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Review article

Exposure to per- and poly-fluoroalkyl substances and lung, head and neck, and thyroid cancer: A systematic review and meta-analysis

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ABSTRACT

Recent evidence suggests that exposure to per- and polyfluoroalkyl substances (PFAS) may increase the risk of different cancer types, such as kidney and testicular cancers. Instead, evidence for lung, head and neck, and thyroid cancer is sparse. Hence, we aimed to summarize available literature on the topic.

We searched Pubmed and Scopus in January 2024 to retrieve relevant studies and estimated pooled relative risks (RRs) and 95% confidence intervals (CIs) for lung, head and neck, and thyroid cancers according to PFAS exposure using restricted maximum likelihood method.

Pooled RRs for occupational or environmental PFAS exposure were 1.20 (95% CI: 1.12–1.28; $I^2 = 0.0\%$, $p_{het} = 0.9$; n. studies = 9), 1.15 (95% CI: 0.96–1.37; $I^2 = 0.0\%$, $p_{het} = 0.7$; n. studies = 3), and 1.54 (95% CI: 0.86–2.78; $I^2 = 69.0\%$, $p_{het} = 0.02$; n. studies = 4) for lung, head and neck, and thyroid cancer, respectively. We did not find compelling evidence of publication bias for lung cancer ($p = 0.3$).

Studies on statistically modelled serum PFAS levels did not support associations with these cancers.

We found no positive associations between measured serum levels of 6 different types of PFAS and thyroid cancer. However, the pooled RR of two case-control studies nested within cohorts on the association between natural log-unit increase of perfluorooctanesulfonic acid (PFOS) and thyroid cancer was 1.51 (95% CI: 1.11–2.05; $I^2 = 21.1\%$, $p_{het} = 0.3$).

PFAS exposure may be associated with lung and thyroid cancer. Due to the limited number of studies and their limitations, further prospective studies with appropriate account of co-exposure with other carcinogens and detailed exposure assessment are needed to establish causality of observed associations.

1. Background

Lung cancer currently represents the most common cancer globally, with approximately 2.5 million new cases each year, and is responsible for 1.8 million deaths annually, making it the leading cause of cancer death worldwide (Bray et al., 2024). An estimated 950,000 new head and neck cancer (HNC) cases and 480,000 deaths attributable to HNC occur worldwide each year (Bray et al., 2024). Also, thyroid cancer is the seventh most common cancer globally, with 800,000 new cases each year, while its mortality is substantially lower (47,500 deaths annually) (Bray et al., 2024).

Environmental factors may play a relevant role in affecting the risk of all these cancer types. Among them, per- and polyfluoroalkyl substances (PFAS) are raising concerns in the scientific community due to their potential harmful effects on human health. PFAS are ubiquitous synthetic chemicals, highly resistant to degradation, that have been widely

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; CI, confidence interval; COSMOS-E, Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology; HNC, head and neck cancer; IARC, International Agency for Research on Cancer; NOS, Newcastle-Ottawa Scale; PECO, Population Exposure Comparator Outcomes; PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctanesulfonic acid; PPARα, peroxisome proliferator-activated receptor alpha; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, Prospective Register of Systematic Reviews; REML, restricted maximum likelihood method; RR, relative risk.

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used both for industrial applications and for consumer products (Glüge et al., 2020). While occupational PFAS exposure mainly occurs through inhalation, and to a lesser extent through dermal adsorption and dust ingestion, diet and drinking water represent the main sources of exposure in the general population (Zahm et al., 2024).

Among different types of PFAS, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) were classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans and possibly carcinogenic to humans, respectively (Zahm et al., 2024). These classifications were based on evidence in experimental animals and mechanistic evidence in humans (i.e., epigenetic alterations and immunosuppression), while evidence for cancer among humans was "limited" (for PFOA) or "inadequate" (for PFOS) (Zahm et al., 2024).

Previous meta-analyses have investigated the association between PFAS exposure and kidney, liver, testicular, breast, and thyroid cancer (Seyyedsalehi and Boffetta, 2023; Cong et al., 2023; Bartell and Vieira, 2021; Chang et al., 2024; van Gerwen et al., 2024). As for the latter, however, the previous meta-analysis was limited to thyroid cancer incidence, not including studies on mortality. In addition, to our knowledge, no meta-analyses on the potential association between PFAS exposure and lung and head and neck cancer have been conducted so far. Hence, we aimed to provide an overview of currently available literature and to summarize findings from previous epidemiological studies on the potential association between PFAS exposure and lung, head and neck, and thyroid cancer.

2. Material and methods

We conducted a systematic review on the association between PFAS exposure and cancer of any sites other than liver, kidney, and testis, which we investigated previously (Seyyedsalehi and Boffetta, 2023).

