between toxic environmental exposures and development of MetS. Therefore, prompted by the worldwide exposure to PFAS and the essential role of the MetS as responsible for large health and socio-economic costs in most nations, with performing a systematic review, we aimed to assess the evidence of associations between exposure to PFAS and metabolic syndrome.

Materials and methods

Eligibility criteria and search strategy

Our objective was to answer the question: "Is exposure to PFAS associated with MetS in humans?" We developed a participants, exposure, comparator, and outcomes (PECO) statement, which we used as an aid to develop an answerable question [18]. Our PECO statement included the following:

- Participants: humans, studies on general or occupational populations were both eligible.
- Exposures: studies on direct measurement of PFAS levels in a biological matrix not indirect exposure estimation.
- Comparators: continuous PFAS levels or groups categorized according to individual PFAS levels (i.e., a comparison across a range of exposures).
- Outcomes: effects on combination of traits known as MetS including abdominal obesity, hypertension, elevated TG, reduced HDL-C, and hyperglycemia.

We iteratively developed a comprehensive search strategy protocol and performed a systematic review in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19]. An electronic search of the PubMed, Scopus, and Web of Science databases was performed. The initial database searches were conducted on January 2020, and updated on January 2021 to capture any population with any epidemiologic study design and any publication language. The search was supplemented by manually reviewing the reference lists from review articles. We used Boolean logic with search terms including a combination of relevant subject headings and text words for MetS and PFAS. We used controlled vocabularies (e.g., medical subject heading terms) to identify synonyms. More details about search syntax can be found in Supplementary data (Table S1).

Study selection

The first content-relevant screening based on title and abstract of the search results was independently conducted by two authors (R.S. and T.D.Z.) to determine whether a reference met the inclusion criteria. Following this process, all the retained records progressed to literature retrieval, where full-text versions located and imported for full-text eligibility screening. In the case of discrepant results between the initial two reviewers, a third author was consulted (M.Z.J.) to discuss and decide on the status (include/exclude) of each discrepancy.

Ineligible document type including review articles, editorials, case reports, and studies only reporting methodology for chemical analyses and identification were excluded.

Assessment of the methodological quality of the articles

A validated tool to evaluate the methodological quality of observational studies is still lacking. We assessed the methodological quality of the studies using a modified version of the Newcastle Ottawa Scale, for cross-sectional studies [20]. For more information see Supplementary data, Table S2.

Data collection

Two investigators independently reviewed and extracted data into standard forms to facilitate data-charting, data synthesis, and results reporting (R.S. and T.D.Z.). Errors in data extraction were resolved by a joint review of the original articles. We extracted each study's investigators, years of conduct, design, setting, population, study size, PFAS studied, methods for assessing PFAS exposure, MetS definition, time of sample collection, statistical analyses, covariates included in the models and major findings.

Data analyses and statistical methods

Focusing on data points with the incidence or prevalence of MetS as the outcome, a meta-analysis was conducted to assess the strength of the association of MetS outcomes with PFAS serum concentrations. The MetS components were described in the findings of individual studies but were not subjected to further meta-analysis. We undertook meta-analysis where there were five or more studies with exposure and outcomes assessments that were reasonably comparable. Therefore the meta-analysis was restricted to the general population because there were an inadequate number of papers (two studies) in occupational settings with comparable outcome measures for inclusion in a meta-analysis.

A random effect model was used to summarize Odds-Ratios (OR) (risk of MetS by one natural log [ln-] unit increase of each PFAS) and the study variance τ^2 was estimated using the DerSimonian and Laird procedure [21]. Therefore, pooled OR was provided using forest plots and estimated using inverse variance weighting. Heterogeneity between studies was determined with Higgins' I^2 statistic and evaluated through Cochran's Q test which describes the proportion of total variation in study estimates that is due to heterogeneity. Heterogeneity was considered statistically significant at $p<0.05$ of the Chi square test, and substantial heterogeneity was defined as $I^2>60\%$.

The potential for publication bias using a funnel plot analysis was not assessed due to limited number of studies per meta-analysis [22].

Sensitivity analyses were conducted to examine a range of factors in the review decision-making process that may impact the robustness of the meta-analytic results. All meta-analyses were undertaken using fixed effects as sensitivity analysis. In addition, we checked the changes in the results by including one specific study [23] with the linear and branched isomers of PFOA and PFOS to examine the stability or strength of the results.

All analyses were conducted with STATA 13 (StataCorp, College Station, TX, USA), using a suite of meta-analysis commands. Type I error was set at 0.05 for all measures of association.

Results

Two thousand six hundred and four studies were screened and assessed for eligibility, leaving 97 articles for examination of the full texts. Of these, 84 were later excluded because they did not meet the inclusion criteria. Hence, we identified 10 eligible studies on the general population and two studies in the occupational settings from the literature searches (Figure 1). A description of the epidemiologic studies is summarized in Table 1. All of the selected studies were cross-sectional studies, and were conducted in Asia, Europe and North America. The sample size of each study varied from around 47 to 15,876 participants. Most of the studies focused on adults from general populations. Only two cross-sectional studies examined association between occupational exposure to PFAS and MetS [24, 25]. All authors adjusted the statistical analyses for age (n=12 studies), followed by two other important cofounders including alcohol intake and smoking status. The other variables of adjustment present a greater variation among studies (Table 1). All included studies achieved a high to moderate score according to the NOS scale (Table 1).

Ten out of the 12 studies used serum for chemical analysis, and two studies used plasma. PFAS were measured using liquid chromatography separation coupled with mass spectrometry (LC/MS) in all the studies. The ranges of the limits of detection (LODs) were 0.025–1.0 µg/L.

