

Human health impacts of PFAS exposure: A second-order meta-analysis

Authors

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Data and code availability

The raw data and the analysis code can be downloaded from our GitHub repository (https://github.com/ThisIsLorenzo/PFAS_health_metametaanalysis)

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Abstract

Per- and polyfluoroalkyl substances (PFAS) are highly persistent synthetic chemicals with pervasive human exposure. Numerous meta-analyses have synthesised results on the association between PFAS exposure and human health, yet findings remain fragmented and often inconsistent across compounds, outcomes, and studies. We assessed the magnitude and consistency of associations between PFAS exposure and human health outcomes by integrating evidence from 23 meta-analyses encompassing 161 primary studies. PFAS exposure was associated with a 5% increase in the odds of adverse health outcomes (overall $OR = 1.05$, 95% CI: 1.03–1.08) and a moderate heterogeneity (overall $I^2 = 64\%$, 95% CI: 42–78%). Perfluorobutanesulfonic acid (PFBS) showed the largest and most consistent association among chemicals ($OR = 1.30$, $I^2 = 38.1\%$), endocrine diseases showed the strongest association among health outcomes ($OR = 1.11$, $I^2 = 61.7\%$), and pregnancy-related outcomes showed the highest consistency ($OR = 1.04$, $I^2 = 35.9\%$). The widespread nature of PFAS exposure means even small relative risks could translate into substantial population-level burdens. These findings strengthen the evidence base for regulatory measures, highlight vulnerable health domains, and identify priority areas for further research, particularly for understudied compounds and outcomes.

Keywords

Meta-meta-analysis, Epidemiology, Endocrine disruptors, Hypertension, Pregnancy, Evidence synthesis, Risk assessment

Synopsis

PFAS contamination is ubiquitous in human populations. This evidence synthesis identifies which chemicals and health outcomes show the strongest and most consistent associations, strengthening the case for regulatory action on these widespread persistent pollutants.

25 **Introduction**

26 Chemical contamination of the environment is a major global public health challenge¹. Over
27 the past century, the expansion of industrial and agricultural activities has released
28 thousands of synthetic chemicals into air, water, and soil, often without adequate
29 understanding of their long-term effects on human health and ecosystems². These substances
30 contaminate drinking water, food supplies, and household dust, resulting in involuntary,
31 continuous exposure^{3,4}. In 2016, the World Health Organization estimated that 24% of global
32 deaths, approximately 3.3 million, were attributable to preventable environmental factors,
33 including chemical pollution¹. Among all chemical classes, per- and polyfluoroalkyl
34 substances (PFAS) have emerged as particularly problematic due to their persistence and
35 widespread detection in both the environment^{5–8} and human biological samples^{9,10}. In
36 humans, long-chain PFAS such as perfluorooctanoic acid (PFOA) and perfluorooctane
37 sulfonate (PFOS) have half-lives of one to eight years^{11,12}, driven in part by renal
38 reabsorption¹³. These features raise substantial concerns about potential health
39 consequences, which have been the subject of increasing investigation in recent years.

40 A large body of primary research links PFAS exposure to various adverse health outcomes,
41 including endocrine disruption, immunotoxicity, developmental effects, metabolic disorders,
42 and increased cancer risk¹⁴. These findings have motivated a proliferation of medical meta-
43 analyses. However, most of these analyses are based on relatively small numbers of studies,
44 which limits their statistical power and increases the risk of false-negative results. For
45 example, two meta-analyses on preterm birth—one reporting a significant association with
46 PFOS exposure¹⁵ and the other finding no association¹⁶—illustrate how inconsistencies can
47 emerge even when assessing the same outcome and overlapping compounds. Similar
48 discrepancies are evident for hypertension^{17,18}, where effect estimates vary across reviews.
49 Such inconsistencies make it difficult to draw firm conclusions about which associations are
50 robust and which reflect noise or limited power. While traditional meta-analyses may struggle
51 with limited evidence and inconsistent findings, second-order meta-analysis provides a
52 means to overcome these challenges.

53 Second-order meta-analysis, or meta-meta-analysis, offers a solution by statistically
54 integrating results across multiple meta-analyses¹⁹. This approach increases power to detect
55 true associations, reducing the likelihood of false negatives that arise in smaller syntheses.
56 Importantly, it also allows for the formal assessment of consistency of findings across
57 compounds, outcomes, and populations. A high pooled effect size from a single meta-analysis

may not be convincing if other meta-analyses yield divergent results; conversely, a modest effect size gains credibility if it is consistently reproduced across independent reviews. By simultaneously quantifying both effect magnitude and consistency, second-order meta-analyses provide a higher-level synthesis that can distinguish robust, reproducible associations from preliminary signals, thereby supporting timely and evidence-based regulatory action. Because regulatory decisions hinge on the weight and consistency of scientific evidence, the need for higher-level synthesis is particularly acute in the case of PFAS.

PFAS have been subject to growing regulatory scrutiny, especially in the European Union (EU). Early restrictions targeted PFOA and PFOS, with more recent measures extending to other long chain perfluorocarboxylic acids and perfluorohexanoic acid (PFHxA) derivatives. In 2023, the European Chemicals Agency (ECHA) proposed a comprehensive ban covering more than 10,000 PFAS under the REACH regulation. The proposal received support from ECHA's scientific committees in early 2025, following by the work done by Committee for Socio-Economic Analysis (expected by the end of 2026), and now awaits final decision by the European Commission and Member States, with implementation anticipated from 2027–2028. Given the exceptional environmental persistence of PFAS, regulatory action alone is unlikely to eliminate population-level exposure. Substances already present in soil, water, and biota will continue to impose health consequences well beyond the point of prohibition. This long shadow underscores the importance of synthesising high-quality epidemiological evidence to inform global policy. Yet the literature remains constrained by inconsistent findings. To address this evidence gap, we conducted a second-order meta-analysis.

In this study, we quantitatively synthesised published meta-analyses to evaluate the magnitude and consistency of reported associations between PFAS exposure and adverse human health outcomes. Our objectives were to (1) quantify the magnitude and variability of these associations; (2) identify PFAS most strongly linked to specific health outcomes; (3) assess the strength of PFAS–health outcome relationships; (4) evaluate the overall consistency of findings across the evidence base.

Methods

Our second-order meta-analysis followed a systematic five-step approach, briefly outlined here and described in detail below. First, we registered our project plan in an open-access repository (<https://osf.io/dc5mx>), specifying hypotheses and methods. Second, we searched multiple databases to identify all relevant meta-analyses on the topic. Third, we extracted and organised the data items we had defined in our project plan from the included literature. Fourth, we quantitatively synthesised the evidence to address our research questions by modelling effect sizes and heterogeneity measures from the meta-analyses, complemented by evidence mapping and alternative impact metrics. Finally, we visualised the results and interpreted the findings. We adhered to the PRISMA reporting guideline²⁰ for data and analysis reporting (Table S01). Throughout this paper, “meta-analyses” refers to the individual published studies (articles) that conducted meta-analytic syntheses, whereas “meta-analytic estimates” refers to the specific model results (effect sizes) reported within those studies. Notably, a single meta-analysis may contribute multiple meta-analytic estimates for different PFAS–health outcome combinations.