The protocol for our review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42024560837). We carried out the review according to the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidelines (Dekkers et al., 2019), and reported it herein in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

2.1. Search strategy and study selection

We searched PubMed and Scopus electronic databases to identify relevant studies. The search strategy was developed according to the Population, Exposure, Comparator, Outcomes (PECO) framework, with the following structure (Morgan et al., 2018):

Population: both workers in multiple industrial settings and general population,

Exposure: exposure to any types of PFAS, including both environmental and occupational exposure, as well as exposure assessed through measurement of PFAS serum levels,

Comparator: individuals not exposed to PFAS or with the lowest exposure in the original study,

Outcomes: incidence, prevalence, and mortality of cancers occurring in any sites other than liver, kidney, and testis.

The complete search strategy can be found in Supplementary Table 1. The search was completed on January 23, 2024.

For the current review, we considered exposure to be occupational if occurring at work, regardless of the source of exposure, and environmental if occurring among the general population in the community setting and due to exposure to any types of contaminated environmental matrices (e.g., water, air, soil).

Retrieved records were screened independently by two researchers according to their title and abstract. Thus, full texts of relevant records were assessed independently by two researchers, following the same procedure. In order to identify additional studies, we also manually searched reference lists of included studies and previous reviews, including the IARC Monograph (International Agency for Research on Cancer, 2017), and the report on the toxicological profile for perfluoroalkyls by the Agency for Toxic Substances and Disease Registry (ATSDR) (Agency for Toxic Substances and Disease Registry, 2021). Any disagreements were solved by discussion.

During the study selection process, we included retrieved records if they were: (1) peer-reviewed reports with original data, (2) studies with cohort, case-control, cross-sectional, or ecological design, (3) studies evaluating the association between occupational or environmental PFAS exposure, including those focused on serum PFAS levels, and incidence, prevalence, or mortality of cancers other than liver, kidney, or testicular cancers, (4) studies on human subjects, (5) studies reporting a relative measure of association, or data allowing its computation.

Conversely, we excluded: (1) studies involving animals or cell cultures, (2) conference proceedings, book chapters, theses, commentaries, and letters to editors, and (3) reviews or meta-analyses.

Where multiple reports were based on the same study population, we only included the most recent update.

From here onwards we use the term incidence in the paper to refer to cancer occurrence (i.e., both incidence and prevalence), as opposed to mortality.

After identifying studies reporting relevant estimates on any cancer types other than those occurring in the liver, kidney, or testis, we included in this report and in the meta-analysis described herein only studies reporting data on lung, head and neck, and thyroid cancer.

2.2. Data extraction and evaluation of study quality

Two researchers independently extracted the following information for included studies, if available: author details, publication year, country, study design, PFAS types representing the main exposure, type of exposure (occupational, environmental), type of reference population (internal, external), cancer types, outcome (incidence, mortality), number of participants, and measures of association with 95% confidence intervals (CI). Any disagreements were resolved by discussion.

Regarding the type of reference population, we considered it internal when a group with no or low exposure from the same study population as the group considered exposed was used as a referent, and external when cancer incidence or mortality in the study population were compared with those of a population not part of the same cohort (typically the general population), by using standardization.

Study quality assessment was carried out independently by two researchers using a modified version of Newcastle-Ottawa Scale (NOS) (Wells et al.) (Supplementary Table 2). The modified scale includes a total of 8 items, with the total score ranging between 0 (highest risk of bias) and 10 (lowest risk of bias), given by the sum of scores for each individual item. Disagreements were solved by involving a third researcher.

2.3. Synthesis of results

We estimated pooled relative risks (RRs) and the corresponding 95% CIs for the association between environmental or occupational PFAS exposure and lung, head and neck, and thyroid cancer with a random-effects approach, specifically using restricted maximum likelihood method (REML) (Langan et al., 2019). Any relative measures of associations other than RR, including hazard ratio, standardized mortality ratio, standardized incidence ratio, and odds ratio, were considered valid approximations of RRs for the purpose of the meta-analysis. Where possible, we included in the meta-analysis estimates for the highest intensity of environmental or occupational exposure, if stratified estimates according to dose/intensity were available. Additionally, we combined study-specific stratified estimates (e.g., by strata of participants' characteristics) using an inverse variance fixed-effects model, where needed, before pooling them with estimates from other studies. In order to assess

between-study heterogeneity we used the I^2 statistic, which represents the amount of between-study variability in estimates due to heterogeneity (i.e., due to clinical or methodological differences, or both, between the studies) rather than to chance (Higgins et al., 2003). Heterogeneity was considered low for values of the I^2 statistic lower than 30%, moderate between 30% and 59%, and high for values equal to 60% or higher (Alba et al., 2016).