PFOA and PFOS were measured in all the studies, while PFHxS and PFNA were determined in 10 and nine of the included studies, respectively. PFOS levels were higher in most of the studies compared to the rest of PFAS concentrations except for one study [26] on a highly exposed population in Italy via contaminated drinking water (PFOA was the most detected PFAS) (Table 2). Most of the studies

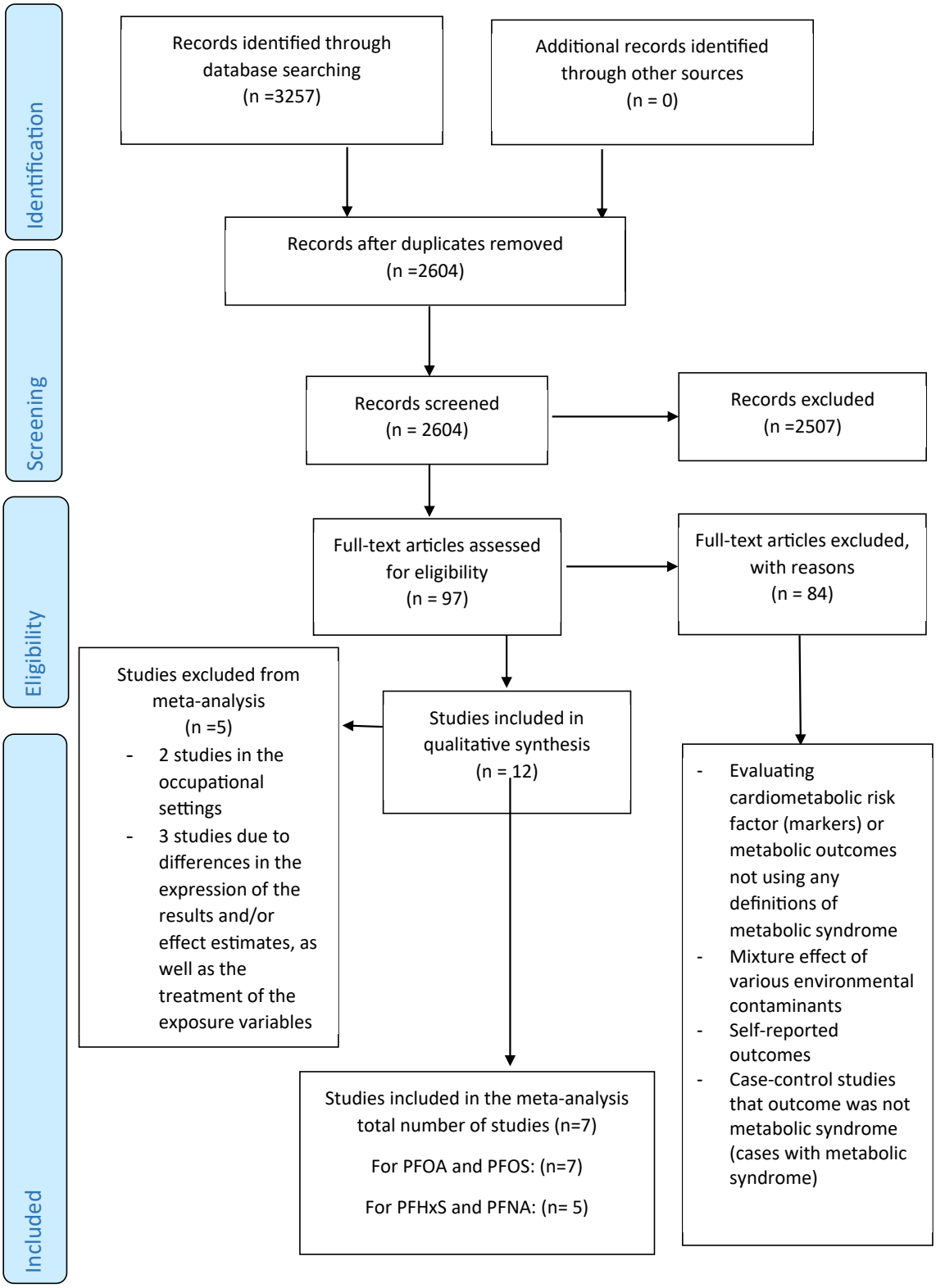

Figure 1: Representation of the search strategy based on PRISMA flow diagram.

Table 1: Description of epidemiological studies on PFAS exposure and metabolic syndrome.

First author (ref)	Sampling year	Location	Population	N sample size	Age range	Sex number	PFAS	PFAS matrix	MetS definition	Statistical analysis	Adjusted variables	MQ
Olsen and Zobel [25]	2000–2001	Belgium	Employees of three chemical plants (3M) with occupationally related exposure; excluded those on cholesterol lowering medications	506	21–67 years	M: 506, F: 0	PFOA, PFOS (only PFOA used for subsequent analysis)	Serum	BMI ≥30; TG ≥150 mg/dL; HDL-C <40 mg/dL; FBG ≥110 mg/dL (NCEP-ATP III, 2001)	Multiple logistic regression analysis between PFAS (in decile) and MetS	Age	8
Lin et al. [31]	1999–2000, 2003–2004	USA	General population (NHANES)	474 adolescents	Adolescence: ≥12–20 years	M: 268, F: 206	PFOA, PFOS, PFHxS, PFNA	Serum	TG ≥110 mg/dL; HDL-C ≤40 mg/dL; WC ≥ the sex-specific 90th percentile; Glucose concentration ≥100 mg/dL or a self-report of taking antihyperglycemic medications; SBP/DBP ≥ the age-, height-, and sex-specific 90th percentile or a self-report of taking antihypertensive medications. Modified NCEP-ATP III, 2001	Multiple logistic regression analysis associated with a 1 unit increase in ln PFASs	Age, sex, race, smoking status, alcohol intake, household income, measurement data (CRP and HOMA/insulin), current medications (antihypertensive, antihyperglycemic, antihyperlipidemic agents), other components of the MetS	9
				969 adults	Adults: >20 years	M: 486, F: 483			If >18 years, WC >88 cm (F) >102 cm (M); TG ≥150 mg/dL; HDL-C <40 mg/dL (M), <50 mg/dL (F); BP ≥130/85 mmHg or a self-report of taking antihypertensive medications; FBG ≥110 mg/dL or a self-report of taking antihyperglycemic medications. NCEP-ATP III, 2001			

Table 1: (continued)