Selection criteria

Following the PECO (Population, Exposure, Comparator, Outcome) framework outlined by Morgan *et al.*²¹, meta-analyses were eligible for inclusion if they met all of the following criteria: (1) Population: Included meta-analyses of primary studies assessing the association between PFAS exposure and health outcomes in any human population. Eligible studies could focus on single PFAS compounds or mixtures containing only PFAS. Meta-analyses of mixtures that included chemicals outside the PFAS family were excluded. (2) Exposure: Assessed exposure to any PFAS compound, including but not limited to perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). Studies examining mixtures containing non-PFAS substances were excluded. (3) Comparator: Compared populations with differing levels of PFAS exposure (including those with minimal or no exposure), as defined in the included primary studies or meta-analyses. Meta-analyses without explicit comparators were eligible if they synthesised observational studies relating PFAS exposure to health outcomes. (4) Outcomes: Reported adverse health outcomes in any age group (e.g., lower birth weight, reduced body mass index, decreased semen quality, hypertension, hyperuricaemia). Eligible meta-analyses were required to present an odds ratio (*OR*) or logarithmic odds ratio (*lnOR*) for the association between PFAS exposure and health outcomes, accompanied by a measure of variability (e.g., standard error or confidence

interval) and a measure of heterogeneity (e.g., I^2). (5) Study design: Synthesised results from primary studies using any study design, including correlational studies examining associations between PFAS exposure levels and health outcomes. Meta-analyses were defined as statistical syntheses of results from multiple independent studies. (6) Other considerations: Published in peer-reviewed journals in English, Russian, Polish, Spanish, Portuguese, Japanese, French, Italian, Simplified Chinese, or Traditional Chinese. No restrictions were placed on publication date. Research published in other languages was excluded.

Literature searches and screening

The literature search strategy was preregistered in May 2024²² and had two main sources: (1) Systematic evidence maps: Meta-analyses were extracted from two recent systematic evidence maps (Morrison et al.²³ and Ricolfi et al.²⁴), (2) Database searches: additional meta-analyses published after the evidence maps' cutoff date (August 4, 2022) were retrieved through comprehensive searches in Scopus, Web of Science Core Collection, PubMed, ProQuest, and BASE. However, while the preregistered strategy included a broader range of chemicals, for the present study we refined the dataset to focus exclusively on meta-analyses examining PFAS exposure. The search parameters, strings, and the number of hits for each database are presented in detail in supplementary materials (Method S01). The literature search generated a collection of studies, which first underwent records deduplication in R using the *RevTools* package²⁵. The refined dataset was imported into the Rayyan screening software (rayyan.ai) for further systematic literature screening. The screening process consisted of two stages: (1) Title, abstract, and keyword screening. Two independent reviewers screened all titles, abstracts, and keywords to identify studies that potentially met the inclusion criteria. (2) Full-text screening. The same reviewers assessed the full texts of the selected studies. Any disagreements between the two reviewers were resolved through discussion. If consensus could not be reached, a third reviewer from the author list was consulted to address unresolved conflicts.

Data extraction, warehousing, and coding strategy

LR utilised the free software Zotero (zotero.org, version 6.0.26) to organise and reference all meta-analyses identified during the literature search. Data extraction was conducted by LR and KM using two interconnected Google Sheets designed to capture the pre-specified data items (Table S02, Supplementary Data). A first table named "ma_details" reports meta-analyses' identification information. A second table titled "ma_e_details" stores meta-

analyses' point estimate identification information. To ensure accuracy, the two reviewers independently verified each other's data from a random 10% sample. Discrepancies between reviewers were below 10%, supporting the decision to complete data extraction for the remaining studies independently. The extracted data were organised into two separate, but relational tables based on the type of information collected. Health outcomes were categorised into groups according to the International Statistical Classification of Diseases (ICD, 11th revision)²⁶ to systematically organise our analysis (Table 1, Table So3). Raw extracted data were stored in the OSF open-source platform (<https://osf.io/g6c53/files/osfstorage>). The analysis code can be downloaded from our GitHub repository (https://github.com/ThisIsLorenzo/PFAS_health_metametaanalysis).

Statistical modelling framework

Our analysis targeted two fundamental aspects of PFAS-health outcome associations: (1) the magnitude of associations, and (2) the consistency of findings across studies. We quantified the magnitude using log odds ratios ($\ln OR$) and consistency using the percentage of observed variation in study results that is due to real differences (heterogeneity) rather than random sampling error (I^2), both of which were extracted from each meta-analysis. Since effective modelling of heterogeneity requires a common effect size with associated sampling error, we transformed I^2 values following the methodology of Higgins & Thompson²⁷:

$$H^2 = \frac{1}{1 - I^2}$$

and

$$\ln H = \ln \sqrt{H^2}$$

This transformation is necessary because I^2 does not have a normal sampling distribution suitable for meta-analysis, whereas $\ln H$ can be modelled with an associated standard error. For interpretability, we subsequently back-transformed $\ln H$ to I^2 and $\ln OR$ to odds ratios (OR). As I^2 is a widely used heterogeneity statistic in environmental epidemiology and readily interpretable, these back-transformations ensure the results remain accessible to a wide readership.

Standard errors for $\ln H$ ($SE_{\ln H}$) were calculated using formulas involving the Q -statistic (test for heterogeneity) and k (number of effect sizes in each meta-analytic estimate)²⁷:

$$Q = H^2(k - 1)$$

$$\text{if } Q > k \text{ then } SE_{lnH} = \frac{1}{2} \frac{\ln(Q) - \ln(k-1)}{\sqrt{(2Q)} - \sqrt{(2k-3)}}$$

$$\text{if } Q \leq k \text{ then } SE_{lnH} = \sqrt{\frac{1}{2(k-2)} \left(1 - \frac{1}{3(k-2)^2}\right)}$$

Confidence intervals were calculated as follows:

$$\exp((\ln H \pm 1.96)(SE_{lnH}))$$

In our interpretation, I^2 values above 75% indicate high heterogeneity (low consistency), 50–75% moderate–high, 25–50% moderate–low, and below 25% low heterogeneity (high consistency)^{27,28}. We recognise that these thresholds are arbitrary, as more appropriate heterogeneity measures such as τ^2 and prediction intervals are rarely reported in the literature and lack widely accepted interpretive benchmarks.

Random-effects models were implemented using the *rma* or *rma.mv* functions from the *metafor* R package²⁹ to generate overall effect estimates and heterogeneity measures. We adopted a consistent modelling strategy for both effect sizes and heterogeneity synthesis. Random effects were specified at two levels: (1) Meta-analysis level, representing study identity; and (2) Meta-analytic estimate level, representing the model outputs (individual effect estimates) nested within each meta-analysis. Our modelling accounted for two key sources of statistical dependence inherent in second-order meta-analyses: 1) Meta-analysis-level dependence, addressed by including random effects for both the meta-analysis and the individual effect sizes nested within it; and 2) Primary study-level dependence, addressed by constructing variance–covariance matrices.