First, we analyzed data on incidence and mortality combined, under the assumption of mortality being a valid indicator for incidence within studies reporting only data regarding the former (Hamra et al., 2014). Since the approach of combining data on incidence and mortality may be appropriate for cancers with low survival, such as lung cancer (5-year

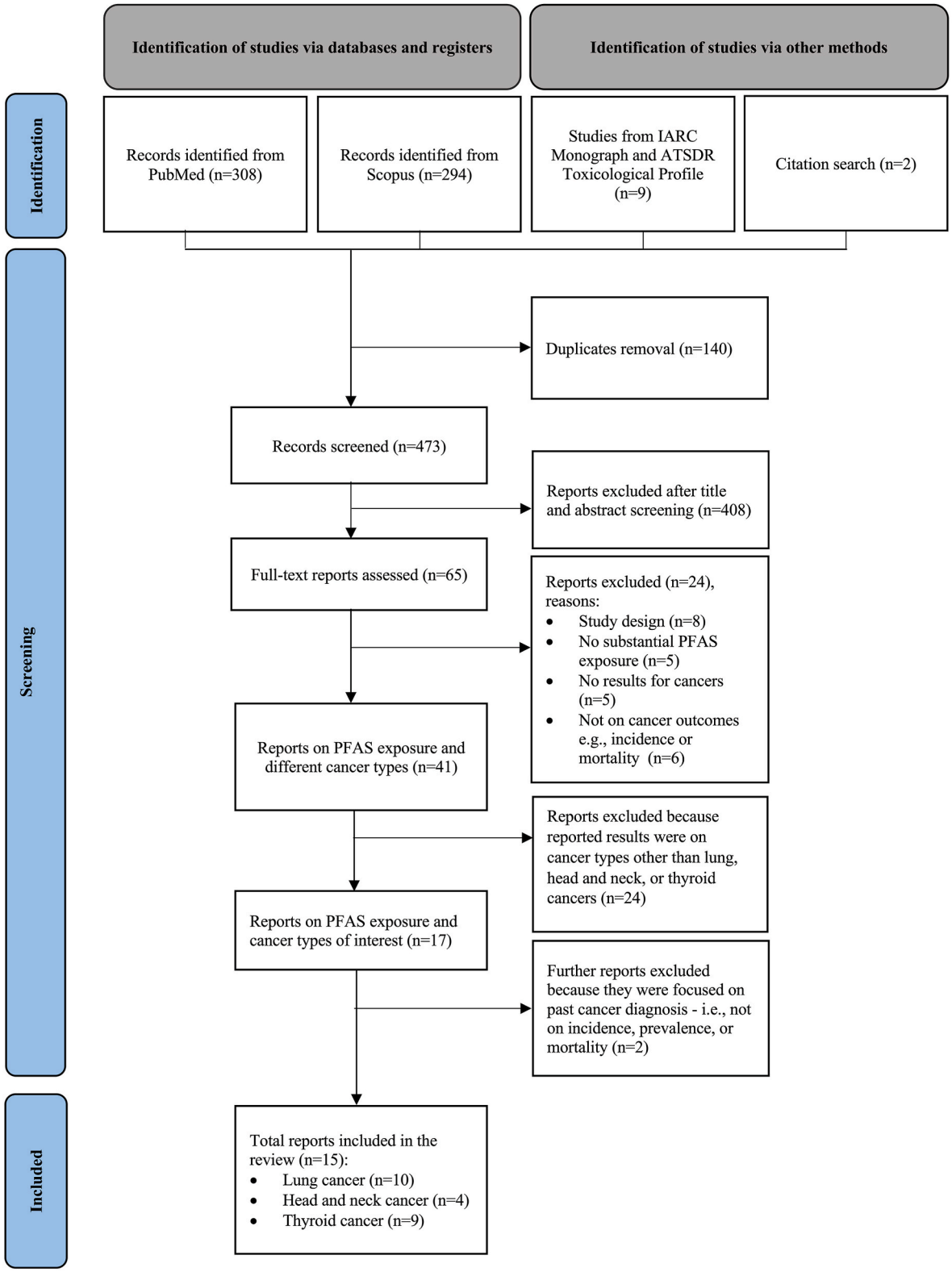

Fig. 1. Flowchart of the study selection process.

survival rate in the USA, years 2014–2020: 26.7%) (Surveillance Research Program - National Cancer Institute, 2024), but not for cancers with lower case-fatality rates, including thyroid cancer and some types of HNC (Surveillance Research Program - National Cancer Institute, 2024), we also analyzed data separately by outcome.

Due to the limited number of studies for other cancer types, we conducted subgroup and sensitivity analyses on environmental or occupational PFAS exposure for lung cancer only. These included analyses restricted to male individuals, stratified by country (USA, any other), restricted to cohort studies, by type of reference population (internal, external), by type of PFAS representing the main exposure (PFOA, PFOS, multiple/not specified), by type of exposure (environmental, occupational), by NOS score (<7, ≥ 7).