First author (ref)	Sampling year	Location	Population	N sample size	Age range	Sex number	PFAS	PFAS matrix	MetS definition	Statistical analysis	Adjusted variables	MQ
Fisher et al. [33]	2007–2009	Canada	General population CHMS, Cycle 1; excluded pregnant women and those on cholesterol lowering medications	2,700	18–74 years	M: 1,297, F: 1,403	PFOS, PFOA, PFHxS	Plasma	WC >102 cm (M), >88 cm (F); TG ≥150 mg/dL; HDL-C <40 mg/dL (M), <50 mg/dL (F); BP ≥130/85 mmHg or currently taking anti-hypertensive medication; FBG ≥100 mg/dL (Alberti et al. [61])	Multiple logistic regressions analysis associated with a 1 unit increase in ln PFASs	Age (continuous), gender, alcohol consumption	10
Yang et al. [29]	2015	China	Chinese general population	148	19–60 years	M: 148, F: 0	PFHpA, n-PFOA, PFNA, PFDA, PFUdA, PFHxS, n-PFOS	Serum	BMI ≥25 kg/m^2; FBG ≥110 mg/dL or 2 h glucose after oral glucose tolerance test ≥140 mg/dL or a self-report of previously diagnosed type 2 diabetes; SBP/DBP ≥140/90 mmHg or a self-report of taking anti-hypertensive medications; TG ≥150 mg/dL or HDL-C <35 mg/dL (M). Modified NCEP-ATP III	Correlations analysis and linear regression models for every PFASs above the median relative to below the median	Age	6
Liu et al. [32]	2013–2014	USA	General population (NHANES)	1,871	≥18 years	M: 875, F: 996	Total, linear and branched PFOA and PFOS isomers	Serum	WC ≥88 cm (F), ≥102 cm (M); TG ≥150 mg/dL; HDL-C <40 mg/dL (M), <50 mg/dL (F); systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or a self-report of taking anti-hypertensive medications; FBG ≥100 mg/dL or a self-report of taking anti-hyperglycemic medications. NCEP-ATP III	Multiple logistic regression analysis associated with a 1 unit increase in ln PFASs	Age, gender, ethnicity, smoking status, alcohol intake, household income, current medications (anti-hypertensive, anti-hyperglycemic, anti-hyperlipidemic agents), other components of MetS	9

Table 1: (continued)

First author (ref)	Sampling year	Location	Population	N sample size	Age range	Sex number	PFAS	PFAS matrix	MetS definition	Statistical analysis	Adjusted variables	MQ
Leary [23]	2013–2014	USA	General population (NHANES)	739	≥20 years	M: 358, F: 381	linear and branched PFOA and PFOS isomers, PFHxS, PFNA	Serum	WC ≥102 cm (M) or WC ≥88 cm (F), BP ≥130/90 mmHg; TG ≥150 mg/dL; HDL-C <40 mg/dL (M) or 50 mg/dL (F); and FBG ≥100 mg/dL. Or taking medication (lowering BP, cholesterol, blood sugar) or treatment such as insulin (2005 NECP-ATP III)	Multiple logistic regression analysis associated with a 1 unit increase in ln PFASs	Age, race/ethnicity, smoking (serum cotinine), annual household income, gender	8
Chen et al. [28]	2007–2008	Croatia	General population	123	44–56 years	M: 54, F: 68	PFOS, PFOA, PFHxS, PFNA	Plasma	WC ≥102 cm (M) or WC ≥88 cm (F), BP ≥130/85 mmHg; TG ≥150 mg/dLl; HDL-C <40 mg/dL (M) or 50 mg/dL (F); and FBG ≥100 mg/dL (NCEP-ATP III)	Multiple logistic regression analysis associated with a 1 unit increase in ln PFASs	Age, sex, education, socioeconomic status, smoking, dietary pattern, physical activity	8
Christensen et al. [30]	2007–2014	USA	General population (NHANES)	2,975	≥20 years	M(%): 50.7, F(%): 49.3	PFDE, PFOA, PFOS, PFHxS, PFOSA, MPAH, PFNA, PFUnDA	Serum	WC ≥102 cm (M) or WC ≥88 cm (F), BP ≥130/85 mmHg; TG ≥150 mg/dL; HDL-C <40 mg/dL (M) or 50 mg/dL (F); and FBG ≥100 mg/dL (Alberti et al. [61])	Multiple logistic regression analysis associated with a 1 unit increase in ln PFASs or PFASs in quartiles	Sex, age, race/ethnicity, family income, alcohol intake, smoking status	9

Table 1: (continued)

First author (ref)	Sampling year	Location	Population	N sample size	Age range	Sex number	PFAS	PFAS matrix	MetS definition	Statistical analysis	Adjusted variables	MQ
Leary et al. [24]	2013–2014	USA, Southwest Ohio region	Firefighters High exposed airport workers and suburban workers with negligible exposure Occupationally exposure to all PFOS-based aqueous film forming foams (AFFF)	47 (Airport n=38, suburban n=9)	≥18 years	M: 47, F: 0	PFOS, PFOA, PFHxS, PFNA	Serum	WC ≥102 cm (M) or WC ≥88 cm (F), BP ≥130/85 mmHg; TG ≥150 mg/dL; HDL-C <40 mg/dL (M) or 50 mg/d (F); and FBG ≥100 mg/dL (2005 NCEP-ATP III)	Spearman correlations and multiple logistic regression analysis	Included covariates in the multivariable logistic regression analysis were not specified	7
Lin et al. [27]	2016–2017	Taiwan	Elderly population living near Keya river (near the largest Science Park)	397	55–75	M: 133, F: 264	PFHxA, PFOA, PFNA, PFDA, PFUnDA, PFDoA, PFBuS, PFHxS, PFOS	Serum	WC ≥90 cm (M) or ≥80 cm (F) (criterion for Chinese population); BP ≥130/85 mmHg; FBG ≥100 mg/dL; TG ≥150 mg/dL; HDL-C <40 mg/dL (M), or <50 mg/dL (F) (NCEP-ATP III)	Logistic regression model for metabolic syndrome status, linear regression model for continuous related outcomes	Age, sex, drinking status, smoking status (BMI, education level, household income, dietary pattern, exercise, and menopausal status considered but not included in the model due to changes in effect estimates less than 10%)	10
Wan-Lin Ye et al. [62]	Jul 2015–Oct 2016	China	General population	1,501	Adults	M: 1,143, F: 358	Isomers of PFOA and PFOS, PFHS, PFNA, PFHxS, PFDA, PFDoA, PFTrDA, PFUnDA	Serum	WC ≥90 cm (M) or ≥80 cm (F) (criterion for Chinese population); FBG ≥101 gm/dL; HDL-C ≥40 mg/dL (M) or ≥50 mg/dL (F); BP ≥130/85 mmHg, TG ≥150 mg/dL (NCEP-ATP III)	Logistic regression models, restricted cubic spline models	Age (continuous), sex, income status, smoking, alcohol consumption, regular exercise, seafood consumption	9