To account for statistical dependence among meta-analytic estimates arising from shared primary studies, we constructed a variance–covariance matrix using the list of primary studies included in each meta-analysis (Supplementary Data). Because primary cohorts are frequently reused across multiple PFAS–outcome analyses and across meta-analyses, we allowed dependence between any pair of meta-analytic estimates that shared one or more primary studies. For each meta-analytic estimate i , we defined the set of unique primary studies S_i (identified by DOI). For each pair of estimates (i, j) , we quantified overlap as $n_{ij} = |S_i \cap S_j|$, with $n_i = |S_i|$ and $n_j = |S_j|$. We then defined the correlation between estimates (i, j) as a function of overlap:

$$\rho_{ij} = \frac{n_{ij}}{\sqrt{n_i n_j}}$$

which equals zero when no studies are shared and approaches 1 when the same primary studies underlie both estimates. The corresponding sampling covariance was computed as:

$$\text{Cov}_{ij} = \rho_{ij} \sqrt{v_i v_j}$$

where v_i and v_j are the sampling variances of the two meta-analytic estimates. The diagonal elements were set to the sampling variances ($\text{Var}_i = v_i$). This overlap-based matrix was used as the sampling variance–covariance structure in multilevel meta-analytic models fit with the *metafor* package.

P-values were computed using the *t*-distribution, as implemented in the *metafor* package. To address our subsequent objectives, we fitted subgroup meta-regression models using the *Subgroup Correlated Effects* approach³⁰ to estimate pooled *OR* and *I*² for each chemical and health outcome group separately and specific chemical–outcome combinations, thereby relaxing the assumption that all chemicals and health outcomes share the same variance.

Additional analyses of evidence and impact

LR and YY leveraged evidence mapping and alternative impact metrics to enrich our meta-analytic workflow, following the framework by Yang et al.³¹. Specifically, LR mapped the breadth and characteristics of studies, revealing gaps, biases and contextual factors. Additionally, LR and YY used alternative impact metrics (policy and clinical citations and media attention) to assess societal influence and real-world translation beyond academic citations. Alternative impact metrics were extracted from PlumX Metrics (plu.mx), an altmetrics tool developed by Elsevier that tracks and displays how research outputs are used, shared, and discussed across multiple platforms. This framework enriched meta-meta-analyses by moving beyond statistical pooling to expose how evidence is produced, disseminated, and applied, enhancing transparency and informing more nuanced interpretations of pooled effects.

Risk of bias and sensitivity analyses

LR evaluated the included meta-analyses to assess their reporting quality and potential biases, employing the AMSTAR2 tool³² for this assessment. Additionally, LR performed two sensitivity analyses to ensure the robustness of our findings: (1) Leave-one-out analysis: We iteratively took out one meta-analysis at a time from our model to test whether individual

studies had a disproportionate effect on the overall result. (2) Leave-one-out analysis using AMSTAR2 items: We tested the impact of the meta-analyses' methodological quality by using the results of the critical appraisal tool. For each of the 16 AMSTAR2 items, we iteratively run our model excluding meta-analyses with a poor methodological quality for that specific item.

Deviations and additions to the protocol

We implemented three modifications to our pre-registered protocol. First, we integrated the assessment of effect magnitude (*OR*) and consistency of results (I^2) within the three research questions, treating these dimensions together rather than separately. Second, we included a leave-one-out analysis in our sensitivity analyses to enhance confidence in the robustness of our results. Third, we did not perform the planned "exclusion of converted effect sizes" sensitivity analysis because we restricted our inclusion criteria to meta-analyses using only *OR* and *lnOR* effect size metrics. Originally, we intended to include meta-analyses regardless of the type of effect size; however, since preliminary meta-regression analysis revealed that conversion strategies significantly impacted overall results (Figure S01), we decided to limit our dataset to meta-analyses using *lnOR* or *OR* to ensure methodological consistency. Fourth, after compiling the list of primary studies included in each meta-analysis, we replaced the preregistered constant-correlation approach for modelling primary study-level dependence with an overlap-based variance–covariance matrix that reflects the observed sharing of primary studies across meta-analytic estimates.

Results

The systematic database searches yielded 1,413 articles. We screened titles and abstracts, removed duplicates, and conducted the full-text screening, ultimately retaining 63 studies. After combining these bibliographic records with the two previous evidence maps, we obtained a total of 106 meta-analyses. Finally, 83 studies were excluded to narrow down the dataset to meta-analyses using *OR* or *lnOR* as an effect size metric to estimate the impact of PFAS on human health (Figure 1). A total of 23 meta-analyses were included in our second-order meta-analysis^{15–18,33–51} (Table 1).