Eventually, we evaluated occurrence of publication bias with contour-enhanced funnel plots and Egger's tests for lung cancer only (Higgins et al., 2019; Peters et al., 2008; Egger et al., 1997), while we did not assess it for other cancer types due to the limited number of included studies (Higgins et al., 2019; Peters et al., 2008). In particular, results of a meta-analysis can be biased due to missing evidence when estimates from an otherwise eligible study are not available (i.e., not published) due to lack of statistical significance or because of magnitude or direction of study results (Page et al., 2024). Funnel plots are graphical ways to evaluate occurrence of such bias, in which point estimates from individual studies are plotted against a measure of study precision (typically standard errors), which is related to sample size. Hence, funnel plots can be assessed visually or statistically (i.e., using Egger's test or other types of similar tests) for asymmetry, which indicates that results may indeed be biased (Page et al., 2024).

As for serum PFAS levels, we estimated RRs and 95% CI for the association between a natural log-unit increase in their measured concentration and thyroid cancer using REML method, overall and by study design (case-control, nested case-control). Instead, the limited number of studies did not allow to carry out a comparable meta-analysis also for lung and head and neck cancer. The analysis was limited to the types of PFAS investigated by at least 3 studies, and results from a single study on different isomers of the same type of PFAS (e.g., linear and branched) were combined with an inverse variance fixed-effects model before pooling them with those from other studies. Additionally, we excluded from the meta-analysis studies on serum PFAS levels that were statistically modelled or estimated, rather than being measured among all study participants. Nevertheless, studies on modelled serum PFAS levels, as well as those on lung and head and neck cancers (i.e., regardless of whether measured and modelled PFAS concentrations were used), were retained in qualitative review and their results were reported narratively.

Statistical analyses were performed with Stata software version 18.5 (StataCorp LLC, College Station, Texas, USA).

3. Results

3.1. Selection process and study characteristics

The study selection process is described in Fig. 1. A total of 471 records were screened by title and abstract, and subsequently 63 full-text articles were assessed. Overall, 17 articles reported relevant data on PFAS exposure and cancer. Notably, 2 of these studies were excluded because they investigated the association between serum PFAS levels and self-reported past diagnosis of cancer (i.e., without further information on cancer status at the time of blood sample collection) (Cathey et al., 2023; Moon and Mun, 2024), rather than being focused on cancer incidence, prevalence, or mortality, with potential reverse causation. Hence, a total of 15 studies were included in our systematic review (Gilliland and Mandel, 1993; Alexander et al., 2003; Olsen et al., 2004; Lundin et al., 2009; Steenland and Woskie, 2012; Barry et al., 2013; Vieira et al., 2013; Girardi and Merler, 2019; Li et al., 2022, 2023; Law et al., 2023; Leonard et al., 2008; Liu et al., 2022; van Gerwen et al., 2023; Madrigal et al., 2024), 11 of them with data on lung cancer (Gilliland and Mandel, 1993; Alexander et al., 2003; Olsen et al., 2004; Lundin et al., 2009; Steenland and Woskie, 2012; Barry et al., 2013; Vieira et al., 2013; Girardi and Merler, 2019; Li et al., 2022; Law et al., 2023; Leonard et al., 2008), 4 on HNC (Barry et al., 2013; Li et al., 2022; Law et al., 2023; Leonard et al., 2008), and 9 on thyroid cancer (Barry et al., 2013; Vieira et al., 2013; Li et al., 2022, 2023; Law et al., 2023; Leonard et al., 2008; Liu et al., 2022; van Gerwen et al., 2023; Madrigal et al., 2024), respectively.

Main characteristics of included studies are reported in Table 1. They were published between 1993 and 2024, and the majority of them were carried out in the USA (60.0%, n = 9) (Gilliland and Mandel, 1993; Alexander et al., 2003; Olsen et al., 2004; Lundin et al., 2009; Steenland and Woskie, 2012; Barry et al., 2013; Vieira et al., 2013; Leonard et al., 2008; van Gerwen et al., 2023). Most studies had a cohort study design (66.7%, n = 10) (Gilliland and Mandel, 1993; Alexander et al., 2003; Olsen et al., 2004; Lundin et al., 2009; Steenland and Woskie, 2012; Barry et al., 2013; Girardi and Merler, 2019; Li et al., 2022; Law et al., 2023; Leonard et al., 2008), while a minority of them were case-control studies (33.3%, n = 5), either nested (van Gerwen et al., 2023; Madrigal et al., 2024) or not (Vieira et al., 2013; Li et al., 2023; Liu et al., 2022) within a cohort.