Table 1: (continued)

First author (ref)	Sampling year	Location	Population	N sample size	Age range	Sex number	PFAS	PFAS matrix	MetS definition	Statistical analysis	Adjusted variables	MQ
Zare-Jeddi et al. [26]	2017–2019	Italy, Veneto Region	Population living in a highly exposed community	15,876	20–39	M: 7,717, F: 8,159	PFOS, PFOA, PFHxS, PFNA	Serum	BMI ≥30; TG ≥150 mg/dL; HDL-C <40 mg/dL (M) or <50 mg/dL (F); BP ≥130/85 mmHg; HBA1c ≥6.1% or ≥43 mmol/mol (modified JIS)	t-test, chi-square, Spearman correlation, thin plate spline smooth terms, linear regression coefficient and 95% CI. p-value for trend across the quartiles. ORs using Multivariable Generalized Additive Models with a binomial link function	Gender, age, country of birth, smoking status, diet, alcohol consumption, time-lag between enrollment and beginning of the study, number of deliveries, clinical centers of blood pressure measurement & questionnaire fulfillment, education, physical activity	

ATP III, adult treatment panel III; BMI, body mass index; BP, blood pressure; CHMS, Canadian Health Measures Survey; cm, centimeters; CRP, C reactive protein; DBP, diastolic blood pressure; Et-PFOSA-AcOH, 2-(*N*-ethyl-perfluorooctane sulfonamide) acetic acid; F, female; FBG, fasting blood glucose; HDL-C, high density lipoproteins-cholesterol; HOMA, homeostatic model assessment; IDF, International Diabetes Federation; JIS, joint interim statement on MetS definition; kg/m^2, kilogram per meter squared; ln, natural logarithm; M, male; Me-PFOSA-AcOH, 2-(*N*-methyl-perfluorooctane sulfonamide) acetic acid; MetS, metabolic syndrome; mg/dL, milligrams per deciliters; mmol/L, milli mol per liter; mmHg, millimeters of mercury; MPAH, 2-(*N*-methyl-PFOSA) acetate; MQ, methodological quality; NCEP, National Cholesterol Education Program; NHANES, National Health and Nutrition Examination Survey; n-PFOA, linear perfluorooctanoic acid; n-PFOS, linear perfluorooctanesulfonate; OR, odds ratio; PFAS, perfluoralkyl substances; PFBuS, perfluorobutane sulfonic acid; PFDA, perfluorodecanoate; PFDE, perfluorodecanoic acid; PFDoA, perfluorododecanoic acid; PFHpA, perfluoroheptanoic acid; PFHxS, perfluorohexanesulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonate; PFOSA, perfluorooctanesulfonamide; PFTrDA, perfluorotridecanoic acid; PFUnDA, perfluoroundecanoic acid; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference; %, in percent.

used different methods to determine biochemical traits (data not shown).

Relatively few studies examined the association between PFAS exposure and MetS (n=12), among which only three studies reported statistically significant associations between PFOA and PFNA (Table 3) [27–29].

Of the 12 citations selected, those investigating the association between occupational exposure to PFAS and MetS (n=2) were reviewed and summarized without further meta-analysis. Biomonitoring data provided by 3M on 506 male employees between 21 and 67 years of age in a fluorochemical medical surveillance program has shown that PFOA was not associated with MetS in occupationally exposed workers (Tables 1, 2) [25]. Another cross-sectional study in a small scale was conducted on 47 male firefighters aged 18–62 years of two fire departments in the Southwest Ohio region among which 38 participants working at military base airport reported exposure to aqueous film forming foams (AFFF) which contains many PFAS including PFOS, and PFHxS. Nine volunteer firefighters from the suburban firefighting unit comprised the control group owing to a negligible AFFF exposure. Median PFAS serum concentrations in this study were comparable to PFAS levels in the general population. MetS prevalence among overall firefighters was 44%, and when compared to two other fire departments, the difference was not statistically significant. This study reported that serum PFAS levels in male firefighters were not associated with an elevated risk of MetS, although a positive association was observed between elevated diastolic blood pressure (DBP) (a component of MetS) and PFOS [24].

The result of the study on the firefighters was in line with the results of the study on occupationally exposed workers of 3M while PFOA and PFOS serum concentrations in 3M workers was 1,027 and 122 times higher, respectively. Whereas, the prevalence rate of MetS in the firefighters was higher than 3M workers and this may be more related to overall higher mean BMIs in firefighters (30.58) compared with the 3M workers (27.4). On the other hand, Olsen et al. did not consider elevated blood pressure in categorizing the MetS criteria.

Among all the included studies on the general population, four studies were conducted using the National Health and Nutrition Examination Survey (NHANES) data from 1999–2004 to 2007–2014 [23, 30–32]. One of these four studies only examined the different isomers of PFOA and PFOS (linear vs. branched), but not total PFOA and PFOS, using data from NHANES 2013–2014 [23]. Therefore,

Table 2: Summary of PFAS concentrations (μg/L).