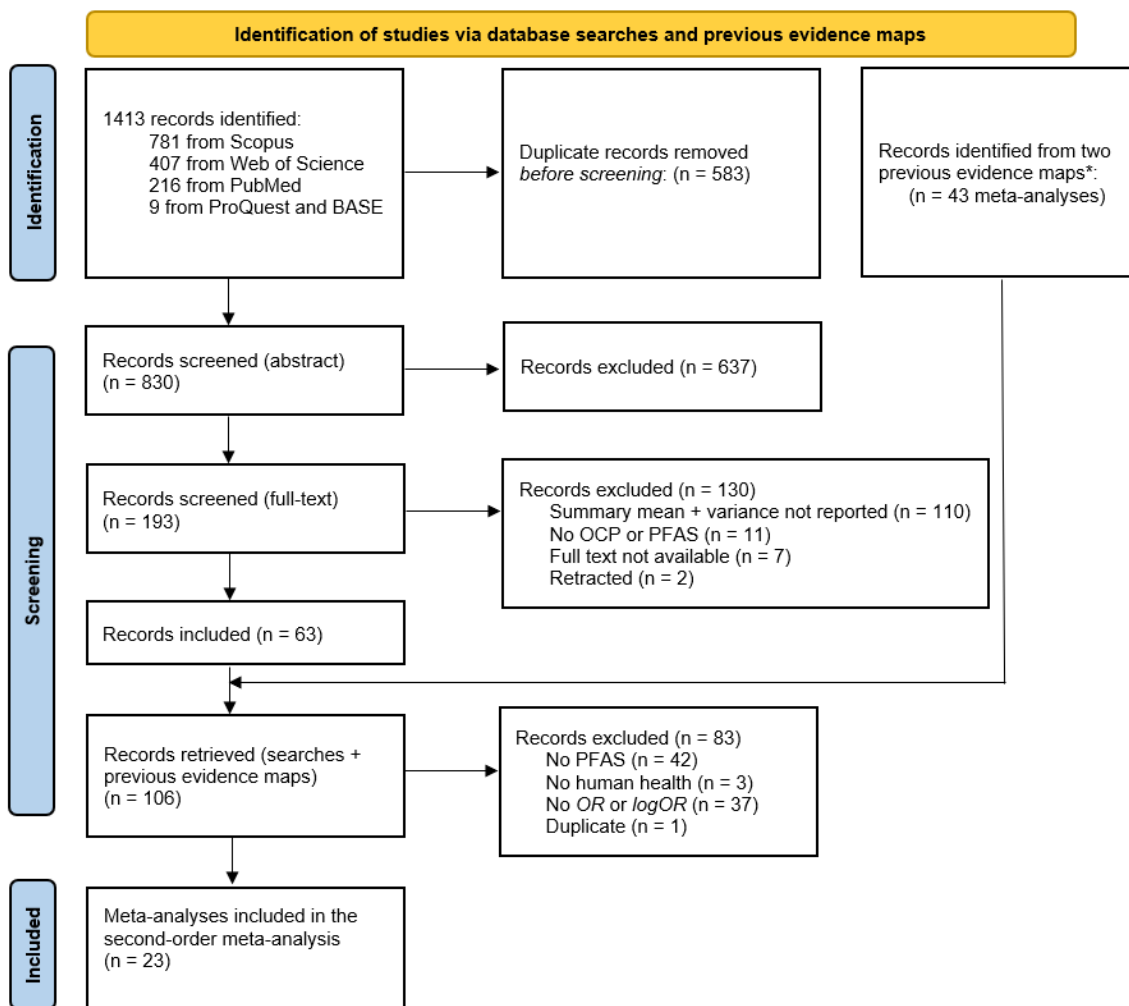


Figure 1 | PRISMA flowchart. Diagram illustrating the study selection process for the systematic review aimed at retrieving meta-analyses on the association between PFAS exposure and adverse health outcomes.

The dataset comprised 240 model results from 23 meta-analyses, along with their respective heterogeneity measures, representing over a thousand individual effect sizes from 161 primary studies. On average, each meta-analysis included 12 primary study results (median = 11, range = 8–29), underscoring their limited statistical power and motivating the use of a

second-order meta-analysis. The included meta-analyses examined 12 individual PFAS and 30 specific adverse health outcomes in humans. We categorised these health outcomes into 11 groups according to the International Statistical Classification of Diseases (ICD, 11th revision)²⁶ (Table S03), a global diagnostic ontology tool (icd.who.int/en/) maintained by the World Health Organisation and developed to standardise the classification of human diseases and health conditions. Across all model results, 48 (20%) showed statistically significant associations between PFAS exposure and adverse outcomes. At the level of meta-analyses, 17 of the 23 (74%) included at least one statistically significant association, whereas six (26%) reported only null findings. For a detailed mapping overview of our dataset, including the number of meta-analyses and effect sizes across individual health outcomes, health outcome groups, and PFAS compounds, refer to supplementary Figures S02–S04. The circulatory disease category consisted exclusively of hypertension outcomes, so our results for circulatory diseases specifically reflect associations with hypertension (Figure S04).

According to the data retrieved from PlumX Metrics, none of the included meta-analyses were cited in clinical guidelines, used to guide treatment, or contributed directly to clinical decision-making. In contrast, 13 out of the 23 meta-analyses were cited by policy or regulatory organisations (see Table S04 for alternative impact metrics results). The study most frequently cited by policy or regulatory organisations was a 2021 meta-analysis examining the association between PFOA and PFOS exposure and low birth weight (i.e., Cao et al. 2021³⁴), which received ten policy citations. The meta-analysis with the highest level of social media attention was published in 2022 and synthesised evidence on the association between PFOA, PFNA, PFHxS, and PFOS and breast cancer (i.e., Jiang et al. 2022⁴⁰). The journal that published the highest number of meta-analyses included in our synthesis was Environmental Research (n = 4), followed by Environmental Science and Pollution Research, and Ecotoxicology and Environmental Safety (each n = 3). An additional 11 journals published one or two meta-analyses each.

Table 1 | Details of the included meta-analyses in the second-order meta-analysis. “Chemicals”, “Population”, and “Health outcomes” are the main chemicals, population type, and outcomes investigated in a meta-analysis, respectively. “ICD11 code” stands for International Statistical Classification of Diseases (ICD, 11th revision). “ICD11 group” represents the highest grouping level in the classification of human diseases and health conditions. “k” is the number of individual effect sizes from primary studies included in the respective meta-analysis. For a description of ICD-11 groups, see Table S03.

Study reference	Chemicals	Population	Health outcomes	ICD-11 code	ICD-11 group	k
Cao et al., 2021 ³⁴	PFOA, PFOS	Newborns	Low birth weight	KA21.2Z	Certain conditions originating in the perinatal period	12

Cong et al., 2023 ⁴⁸	PFOA, PFOS, PFNA, PFHxS	Women	Breast cancer	2C6Z	Neoplasms	34
Gao et al., 2021 ³⁷	PFDA, PFHxS, PFNA, PFOA, PFOS, PFOSA-AcOH, PFUnDA, PFHpA	Newborns, Pregnant women	Preterm birth	KA21.4Z	Certain conditions originating in the perinatal period	103
			Gestational diabetes mellitus, miscarriage, preeclampsia	JA63.2, JA00.08, JA24.Z	Pregnancy, childbirth or the puerperium	
Hirke et al., 2023 ⁴³	PFOA, PFOS, PFHxS, PFNA, PFDA, PFHpA, PFUnDA	Pregnant women	Preeclampsia, gestational hypertension	JA24.Z	Pregnancy, childbirth or the puerperium	58
Jiang et al., 2022 ⁴⁰	PFOA, PFNA, PFHxS, PFOS	Women	Breast cancer	2C6Z	Neoplasms	68
Khosrojerdi et al., 2024 ⁴⁹	PFOA, PFOS, PFHxS, PFNA	Children, Adults	Osteoporosis	FB83.1Z	Diseases of the musculoskeletal system or connective tissue	12
Liu et al., 2018 ³³	PFOA	Children	Risk of overweight	5B80.00	Endocrine, nutritional or metabolic diseases	3
Liu et al., 2023 ⁴⁴	PFDA, PFDODA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFTrDA, PFUnDA	Women	Breast cancer	2C6Z	Neoplasms	53
Liu et al., 2024 ⁴⁵	PFOS, PFOA, PFNA, PFHxS, PFDA, PFDODA, PFHpS, PFHpA, PFUnDA	Newborns, Pregnant women	Preterm birth	KA21.4Z	Certain conditions originating in the perinatal period	170
			Small for gestational age (SGA)	KA20.0Z		
			Miscarriage	JA00.08	Pregnancy, childbirth or the puerperium	
Luo et al., 2020 ³⁹	PFAS, PFOS, PFHxS, PFNA	Children	Asthma	CA23.0	Diseases of the respiratory system	107
			Allergic rhinitis	CA08.0Z	Diseases of the skin	
			Eczema, atopic dermatitis	EA80.1		
			Wheeze	MD11.C	Symptoms, signs or clinical findings, not elsewhere classified	
Pan et al., 2023 ¹⁷	PFNA, PFOA, PFOS, PFHxS, PFUnDA	Adolescents, Adults, Elderly	Hypertension	BA00.Z	Diseases of the circulatory system	85
Pang et al., 2024 ⁵¹	PFOA, PFOS, PFHxS, PFNA, PFDA, PFBS, PFUnDA, PFDODA, PFHpA	Pregnant women	Gestational diabetes mellitus	JA63.2	Pregnancy, childbirth or the puerperium	186
			Hypertensive disorders of pregnancy (HDP), gestational hypertension, preeclampsia	JA24.Z		