Cancer incidence or mortality were ascertained by most studies (80.0%, n = 12) using cancer registries, vital records, death certificates, or medical records (Gilliland and Mandel, 1993; Alexander et al., 2003; Olsen et al., 2004; Lundin et al., 2009; Steenland and Woskie, 2012; Vieira et al., 2013; Girardi and Merler, 2019; Li et al., 2022; Law et al., 2023; Leonard et al., 2008; van Gerwen et al., 2023; Madrigal et al., 2024). In one study, participants used questionnaires to report cancer occurrence, which was further validated with information from cancer registries and medical records (Barry et al., 2013). In two studies, cases were individuals diagnosed or undergoing treatment for cancer at hospital and with histological confirmation of cancer diagnosis (Li et al., 2023; Liu et al., 2022). As for exposure assessment, 5 studies used work history records to identify exposed workers (Gilliland and Mandel, 1993; Alexander et al., 2003; Olsen et al., 2004; Lundin et al., 2009; Leonard et al., 2008), 2 studies used residence in contaminated regions (Li et al., 2022; Law et al., 2023), 4 used direct measurement of serum PFAS levels (Li et al., 2023; Liu et al., 2022; van Gerwen et al., 2023; Madrigal et al., 2024), one used residence and modelled serum PFAS levels (Vieira et al., 2013), one work history records and modelled serum concentrations (Girardi and Merler, 2019), one adopted a job exposure matrix (Steenland and Woskie, 2012), and one used both a job exposure matrix and models to estimate serum levels (Barry et al., 2013). Regarding the timing of exposure in the studies either measuring or modelling serum PFAS levels, most studies evaluated exposure occurring prior to cancer incidence or death (Steenland and Woskie, 2012; Barry et al., 2013; Girardi and Merler, 2019; van Gerwen et al., 2023; Madrigal et al., 2024), while 2 studies assessed exposure after (Li et al., 2023; Liu et al., 2022) and one at outcome occurrence (Vieira et al., 2013), respectively.

Median NOS scores were 7.0 (interquartile range [IQR]: 1.0; range: 6.0, 8.0), 7.0 (IQR: 1.0; range: 6.5, 7.5), and 7.5 (IQR: 0.5; range: 6.5, 8.0) among studies included in the review on lung, head and neck, and thyroid cancer, respectively (Supplementary Table 3).

3.2. Lung cancer

We found a pooled RR (Fig. 2) for the association between environmental or occupational PFAS exposure and combined lung cancer incidence and mortality of 1.20 (95% CI: 1.12, 1.28), based on estimates from 9 studies (Gilliland and Mandel, 1993; Alexander et al., 2003; Olsen et al., 2004; Lundin et al., 2009; Steenland and Woskie, 2012; Vieira et al., 2013; Girardi and Merler, 2019; Li et al., 2022; Law et al., 2023). The pooled estimate for lung cancer incidence was 1.21 (Figs. 2 and 95% CI: 1.13, 1.29), while we observed no association for lung cancer mortality (Fig. 2, RR: 1.01; 95% CI: 0.73, 1.41). Despite

Table 1
Main characteristics of the studies included in the review.

Authors, year	Country	Study design	Study period	Type of exposure	Type of population/ workers	Type of reference	Types of PFAS, main exposure	Exposure assessment method	Cancer types	Outcome	Outcome assessment	Sample size	NOS score
Gilliland and Mandel, 1993	USA	Cohort	1947–1989	Occupational	Workers of a chemical plant	External	PFOA	Work history records	Lung	M	Vital records	3537	8
Alexander et al., 2003	USA	Cohort	1961–1998	Occupational	Workers of a chemical plant	External	PFOS	Work history records	Lung	M	Vital records, death certificates	2083	6.5
Olsen et al., 2004	USA	Cohort	1993–1998	Occupational	Workers of a chemical plant	Internal	PFOS	Work history records	Lung	I	Health claims records	1311	6
Leonard et al., 2008	USA	Cohort	1948–2002	Occupational	Workers of a polymer production plant	External	PFOA	Work history records	Oral cavity and pharynx, larynx, lung[a], thyroid	M	Vital records	6027	6.5
Lundin et al., 2009	USA	Cohort	1947–2002	Occupational	Workers of an ammonium perfluorooctanoate manufacturing facility	External	PFOA	Work history records and experts' assessment	Lung	M	Vital records	3993	8
Steenland and Woskie, 2012	USA	Cohort	1948–2008	Modelled serum PFAS levels, occupational	Workers of a chemical plant	External	PFOA	Job exposure matrix based on serum data	Lung	M	Vital records, death certificates	5791	6
Barry et al., 2013 [b]	USA	Cohort	1952–2011	Modelled serum PFAS levels (environmental, occupational)	Individuals who resided in contaminated water districts or worked at a local chemical plant	Internal	PFOA	Statistically estimated serum levels, job exposure matrix	Lung, oral cavity, thyroid	I	Self-reported, validated with cancer registries and medical records	32,254	7.5
Vieira et al., 2013	USA	Case-control	1996–2005	Modelled serum PFAS levels, environmental	Individuals who resided in contaminated water districts close to a chemical plant	Internal	PFOA	Statistically estimated serum levels, area of residence	Lung, thyroid	I	Cancer registries	25,107	7
Girardi and Merler, 2019	Italy	Cohort	1970–2018	Modelled serum PFAS levels, occupational	Workers of a chemical plant	External	Multiple types	Statistically estimated serum levels, work history records	Lung	M	Vital records, death certificates	462	7
Li et al., 2022	Sweden	Cohort	1985–2016	Environmental	Individuals who resided in contaminated water counties	Internal for lung and thyroid cancers, external for other cancer types	Multiple types	Resident register	Larynx, lip, lung, oral cavity, pharynx, thyroid	I	Cancer registries	60,507	7.5
Liu et al., 2022	China	Case-control	2016–2017	Measured serum levels	Cases: individuals diagnosed with thyroid cancer undergoing medical treatment in the hospital. Controls: randomly selected patients undergoing routine	Internal	PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS, C8 Cl-PFESA	Measurement of serum levels	Thyroid	I	Histological examination	319	7