First author (ref)	Analytic method	LOQ/LOD	PFOA	PFOS	PFHxS	PFNA
Serum						
Olsen and Zobel [25]	LC/MS–PE	5.80/NA	2,210	1,050	–	–
Yang et al. [29]	HPLC–MS/MS	NA/0.0–0.19	2.14	3.69	4.02	0.50
Liu et al. [32]	HPLC–MS/MS	NA/1.00	1.86	5.28	–	–
Leary [23][a]	HPLC–IS/MS	NA/0.10	1.90 (IQR: 1.80)	3.80 (IQR:4.70)	1.40 (IQR: 1.70)	0.70 (IQR:0.60)
Christensen et al. [30][b]	HPLC–IS/MS	NA/0.10	2.80	8.40	1.60	1.00
Chen et al. [28]	HPLC–MS/MS	NA/0.10	2.87	8.91	0.77	1.29
Leary et al. [24]	LC/MS/MS	0.02/NA	2.15	8.63	6.15	0.46
Lin et al. [27]	UPLC–LCMS	0.19–1.68/NA	9.54	20.4	3.85	3.42
Wan-Lin Ye [62][b]	HPLC–MS/MS	NA/0.02–0.1				
MetS subjects			6.6	11.87	1.26	2.14
Non MetS subjects			5.73	11.18	0.53	1.78
Zare-Jeddi et al. [26]	HPLC–MS/MS	0.5/0.1	59.76	4.623	5.972	0.535
Plasma						
Fisher et al. [33]	UPLC–MS/MS	NA/0.30	2.46	8.40	2.18	NS
Lin et al. [27][a]	HPLC–MS/MS	NA/0.05–0.80				
Adults			1.48	3.19	–	–
Adolescents			1.51	3.11	–	–

HPLC–IS/MS, high performance liquid chromatography-turbo ion spray ionization tandem mass spectrometry; HPLC–MS/MS, high-performance liquid chromatography (HPLC)–tandem mass spectrometry (MS/MS); LC/MS–PE, liquid chromatography/tandem mass spectrometry using a PE Sciex API 3000; LOD, limit of detection; LOQ, limit of quantification; NA, not available; n-PFOA, linear pentadecafluorooctanoic acid; n-PFOS, linear perfluorooctanesulfonate; P, percentile; PFAS, perfluoralkyl substances; PFHxS, perfluorohexanesulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonate; UPLC–MS/MS, waters acquity ultra performance liquid (UPLC) coupled to waters quattro premier XE mass spectrometer (MS) and waters mass LYnx software (MS); μg/L, micrograms per liter. [a]Reported results are for the linear isomers. [b]Reported results are for the median concentrations. [c]Reported results have been calculated by natural logarithm.

Table 3: Summary of ORs of metabolic syndrome associated with PFAS.

First author (ref)	Expression of results	N	Associations between PFAS and MetS			
			PFOA	PFOS	PFHxS	PFNA
Occupational exposure per µg/L PFAS exposure						
Olsen and Zobel [25]	Decile 6th	506	1.00(0.30–3.50)	–	–	–
	Decile 7th		0.50(0.10–2.00)	–	–	–
	Decile 8th		0.90(0.30–3.00)	–	–	–
	Decile 9th		1.10(0.30–3.60)	–	–	–
	Decile 10th		1.00(0.30–3.60)	–	–	–
Leary et al. [24]		47	0.54(0.85–3.43)	0.67(0.24–1.86)	0.77 (0.25–2.71)	0.35(0.05–2.35)
General population per 1-unit increase in log PFAS						
Lin et al. [27]	Adults	969	1.07(0.73–1.57)	1.25(0.86–1.82)	0.93(0.73–1.24)	0.92(0.69–1.24)
	Adolescents	474	0.79(0.30–2.12)	0.49(0.18–1.30)	0.56(0.22–1.45)	**↓:0.37(0.21–0.64)**
Fisher et al. [33]	Unweighted	2,700	1.26(0.92–1.73)	0.86(0.66–1.11)	1.00 (0.83–1.21)	–
	Weighted		1.13(0.46–2.77)	0.7(0.41–1.2)	0.93(0.63–1.38)	–
Yang et al. [29][a]	Exposure considered dichotomous	148	**↑:29.40(2.90–299.70)**	0.91[a](0.23–3.52)	1.60(0.44–5.87)	6.47(0.89–47.15)
Liu et al. [32]	Total	1,871	0.86(0.67–1.08)	0.93(0.59–1.15)		
	Linear isomers		0.87(0.70–1.07)	0.91(0.75–1.11)	–	–
	Branch isomers		0.78(0.59–1.03)	0.99(0.79–1.24)	–	–
Leary [23]	Linear isomers	739	0.85(0.68–1.07)	0.88(0.73–1.05)	NS: 0.91(0.75–1.11)	NS: 0.84(0.66–1.06)
	Branch isomers		0.91(0.62–1.33)	0.96(0.79–1.17)		
Chen et al. [28]	Total	123	2.19(0.88–5.44)	1.89(0.93–3.86)	–	**↑:2.95(1.12–7.8)**
Christensen et al. [30]	Total ln(PFAS)	2,975	0.93(0.77–1.12)	0.91(0.78–1.06)	0.87(0.76–0.99)	1.1(0.92–1.33)
	Quartile 2		0.89(0.59–1.33)	0.83(0.54–1.29)	0.77(0.56–1.07)	1.08(0.74–1.58)
	Quartile 3		0.76(0.52–1.10)	0.84(0.58–1.22)	0.80(0.57–1.12)	1.25(0.87–1.82)
	Quartile 4		0.83(0.58–1.19)	0.79(0.57–1.07)	0.88(0.65–1.18)	1.10(0.80–1.53)
Lin et al. [27]		397				
	Quartile 2		0.94(0.51–1.73)	1.09(0.60–1.98)	0.93(0.51–1.69)	0.94(0.51–1.71)
	Quartile 3		1.37(0.75–2.49)	0.57(0.30–1.09)	0.85(0.46–1.57)	1.04(0.57–1.89)
	Quartile 4		1.47(0.80–2.68)	1.71(0.93–3.13)	1.22(0.66–2.25)	1.48(0.82–2.67)
Wan-Lin Ye [62][a]	ln(PFAS)	1,501	**↑: 1.35(1.16–1.58)**	1.09(0.94–1.25)	1.01(0.97–1.05)	**↑: 1.29(1.12–1.48)**
Zare-Jeddi et al. [26]	ln(PFAS) Total	15,876	1 (0.93–1.07)	**↓: 0.7(0.61–0.79)**	1.02(0.94–1.11)	0.81(0.65–1)
	Quartile 2		1(0.8–1.26)	**↓: 0.8(0.64–0.99)**	0.97(0.76–1.24)	–
	Quartile 3		1.04(0.82–1.32)	**↓: 0.78(0.62–0.97)**	1.23(0.97–1.57)	–
	Quartile 4		0.99(0.77–1.26)	**↓: 0.55(0.43–0.7)**	1.06(0.82–1.37)	–

CI, confidence interval; ln, natural logarithm; MetS, metabolic syndrome; N, sample size; OR, odds ratio; PFHxS, perfluorohexanesulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonate; ↑ positive association; ↓ negative association; *p>0.05; – not studied. [a]The results are regarding linear isomer. Bold values mean a significant association.

this study was excluded from the main meta-analysis. This study concluded that among non-institutionalized U.S. civilians aged 20 and older, serum concentrations of linear and branched PFOA and PFOS isomers, PFHxS and PFNA were not significantly associated with risk of MetS in multivariable analysis adjusting for potential confounders [23].