Qu et al., 2021 ³⁶	PFOA, PFOS, PFHxS, PFNA, PFDA	Children	Attention-deficit hyperactivity disorder (ADHD)	6A05.Z	Mental, behavioural or neurodevelopmental disorders	27
Wang et al., 2023 ⁴²	PFOA, PFOS, PFNA, PFDA, PFHxS	Women	Fecundability. infertility	GA31.Z	Pregnancy, childbirth or the puerperium	74
Wang et al., 2024 ³⁵	PFOA, PFOS, PFHxS, PFNA	Pregnant women	Gestational diabetes mellitus	JA63.2	Pregnancy, childbirth or the puerperium	28
Wu et al., 2022 ¹⁶	PFOS, PFUnDA, PFOA, PFNA, PFHxS, PFDA	Newborns	Preterm birth	KA21.4Z	Certain conditions originating in the perinatal period	39
Yan et al., 2022 ⁴¹	PFHxS, PFDA, PFNA, PFOA, PFOS, PFUnDA, PFBS, PFDODA	Pregnant women	Gestational diabetes mellitus	JA63.2	Pregnancy, childbirth or the puerperium	55
Yang et al., 2023 ⁴⁵	PFOA, PFOS, PFHxS, PFNA, PFDA	Children, Adults	Hypertension	BA00.Z	Diseases of the circulatory system	39
Yang et al., 2024 ⁴⁷	PFAS, PFOA, PFOS, PFNA, PFHxS, PFDA, PFUnDA	Adults	Risk of total cancer, gastrointestinal tract cancer (GIC), genitourinary cancer, breast cancer, thyroid cancer, hematologic cancer, lung cancer, skin cancer	2C6Z	Neoplasms	864
Yao et al., 2023 ⁵⁰	PFOA, PFOS, PFNA, PFHxS	Children	Attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD)	6A05.Z	Mental, behavioural or neurodevelopmental disorders	34
Xiao et al., 2023 ¹⁸	PFOS, PFOA, PFNA, PFHxS	Adults	Hypertension	BA00.Z	Diseases of the circulatory system	50
Yu et al., 2023 ⁵²	PFDA, PFHxS, PFNA, PFOA, PFOS	Adults	Hyperuricemia	5C55.Y	Endocrine, nutritional or metabolic diseases	27
Zare Jeddi et al., 2022 ³⁸	PFOA, PFOS, PFNA, PFHxS	Adults	Risk of metabolic syndrome	5A44	Endocrine, nutritional or metabolic diseases	24

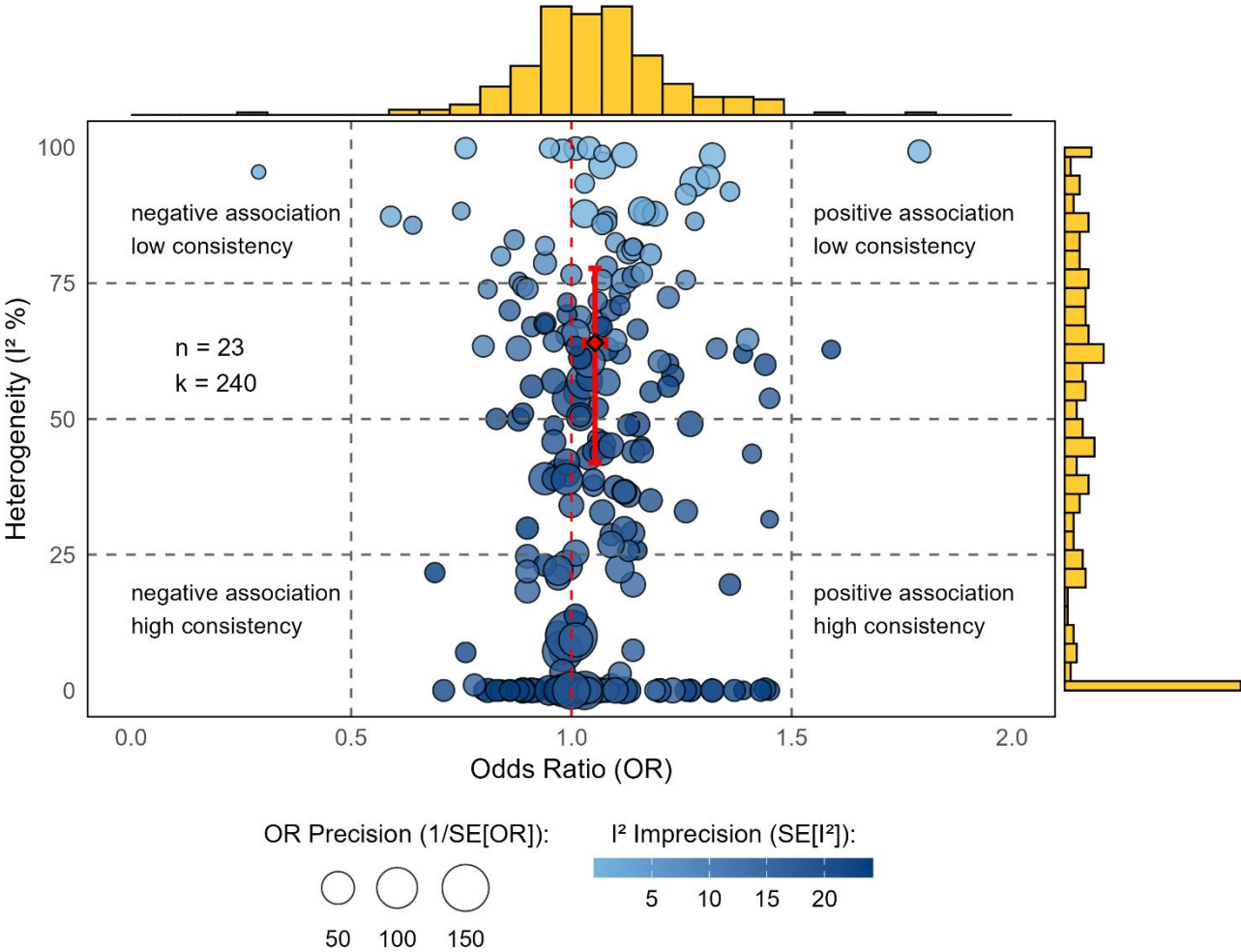
306

307 Overall meta-meta-analytic result

308 The pooled random-effects odds ratio (*OR*) across all PFAS-health outcome associations was
309 1.05 (95% CI [1.03-1.08] hereafter in square brackets, 95% PI = 0.85-1.28, $t_{[df = 239]} = 3.129$, p
310 = 0.002; Figure 2), indicating a 5% [3-8%] increase in odds in PFAS-exposed populations
311 compared to unexposed or less exposed groups. The total between-study heterogeneity in the

312 model of log odds ratios was high ($I^2_{OR}=84\%$), indicating substantial variation in effect sizes
313 across meta-analyses.