(*continued on next page*)

Table 1 (*continued*)

Authors, year	Country	Study design	Study period	Type of exposure	Type of population/ workers	Type of reference	Types of PFAS, main exposure	Exposure assessment method	Cancer types	Outcome	Outcome assessment	Sample size	NOS score
					medical visits at the same hospital as cases.								
Law et al., 2023	Australia	Cohort	1983–2019	Environmental	Individuals who resided in areas with water and soil contamination	External	Multiple types	Reported residence in areas of interest from healthcare insurance provider records	Head and neck (excl. larynx), larynx, lung, thyroid	I	Cancer registries	318,887	6.5
Li et al., 2023	China	Case-control	2022	Measured serum levels	Cases: individuals with newly diagnosed thyroid cancer at the hospital. Controls: randomly selected healthy individuals undergoing routine physical examinations at the same hospital as cases.	Internal	PFOA, PFOS, PFNA, PFHxS, PFDA, PFUnDA, total PFAS	Measurement of serum levels	Thyroid	I	Histological examination	300	7.5
van Gerwen et al., 2023	USA	Nested case-control	From 2007 onwards	Measured serum levels	Cancer cases and healthy controls were selected from a medical record-linked biobank	Internal	PFHxS, PFOA, PFHpS, PFOPA, Sb-PFOS, n-PFOS, PFNA, NMeFOSAA	Measurement of serum levels	Thyroid	I	Medical records	176	8
Madrigal et al., 2024	Finland	Nested case-control	1987–2016	Measured serum levels	Cancer cases and healthy controls were selected from a population-based cohort of women enrolled during pregnancy	Internal	PFOA, PFOS, PFNA, PFHxS, EtFOSAA, MeFOSAA, PFDA, PFUnDA, PFHpS, PFHpA, PFTeDA, 6:2 diPAP, PFHxA, MeFOSA	Measurement of serum levels	Thyroid	I	Cancer registries	800	8

I: incidence, M: mortality, NOS: Newcastle-Ottawa Scale, PFAS: per- and polyfluoroalkyl substances.

PFHxA: perfluorohexanoic acid, PFHpA: perfluoroheptanoic acid, PFOA: perfluorooctanoic acid, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFUnDA: perfluoroundecanoic acid, PFDoDA: perfluorododecanoic acid, PFTrDA: perfluorotridecanoic acid, PFTeDA: perfluorotetradecanoic acid, PFHxS: perfluorohexanesulfonic acid, PFHpS: perfluoroheptanesulfonic acid, PFOS: perfluorooctanesulfonic acid, Sb-PFOS: branched perfluorooctanesulfonic acid, n-PFOS: linear perfluorooctanesulfonic acid, PFDS: perfluorodecanesulfonic acid, MeFOSAA: N-methyl-perfluorooctane sulfonamidoacetic acid, EtFOSAA: N-ethyl-perfluorooctane sulfonamidoacetic acid, FOSA: perfluorooctane sulfonamide, MeFOSA: N-methyl-perfluorooctane sulfonamide, EtFOSA: N-ethyl-perfluorooctane sulfonamide, 6:2 diPAP: 6:2 polyfluoroalkyl phosphoric acid diesters, C8 Cl-PFESA: C8 chlorinated polyfluoroalkyl ether sulfonic acid, PFOPA: perfluorooctylphosphonic acid, N-MeFOSAA: n-methylperfluorooctanesulfonamidoacetic acid.

[a] The study by Leonard RC et al., 2008 (Leonard et al., 2008) was excluded from the meta-analysis on the potential association between environmental or occupational PFAS exposure and lung cancer, since updated results for this cancer type based on the same study population were provided by Steenland K et al., 2012 (Steenland and Woskie, 2012).

[b] The study by Barry et al., 2013 (Barry et al., 2013) is the only one that was not included in any of the analyses (although retained in review), since it provided estimates according to modelled serum PFAS levels only.