Differences in the expression of the results and/or effect estimates, as well as the treatment of the exposure variables (PFAS serum concentrations were dichotomized as above the median vs. below the median), prevented us from combining effect estimates of the study conducted by Yang et al. and Lin et al. in the meta-analysis [27, 29]. In the cross-sectional study on the Chinese general population a total of 148 men aged 19–60 years were recruited and using MetS criteria participants were divided into MetS cases (54.7%) and non-MetS controls (45.3%). Age adjusted models demonstrated that only for PFOA, serum levels above the median were positively associated with increased risks of MetS [29]. However, the sample size of the study group was relatively small, which might have limited statistical power.

In the other study on 397 Taiwanese adults aged 55–75 years living near the Keya River in the largest Science Park in Taiwan, the serum levels of PFOS and PFOA were higher than the background-exposed populations in Taiwan and in the NHANES 2013–2014 in the United States. However, in this community resident, associations were consistently null between PFAS and metabolic syndrome in the adjusted logistic regression models [27].

As there was only one study on children and adolescents, we could not examine the association among this age group. The study by Lin et al. reported that, among adolescents (age at ≥12–20 years), serum PFAS levels were not associated with MetS, though inverse association was detected between increased serum PFNA levels with the prevalence of the MetS [31].

Eventually, a meta-analysis was undertaken on the results from seven papers (Figure 1). All studies reported the association between both PFOA and PFOS and outcomes; PFHxS was not considered by Liu et al. [32] and Chen et al. [28] and PFNA was not considered by Liu et al. [32] and Fisher et al. [33], thus there were seven potential studies for PFOA and PFOS, and five for PFHxS and PFNA. All studies were focused on adult population above 18 years old, have used a dichotomous definition of metabolic syndrome based on the presence of a selection of criteria and have considered continuous concentration of PFAS as exposure variable. The cumulative sample of studies included in this meta-analysis consisted of 26,015 participants for PFOA and PFOS, 24,021 participants for PFHxS and 21,444 participants for PFNA. According to the random effect meta-analysis of seven effect sizes extracted from the studies, PFOA (Pooled OR, 1.06; 95% CI, 0.91–1.23; I^2=67.6%) and PFOS (Pooled OR, 0.94; 95% CI, 0.79–1.10; I^2=78.7%) were not associated with the risk of the MetS (Figure 2A, B). As for PFNA and PFHxS, sufficient data were available from five studies (PFNA: Pooled OR, 1.08; 95% CI, 0.86–1.36; I^2=78.0%; PFHxS: Pooled OR, 0.99; 95% CI, 0.94–1.04; I^2=23.0%) which showed no association with the risk of the MetS (Figure 2C and D). However, there was substantial heterogeneity in study effects regarding MetS for PFOA, PFOS and PFNA. Sensitivity analysis showed the robustness of findings after including the study that

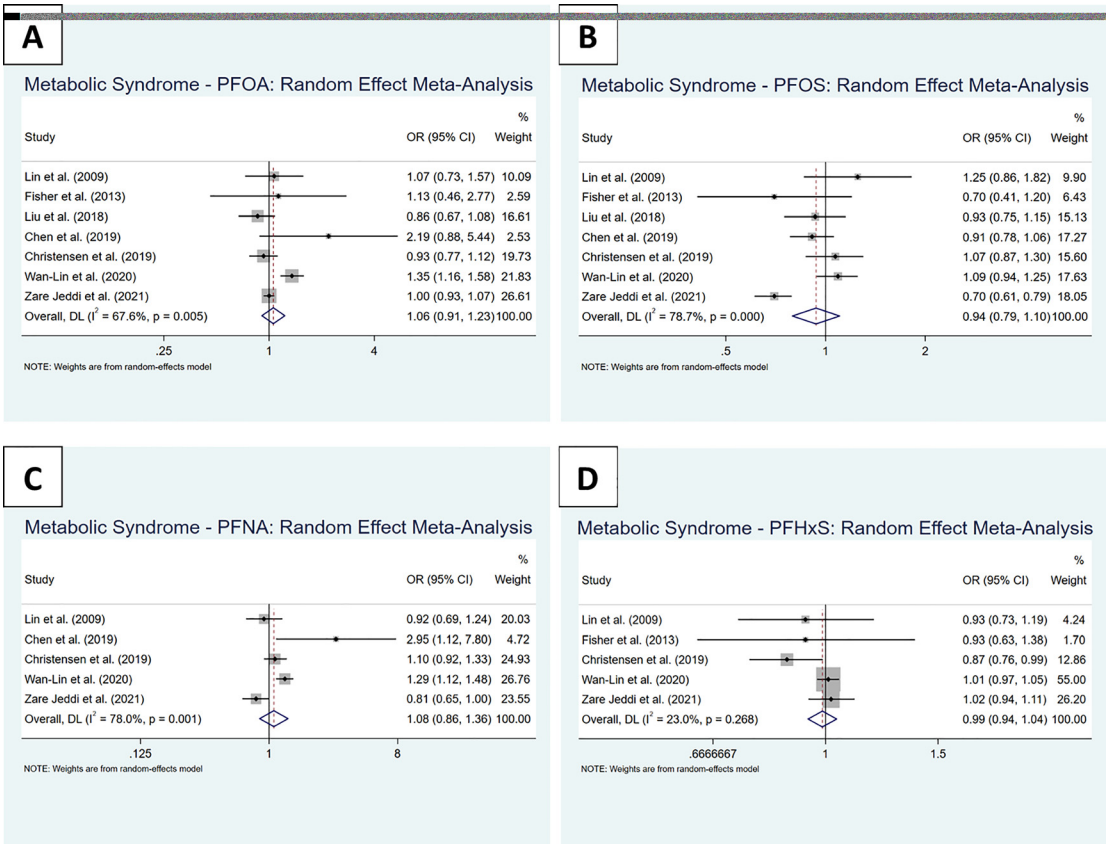

Figure 2: Random effects meta-analysis of the effects of PFAS on metabolic syndrome (pooled OR value with corresponding 95% CI). A. Correlation between PFOS and metabolic syndrome. B. Correlation between PFOA and metabolic syndrome. C. Correlation between PFHxS and metabolic syndrome. D. Correlation between PFNA and metabolic syndrome.