314 When we instead modelled the heterogeneity estimates (I^2) reported by the individual meta-
315 analyses, the pooled mean I^2 was 64.0% [41.9-77.7%] (95% PI = 0-98%, $t_{[df = 218]} = 4.436$, $p <$
316 0.001; Figure 2), indicating moderate variation in the consistency of findings. Finally,
317 modelling these I^2 values themselves revealed high between-meta-analysis variability in
318 heterogeneity measures ($I^2_{I^2}=98\%$). We observed an artificial clustering of I^2 values at zero
319 (Figure 2), reflecting truncated rather than true zero heterogeneity estimates, likely due to
320 limitations of the estimation methods used in the meta-analyses included in our study.
321 Additionally, we observed a few data points with large I^2 model weights (small standard
322 errors), which greatly contributed to the overall I^2 value.



323

324 **Figure 2 | Overall association and consistency of PFAS-related adverse health outcomes across meta-**
325 **analyses.** Each blue circle represents the combination of a meta-analytic effect size and associated heterogeneity measure
326 from 23 published meta-analyses on PFAS exposure and human health outcomes. The x-axis shows the pooled odds ratio
327 (OR), where values above 1 indicate increased odds of adverse outcomes. The y-axis depicts heterogeneity (I^2), representing
328 the percentage of variation across studies not due to chance. Bubble sizes are scaled by OR's precision (inverse of standard

error), and the colour gradient is according to I^2 's imprecision (standard error). The black diamond filled in red indicates the overall pooled estimate from a meta-meta-analysis, with red horizontal and vertical error bars showing its 95% confidence intervals for OR and I^2 , respectively. Grey dashed lines indicate thresholds for heterogeneity and OR . Quadrant annotations help interpret the strength and consistency of associations. The yellow histogram at the top and the yellow histogram on the right represent data distributions of odds ratios and heterogeneity measures, respectively. An explanation for the large number of I^2 values at zero is provided in the discussion section.

Compound-specific associations

Subgroup analyses by individual PFAS revealed differential patterns of association (Figure 3A). Among the 12 compounds examined, 10 were investigated in two or more meta-analyses and thus were included in subgroup analyses. Of these 10 compounds, 4 showed statistically significant positive associations with adverse health outcomes (PFOA: $OR = 1.09$ [1.04-1.15], $p < 0.001$; PFOS: $OR = 1.07$ [1.04-1.12], $p < 0.001$; PFHxS: $OR = 1.06$ [1.00-1.12], $p = 0.036$; PFBS: $OR = 1.30$ [1.17-1.45], $p = 0.002$). Three additional compounds (PFNA, PFHpA, and PFAS mixtures) showed positive but non-significant associations (Table S05). All compounds with positive and significant associations demonstrated medium to low consistency, except for PFBS which showed higher consistency (PFOA: $I^2 = 65.3\%$ [46.9-77.3%], PFOS: $I^2 = 71.5\%$ [48.5-84.2%], PFHxS: $I^2 = 66.1\%$ [37.1-81.7%], PFBS: $I^2 = 38.1\%$ [0.0-99.9%]).

In contrast, three longer-chain PFAS (PFDA, PFUnDA, and PFDoDA) showed no significant associations and medium heterogeneity, indicating more consistent null findings across studies (PFDA: $OR = 1.00$ [0.99-1.03], $p = 0.508$; $I^2 = 48.8\%$ [16.7-68.5%]; PFUnDA: $OR = 0.92$ [0.84-1.02], $p = 0.097$, $I^2 = 64.4\%$ [34.1-80.7%]; PFDoDA: $OR = 0.89$ [0.67-1.18], $p = 0.357$, $I^2 = 42.8\%$ [0.0-84.0%]).

Health outcome-specific associations

Analysis by health outcome categories revealed positive associations across all six groups examined, with two reaching statistical significance (i.e., diseases of the circulatory system and pregnancy or childbirth-related outcomes, Figure 3B). Within the circulatory disease category, hypertension was the sole health outcome examined; thus, our findings are explicitly reported to hypertension risk. Hypertension showed the strongest significant association ($OR = 1.09$ [1.05-1.12], $p < 0.001$) with moderate to low consistency ($I^2 = 71.5\%$ [58.0-80.7%]), while pregnancy and childbirth-related outcomes demonstrated a modest but significant association ($OR = 1.04$ [1.01-1.08], $p = 0.007$) with moderate to high consistency ($I^2 = 35.9\%$ [21.7-47.5%]).

Four additional outcome categories showed positive but non-significant associations: endocrine/metabolic diseases ($OR = 1.11$ [0.93-1.31], $p = 0.210$), neoplasms ($OR = 1.03$ [0.96-1.10], $p = 0.396$), perinatal conditions ($OR = 1.04$ [0.99-1.10], $p = 0.121$), and

neurodevelopmental disorders ($OR = 1.01 [0.92-1.11]$, $p = 0.862$). Notably, neoplasms exhibited the lowest consistency ($I^2 = 92.7\% [49.3-98.9\%]$) despite a modest pooled effect size, suggesting substantial variability in cancer-related findings across studies (Table So6).