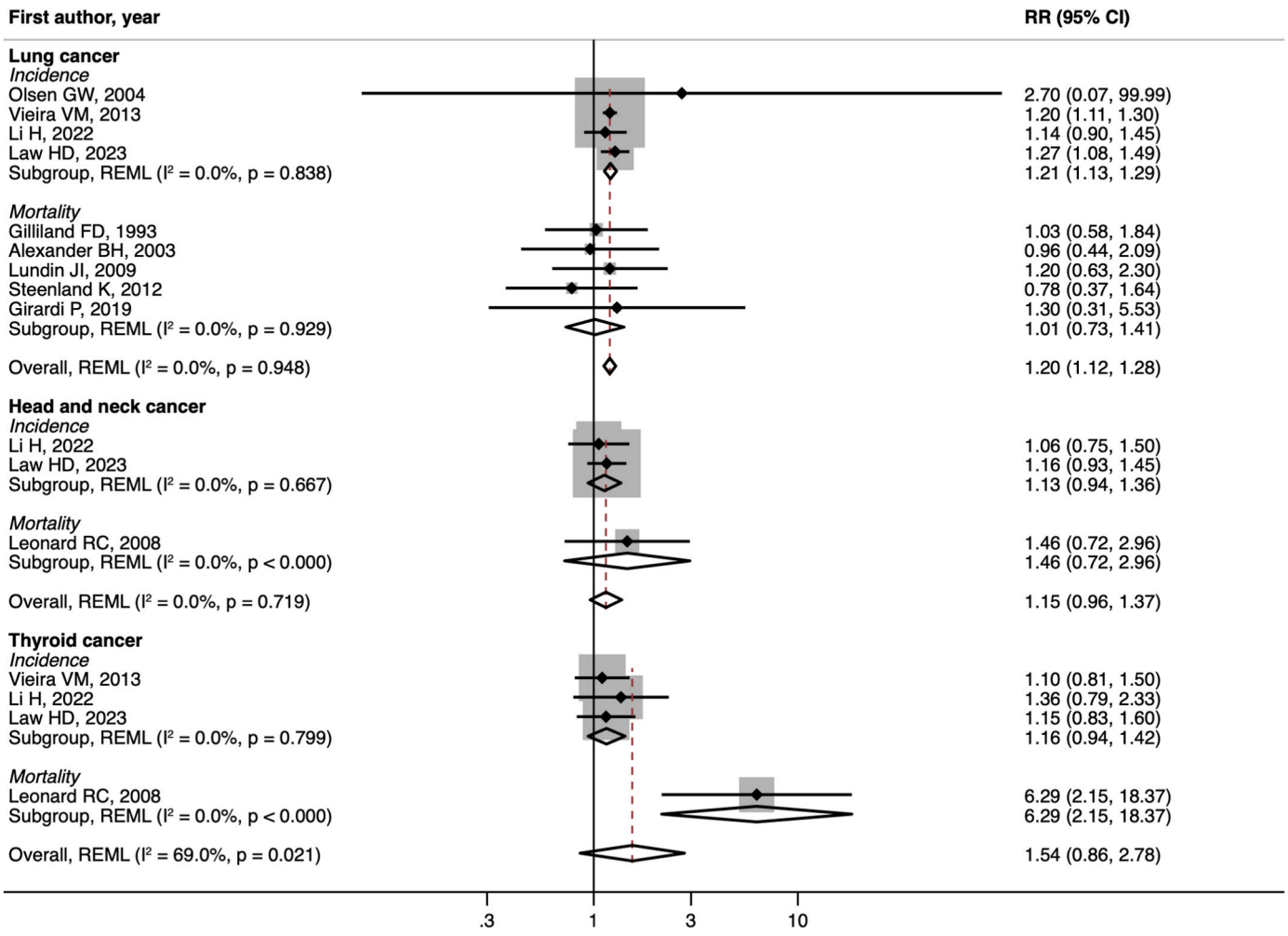

Fig. 2. Pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) for the association between environmental or occupational exposure to per- and polyfluoroalkyl substances and lung, head and neck, and thyroid cancers.
The study by Leonard et al. (2008) was excluded from the meta-analysis on the potential association between environmental or occupational PFAS exposure and lung cancer, since updated results for this cancer type based on the same study population were provided by Steenland and Woskie (2012).
Reference was no or low PFAS exposure, according to the individual studies.

occasional variation in results, we observed no heterogeneity according to country, type of reference population, type of PFAS, type of exposure, NOS score (Table 2). Also, results did not substantially change when restricting the meta-analysis to male individuals or to cohort studies (Table 2). Statistical heterogeneity was low for most analyses (Table 2). In addition, we observed a slight asymmetry at inspection of the contour-enhanced funnel plot, with potential missing studies with estimates of negative associations, albeit mainly concentrated in the area of no significance (Fig. 3) and not confirmed by the result of the Egger's test ($p = 0.343$). No included studies measured serum PFAS levels among all study participants. Instead, 4 studies reported no association between modelled or estimated serum PFAS levels and lung cancer (Steenland and Woskie, 2012; Barry et al., 2013; Vieira et al., 2013; Girardi and Merler, 2019). Their main results can be found in Supplementary Table 3.