measured the linear and branched isomers of PFOA and PFOS (Supplementary Figure S1). Results for fixed effects models were consistent with those of random effects, with roughly similar pooled point estimate but narrower confidence intervals mainly for PFOS and PFNA and hence provides a weak evidence for an inverse and positive association with MetS, respectively (Supplementary Figure S2). This is suggestive of an inverse association between PFOS and the risk of MetS where 4/7 studies showed point estimates <1 but with a substantial heterogeneity across the seven comparable studies. The strong inverse association of Zare Jeddi et al. is the dominant result in this analysis [26]. Overall, these results provide little evidence for any trend in the risk of MetS with increasing exposure to PFAS.

Discussion

The pathological mechanisms of MetS are multifactorial, due to the complex and largely unknown interplay of environmental, nutritional and genetic factors. We found a few relevant papers (n=12) on this specific subject when it comes to exposure to PFAS, ubiquities environmental contaminants. This is the first meta-analysis attempting to comprehensively analyze the association between PFAS and the risk of MetS. The results manifested that overall multivariable-adjusted odds ratios for the presence of MetS identified by the different criteria, and the certain PFAS (PFOA, PFOS, PFHxS and PFNA) were not associated in adult population older than 18 years old. These results should be interpreted with caution, due to the between-study heterogeneity.

In order to draw our conclusion, we have assessed the evidence of a possible association between PFAS and MetS by assessing the exposure and outcomes for consistency and coherence, strength of the association and biological plausibility.

Consistency and coherence

Among the included studies in the meta-analysis, there are slight differences in the method of chemical analysis used to determine PFAS although the sample pre-treatment procedure for chemical extraction varied between studies. Moreover, studies differ in the LOD or LOQ and there are differences in how PFAS concentrations below these limits were handled with replacement by LOD or LOQ/$\sqrt{2}$, or LOD/2. Nevertheless, the percentages of samples below LOD or LOQ were small in most of the studies mainly for PFOA and PFOS. Although the PFAS concentrations were measured in different blood compartments (plasma n=2 or serum n=10), the results of studies on across-compartment comparisons have showed roughly similar ratio between plasma and serum for certain PFAS [2, 34, 35]. On the other hand, PFAS concentrations in blood samples appear to follow an overall order as: serum > plasma > whole blood [36]. Among the included studies for the current systematic review, the levels of PFAS isomers, particularly PFOS/PFOA linear and branched counterparts, were examined in three studies that were found no significant associations with MetS prevalence regardless of how they were included in statistical models. In the meta-analysis, we were unable to do this sub-sample assessment, as the number of studies considering isomers of PFAS was too small.

The association between legacy PFAS (PFOA, PFOS, PFHxS and PFNA) have been studied in most of the included studies while only five studies measured other PFAS such as perfluorodecanoic acid (PFDE), 2-(*N*-methyl-PFOSA) acetate (MPAH), perfluoroundecanoic acid (PFUnDA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUdA), perfluoroheptanoate (PFHpA), and perfluorohexanoate (PFHxA) (Table 1). However, considering inaccuracy of quantitative process, PFAS with the detection rate usually less than 30% were omitted for further analyses in most studies. Other PFAS were detected with much lower concentrations than those of PFOS and PFOA, generally <2 µg/L. Therefore, the health effects of other PFAS substances have not been studied in humans to the same degree as legacy PFAS.

Except for the study on the occupational exposed workers [25] and one study on a highly exposed population of community residents in Italy [26], the mean concentrations of PFOA, PFOS, PFHxS and PFNA were approximately in the same order of magnitude in different studies. Such observation is consistent with previous findings that PFOS was found at a higher concentration in serum of the general population than PFOA. This could be explained by the lower affinity of PFOA to serum albumin which might lead to higher renal clearance [36, 37].

Most of the studies reported strong to moderate positive correlation between any two of most prominent PFAS in general populations. Although the correlations varied to a certain extent for all compounds, high correlation indicate similar exposure pathways among PFAS and might be attribute to similar half–lives. The shape of a possible dose-response relationship is not yet known.

For PFOA, PFHxS and PFNA, the range of exposures is relatively narrow and similar among all the studies on the general population whereas, for PFOS, the range of exposure is wider. However, the data we have are too sparse

to reach conclusions about the overall shape of the relationship.

The discrepancies in the concentrations of PFAS in human could be explained by differences in the sampling timing and exposure sources, geographical locations, diet habits and working habits. In addition, the different regulations of PFAS led to time or region-dependent production or environmental distributions of PFAS.

In many studies serum concentrations of PFOA, PFHxS and PFOS in males were significantly higher than in females [36, 38]. Although evidence revealed that the serum PFAS concentrations are higher in men than in women also in the studies included in this review, sex-stratified associations with MetS were only addressed in one study [26]. Nevertheless, studies are available indicating that the effects of PFAS on certain health outcomes might not be dose-related [39].

Strength of the association and biological plausibility

The recent meta-analysis conducted by Rashidbeygi et al. demonstrated that there was a noticeable association between microalbuminuria (urine albumin/creatinine ratio) and the risk of MetS and its components, but not reduced HDL-C [40]. Microalbuminuria is listed as one of the criteria for making a diagnosis of the MetS by the World Health Organization (WHO) definition, whereas it is not an ATP III diagnostic criterion (Supplementary Table S3). The observation that albuminuria is associated with increased excretion of PFAS [41] might be a contributing factor to influence the results of the association between PFAS and the risk of MetS and its components. Thus, microalbuminuria may be a useful criterion to be addressed for making a diagnosis of the MetS to increase the sensitivity for identifying people at risk at the early stage. More often, attention has been focused on diabetes, hypertension, obesity, and dyslipidemia, while the assessment of microalbuminuria is frequently ignored. This criterion was not considered in any of the studies interrogating PFAS associations to MetS.