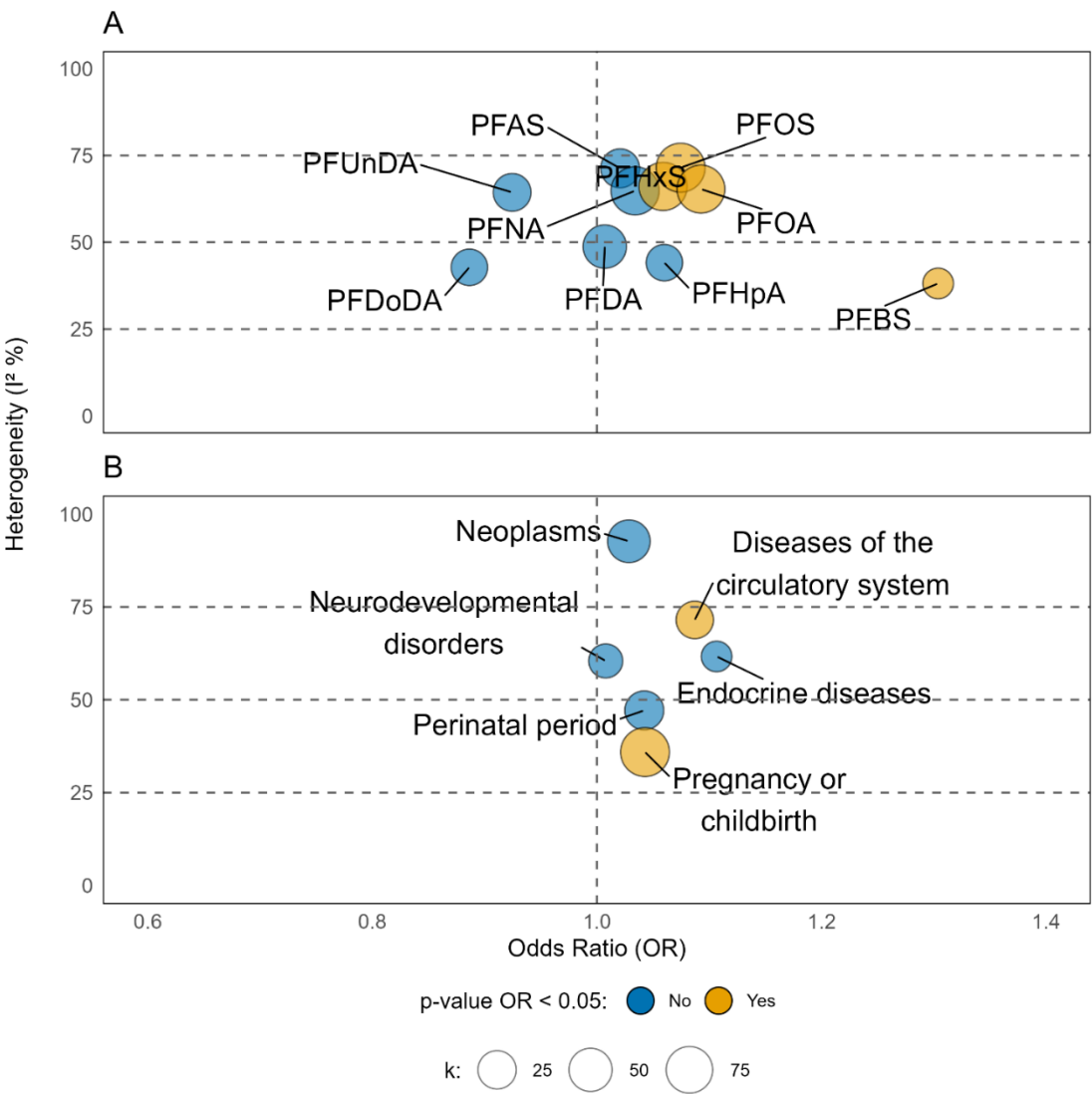


Figure 3 | Compound-specific (A) and outcome-specific (B) associations between PFAS exposure and health outcomes. Each bubble represents the combination of a pooled second-order meta-analytic effect size and associated pooled heterogeneity value. The x-axis shows the pooled odds ratio (OR), where values above 1 indicate increased odds of adverse outcomes. The y-axis depicts pooled heterogeneity (I^2), representing the percentage of variation across primary studies not due to chance. Bubble sizes are scaled by the number of meta-analytic estimates (k) and coloured according to the statistical significance of their pooled odds ratio (blue = $p\ OR < 0.05$ and grey = $p\ OR \geq 0.05$). Grey dashed lines indicate thresholds for heterogeneity. Quadrant annotations help interpret the strength and consistency of associations. “Perinatal period” is an abbreviation for “Certain conditions originating in the perinatal period”, and “Pregnancy or childbirth” is an abbreviation for “Certain conditions occurring during pregnancy, childbirth, or the puerperium”.

Chemical-outcome specific associations

At the most granular level, we conducted subgroup meta-analysis for 33 chemical-outcome combinations that had data from at least two meta-analyses (Table So8). Eight pairs showed statistically significant associations, with seven being positive and one negative. The strongest

381 positive associations were observed between PFBS and pregnancy complications (OR = 1.30
382 [1.06-1.61], $p = 0.039$), PFOS and hypertension (OR = 1.19 [1.04-1.36], $p = 0.033$), and PFOA
383 and hypertension (OR = 1.14 [1.08-1.21], $p = 0.013$). Additional positive and statistically
384 significant associations included PFHxS with hypertension (OR = 1.03 [1.02-1.05], $p =$
385 0.019), PFNA with hypertension (OR = 1.10 [1.01-1.19], $p = 0.042$) and perinatal conditions
386 (OR = 1.13 [1.00-1.26], $p = 0.041$), and PFOA with pregnancy complications (OR = 1.10 [1.02-
387 1.18], $p = 0.022$). Conversely, PFUnDA showed a statistically significant negative association
388 with pregnancy complications (OR = 0.87 [0.82-0.92], $p = 0.006$).

389 The associations between PFOS and PFOA with hypertension showed low consistency ($I^2 =$
390 87.6% [16.1-98.2%]; $I^2 = 79.9\%$ [14.7-95.3%], respectively), whilst the associations between
391 PFHxs and PFNA with hypertension showed medium to low consistency ($I^2 = 57.8\%$ [47.1-
392 66.4%]; $I^2 = 50.4\%$ [22.5-68.3%], respectively). Similarly, the negative association between
393 PFUnDA and pregnancy complications showed medium to low consistency ($I^2 = 53.0\%$ [0.0-
394 93.9%]). A medium to high consistency was observed between PFNA and perinatal conditions
395 ($I^2 = 46.2\%$ [0.0-75.5%]) and PFOA and pregnancy complications ($I^2 = 37.7\%$ [9.1-57.3%]).
396 The small number of meta-analyses reporting both a heterogeneity measure and a pooled
397 effect estimate precluded the assessment of result consistency for the association between
398 PFBS and pregnancy complications (Table So8).

399 **Risk of bias and sensitivity analysis**

400 The leave-one-out analysis demonstrated that no individual meta-analysis exerted a
401 disproportionate influence on the overall pooled estimate (Table So9). When each meta-
402 analysis was iteratively excluded from the model, the resulting effect sizes remained
403 consistent with the original findings, with all confidence intervals overlapping substantially
404 (Figure So5A, Figure So5B). Additionally, we observed a balanced change in the percentage
405 of between-study heterogeneity (τ^2) when individual studies were excluded (Figure So5C).
406 Similarly, the methodological quality-based sensitivity analysis using AMSTAR2 tool
407 revealed stable results across all 16 assessment domains (Figure So6). When meta-analyses
408 scoring poor methodological quality for each AMSTAR2 item were systematically excluded,
409 the pooled estimates showed no meaningful deviations from the primary analysis (Table S10).

Discussion

Pooling all chemicals and health outcomes from the included meta-analyses revealed that PFAS exposure was associated with a modest yet statistically significant 5% increase in the odds of adverse health outcomes. This effect has considerable public health implications, given the ubiquity of PFAS exposure^{9,10} and the large populations at risk globally⁵³. The association was accompanied by moderate to high heterogeneity, indicating meaningful variation in primary study findings across populations and designs.

Compound-specific patterns and implications

PFBS, PFHxS, PFOA, and PFOS showed the strongest and most consistent associations with adverse health effects. PFOA and PFOS have been widely produced, are environmentally persistent, and have been subject to regulatory restrictions in several regions, including the European Union. The long human half-lives of PFOA and PFOS^{11,12} underpin their broad toxicological profiles, with significant associations spanning cardiovascular (hypertension), neurodevelopmental (ASD, ADHD), and reproductive outcomes (gestational diabetes, preeclampsia, miscarriage). Shorter-chain replacements such as PFBS and PFHxS also showed notable associations. PFHxS has a particularly long half-life (~5 years)¹² and is increasingly detected in maternal serum and breast milk, potentially affecting foetal development^{54–56}. PFBS, often used as a PFOS replacement⁵⁷, is less bioaccumulative⁵⁸ but is nonetheless consistently linked to pregnancy complications. Conversely, non-significant results for longer-chain PFAS (e.g., PFDA, PFHpA, PFUnDA, PFDoDA) may reflect the absence of effect or a lower exposure and reduced bioavailability. Biological mechanisms for PFAS toxicity include activation of peroxisome proliferator-activated receptors (PPARs)⁵⁹, disruption of metabolic pathways, and endocrine interference; mechanisms consistent with observed metabolic, reproductive, and developmental outcomes.