Results of the effects of PFAS on individual components of MetS in humans are inconsistent but suggested that certain PFAS may negatively affect metabolic outcomes [7, 42, 43]. It is possible that the inverse associations among the different components with PFAS, would tend to bias associations with MetS towards the null. While increased serum total cholesterol and low-density lipoprotein (LDL)-cholesterol are strongly associated with PFAS exposure in humans, there is insufficient evidence with contradictory results for associations between exposure to PFAS and insulin resistance, diabetes, obesity, and hypertension [6, 7]. Therefore, due to limited studies with discrepancies between findings, we cannot draw a definitive conclusion based on the available evidence.

Largely, the underlying mechanism for the association between PFAS and MetS components is unclear. However, studies have indicated that increase in oxidative/nitrosative stress in the liver and endothelial cells plays an important role in PFAS-mediated metabolic effects in humans [44–47]. The peroxisome proliferator-activated receptors (PPAR) pathway, particularly PPARα, a major component that regulates lipid metabolism and fatty acid oxidation, might also have a role in the relationship between PFAS/oxidative stress (with inducing reactive oxygen species [ROS] production by activating nicotinamide adenine dinucleotide phosphate oxidase [NADPH oxidase]) and PFAS/cholesterol homeostasis [47–51]. The PFAS with a carboxylic acid had a stronger agonistic potential compared to the PFAS with a sulfonic acid, nevertheless the nuclear receptor activation seems to occur at concentrations several magnitudes above the average blood concentration in the general population [52, 53]. Furthermore, it is demonstrated that PFOA affected the expression of cell cycle and lipid metabolism genes and suppressed lipid transport gene, potentially leading to elevated lipid synthesis and fat deposits in liver cells [54]. Overall, MetS is a multifactorial condition that stems from several inter-related anthropometric and biochemical features though the exact mechanism and the role of environmental risk factors needs yet to be determined in the exposome setting. In this context, recent studies suggest using a set of serum biomarkers that are associated to MetS and its components and are known as independent risk factors including the ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT), uric acid (asymptomatic hyperuricemia), and thyroid hormone. Taking into account of independent risk factors might be helpful to increase the sensitivity of the diagnosis among people without comorbidities and to further elucidate the underlying biological mechanism(s) [55–57].

Limitations of the systematic review

Similar to other meta-analyses, our study has some limitations. First, it is important to be considered that all included studies were cross-sectional in design, which are more prone to selection and recall bias than in cohort studies and the temporal association between exposure and outcome cannot be identified. However, the long biological half-lives of PFAS may counteract this

limitation. Second, the majority of the included studies in the meta-analysis have adjusted for variables known to influence MetS and PFAS (age, sex, smoking, alcohol consumption), whereas other variables, including physical activity, family history of metabolic disease, energy intake and dietary were not consistently adjusted for. These potential confounding factors might affect the results. The adjustment of models for BMI is under debate, since BMI might be an intermediate variable between PFAS exposure and MetS development. One critical aspect may be that PFAS are not clearly associated with BMI and fat mass/insulin resistance than other compounds such as polychlorinated biphenyls (PCBs) or organochlorine pesticides (OCPs). Excessive fat mass and insulin resistance are regarded by some researchers as the critical features that may trigger MetS. Third, we were unable to fully examine the impact of adjustment for all known and potential risk factors due to the varying degree of confounder adjustment in individual studies. In addition, potential confounding of results by dietary exposure sources was assessed only in one of the included studies. In the case of PFAS, both negative and positive confounding may be expected since meat and fish are predictors of PFAS, but fish consumption would have benefits for MetS, while meats, especially red and processed meats would tend to increase risk of MetS. Furthermore, either isomer of PFAS might have different associations with metabolic outcomes while most of the studies did not measured the isomers and that may underestimate effects of PFAS exposures on MetS and its individual components. Forth, most studies did not measure other important serum biomarkers which might affect MetS criteria like AST to ALT ratio, microalbuminuria, uric acid, and other possible independent risk factors. Moreover, although children and adolescents are disproportionately exposed to synthetic chemicals and are at risk of developing MetS [58, 59], given the paucity of research on the relation between the MetS and PFAS, the magnitude of association among children and adolescents remained unclear. On the other hand, the different criteria used for the assessment of MetS might influence the frequency of MetS in the general population among the studies.

One limitation of this review was the inability to meta-analyze specific components of MetS, in addition to clinical MetS diagnosis because the research question was focused on overall MetS and not on its individual components. Therefore, future meta-analyses analyzing the relationship between PFAS and specific components, apart from MetS, are needed.

Further, the combined effects and toxicological interactions of PFAS mixtures remain unknown even though PFAS occur as complex mixtures in the environment. The effects of PFAS mixtures on metabolic syndrome may differ from those of single PFAS. The first large prospective study investigated the role of a mixture of 30 environmental contaminants on incident MetS in 452 subjects (50% women, all aged 70 years) free from the MetS at baseline, being followed for 10 years. Based on the results for the relative importance of the investigated variables regarding the association vs. incident MetS, PFAS were not among the most important environmental contaminants (relative importance <1.1) with the following order: PFHxS > PFOS > PFNA > PFOS. The most important variable was HDL-C, followed by two other variables included in the MetS definition, serum triglycerides and waist circumference [60]. However, larger studies are needed to confirm these findings.

Conclusion

The emerging recognition of PFAS as environmental threats reflects a broader need for understanding the complex determinants of potential public health implications and health disparities that might link to increased burdens of chronic diseases. In conclusion, the findings for the relationship between levels of PFAS and MetS were not statistically significant. However, due to limited number of studies and the between-study heterogeneity, we cannot draw a definitive conclusion based on the available evidence. Further translational studies ranging from experimental models, metabolic profiling, to longitudinal life-course epidemiology and cohort studies are needed. It is important to elaborate more on stratification strategies and multicentre designs in future studies to elucidate the association between PFAS and metabolic syndrome in different age groups and ethnicities. In addition, studies need to focus on mainly less well known PFAS, its precursors and their mixtures.

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