Health outcome-specific patterns and implications

Hypertension emerged as the most affected health domain, with statistically significant evidence of a 9% increase in odds of disease. Given hypertension's global prevalence (>1.3 billion adults)⁶⁰, even small relative increases translate into substantial population-level burdens. Mechanistic pathways likely include increased serum cholesterol, oxidative stress, and inflammatory responses that accelerate atherosclerosis⁶¹, suggesting a potential class effect on vascular health.

Pregnancy and perinatal outcomes, including preeclampsia, gestational diabetes, preterm birth, and reduced birth weight, were consistently associated with PFAS exposure. These outcomes are plausibly mediated by endocrine disruption, altered placental function, and impaired foetal growth, with lifelong implications for both mothers and offspring⁶². Notably, PFAS exposure has been linked to decreased estradiol levels (E2)⁶³, which plays a crucial role in maintaining healthy pregnancy outcomes. Cancer-related outcomes showed high heterogeneity, likely due to the diversity of cancer types studied and the multifactorial nature of carcinogenesis⁶⁴. While no significant overall association was detected, PFAS may influence specific subtypes, warranting further investigation. Metabolic and endocrine effects showed the largest effect size, but did not reach statistical significance; however, associations with hyperuricemia⁵², altered lipid/glucose metabolism⁶⁵, and reduced thyroxine levels^{66,67} are supported by mechanistic and observational evidence. Male reproductive effects remain understudied but may include altered testosterone levels and reduced fertility⁶⁸.

Analysis of 33 chemical-outcome combinations revealed patterns obscured in broader analyses. Multiple PFAS (PFHxS, PFNA, PFOA, PFOS) were consistently associated with hypertension, reinforcing the hypothesis of a class cardiovascular effect. PFNA was associated with conditions arising during the perinatal period, such as preterm birth and small-for-gestational-age outcomes, although evidence was borderline significant. The inverse association for PFUnDA with pregnancy complications should be interpreted cautiously, as it may reflect confounding or pharmacokinetic factors³⁷.

Heterogeneity and methodological considerations

Most between-study variation reflected true differences rather than sampling error, driven by variation in exposure assessment, population characteristics, outcome definitions, and study designs. This substantive heterogeneity is an inherent feature of a second-order meta-analysis aggregating evidence across diverse contexts. Readers seeking more detailed assessments of specific exposure thresholds, vulnerable subpopulations, or outcome-specific effect estimates are encouraged to consult the primary meta-analyses and original studies included herein. Some zero I^2 values likely result from statistical truncation in heterogeneity estimation (e.g., using the DerSimonian–Laird estimator, which is the default in software such as STATA, and was employed in 90% of the included meta-analyses), rather than the true absence of heterogeneity (for more details, see Method S02). Statistical truncation in heterogeneity estimation underscores the need for improved reporting and interpretation of heterogeneity in meta-analyses. Practical steps include routinely reporting multiple

474 heterogeneity metrics (e.g., I^2 alongside τ^2 and prediction intervals), clearly stating the
475 estimator used, and avoiding over-interpretation of zero I^2 values as evidence of
476 homogeneity.

477 **Strengths and limitations**

478 This second-order meta-analysis represents the most comprehensive quantitative synthesis
479 to date and the first of its kind to integrate quantitative evidence across multiple PFAS and
480 health outcomes simultaneously. By jointly estimating effect magnitude and between-study
481 consistency, this approach provides a higher-level assessment of robustness that is directly
482 relevant to regulatory and public health decision-making, particularly in the context of
483 widespread, mixed PFAS exposures. The ability to evaluate consistency across a fragmented
484 evidence base is a key strength, allowing broad and reproducible patterns to be distinguished
485 from isolated or unstable associations.

486 Several limitations should nevertheless be acknowledged, most of which reflect inherent
487 constraints of the existing literature rather than the analytical framework itself. First, I^2 is
488 not an absolute measure of heterogeneity and is influenced by study number and precision⁶⁹.
489 Second, biases present in primary studies, including residual confounding and exposure
490 misclassification, necessarily propagate into higher-order syntheses. Third, methodological
491 quality varied across included meta-analyses; however, sensitivity analyses excluding lower-
492 quality reviews produced qualitatively similar results, suggesting that our conclusions are
493 robust to this variability. Additional important limitations include the assumption of broadly
494 comparable exposure levels despite differences in dose and potency of individual PFAS in the
495 mixture, the predominance of studies from high-income countries limiting global
496 generalisability, and the restriction to (log) odds ratios, which may exclude evidence reported
497 using alternative effect measures. Importantly, these constraints are unlikely to alter the
498 overarching patterns identified but instead highlight areas where future evidence synthesis
499 could be further strengthened.

500 Future second-order syntheses would benefit from incorporating risk ratios, hazard ratios,
501 and dose–response relationships together with including relevant mixtures, applying
502 advanced methods to better address confounding and exposure misclassification, and
503 expanding coverage to underrepresented regions to enhance global relevance.

Public health and regulatory implications

This second-order synthesis provides robust evidence that PFAS exposure is associated with multiple adverse human health outcomes, with the strongest and most consistent associations observed for hypertension and pregnancy-related conditions. Although effect sizes are modest at the individual level, their public health significance is amplified by the near-universal exposure to PFAS and the high baseline prevalence of these outcomes, particularly cardiovascular and perinatal disorders. These findings support enhanced PFAS monitoring in vulnerable populations and the consideration of cumulative exposure histories in both clinical risk assessment and population health surveillance. Importantly, the consistency of associations across multiple PFAS compounds and health endpoints reinforces the relevance of class-wide rather than solely chemical-specific risk management strategies. In this context, class-based regulatory approaches, such as those implemented in Canada⁷⁰, offer a pragmatic framework for addressing simultaneous exposure to multiple PFAS, including replacement compounds. As jurisdictions such as the European Union move towards broad PFAS restrictions, comprehensive and integrative evidence syntheses such as this are essential to support proportionate, precautionary, and evidence-based decision-making aimed at reducing long-term population health burdens.

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531 **Author contributions**

532 **Lorenzo Ricolfi:** Writing – review & editing, Writing – original draft, Visualisation,
533 Software, Project administration, Methodology, Investigation, Formal analysis, Data
534 curation, Conceptualisation, Funding acquisition. **Yefeng Yang:** Writing – review & editing,
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540 **Nakagawa:** Conceptualisation, Methodology, Writing – review & editing, Supervision,
541 Funding acquisition.

542 **Competing interests**

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

545 **Data and materials availability**

546 The raw data and the analysis code can be downloaded from our GitHub repository
547 (https://github.com/ThisIsLorenzo/PFAS_health_metametaanalysis).

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