3.3. Head and neck cancer

The findings of our meta-analysis on HNC are reported in Fig. 2. They are based on 3 studies (Li et al., 2022; Law et al., 2023; Leonard et al., 2008) and provide no clear support to the potential association between environmental or occupational PFAS exposure and HNC (incidence and mortality combined, RR: 1.15; 95% CI: 0.96, 1.37), with low statistical heterogeneity.

No studies measured serum PFAS levels among all participants, while one cohort study focused on estimated levels reported no association with oral cancer incidence (Supplementary Table 3) (Barry et al., 2013).

3.4. Thyroid cancer

The estimated pooled RR (Fig. 2) for the association between environmental or occupational PFAS exposure and thyroid cancer incidence and mortality combined was 1.54 (95% CI: 0.86, 2.78), based on results from 4 studies (Vieira et al., 2013; Li et al., 2022; Law et al., 2023; Leonard et al., 2008). Between-study heterogeneity was high, but decreased substantially when considering only studies on cancer incidence (Fig. 2).

An association between modelled serum PFAS levels and thyroid cancer was not supported by 2 studies reporting related estimates (Supplementary Table 4) (Barry et al., 2013; Vieira et al., 2013).

As for measured serum PFAS levels, we included 4 studies in the meta-analysis (Li et al., 2023; Liu et al., 2022; van Gerwen et al., 2023; Madrigal et al., 2024), and all of them were on incidence. We found an inverse association between measured serum PFOA levels and thyroid cancer (RR per natural log-unit increase: 0.73; 95% CI: 0.56, 0.94), while we observed no associations for other types of PFAS included in

Table 2
Pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) for the association between environmental or occupational exposure to per- and polyfluoroalkyl substances and lung cancer, by study and participants' characteristics.

Stratum	n. studies	RR (95% CI)	I^2, p_{het}
Sex, male	2	1.35 (1.08, 1.69)	0.1%, 0.317
Country			
USA	6	1.19 (1.10, 1.29)	0.0%, 0.848
Any other	3	1.23 (1.08, 1.41)	0.0%, 0.754
$p_{between}$		0.658	
Cohort studies only	8	1.20 (1.06, 1.36)	0.0%, 0.905
Type of reference population			
Internal	3	1.19 (1.11, 1.29)	0.0%, 0.797
External	6	1.22 (1.06, 1.41)	0.0%, 0.838
$p_{between}$		0.811	
Type of PFAS			
PFOA	4	1.19 (1.10, 1.29)	59.0%, 0.677
PFOS	2	1.01 (0.47, 2.15)	0.0%, 0.583
Multiple/not specified	3	1.23 (1.08, 1.41)	0.0%, 0.754
$p_{between}$		0.825	
Type of exposure			
Environmental	3	1.21 (1.13, 1.29)	0.0%, 0.719
Occupational	6	1.02 (0.74, 1.42)	0.0%, 0.949
$p_{between}$		0.327	
NOS score			
<7	4	1.18 (0.91, 1.52)	0.0%, 0.534
≥7	5	1.19 (1.11, 1.28)	0.0%, 0.981
$p_{between}$		0.941	

NOS: Newcastle-Ottawa Scale, PFAS: per- and polyfluoroalkyl substances.
The study by Leonard et al. (2008) was excluded from the meta-analysis on the potential association between environmental or occupational PFAS exposure and lung cancer, since updated results for this cancer type based on the same study population were provided by Steenland and Woskie (2012).
Reference was no or low PFAS exposure, according to the individual studies.

the meta-analysis (Fig. 4). We observed moderate heterogeneity for PFOA, and high heterogeneity for the other types of PFAS. In general, pooled results from case-control studies tended to show inverse associations, while estimates from nested case-control studies leaned more towards positive associations. In this regard, we detected heterogeneity by study design for PFOS ($p_{between} = 0.024$) and PFNA ($p_{between} < 0.001$). However, PFOS was the only type of PFAS showing a positive association with thyroid cancer, limited to nested case-control studies (Fig. 4, RR per natural log-unit increase: 1.51; 95% CI: 1.11, 2.05).

4. Discussion

The results of our meta-analysis suggest that environmental or occupational PFAS exposure may be associated with lung cancer incidence, while our findings are not suggestive of an association for head and neck and thyroid cancer. The findings of the meta-analysis on lung cancer were consistent across study and participants' characteristics. Studies on modelled serum PFAS levels did not report associations with any of the investigated cancer types. Also, our meta-analysis on the association between measured serum PFAS level and thyroid cancer showed a positive association for PFOS, but limited to case-control studies nested within cohorts (i.e., with serum sample collected before cancer diagnosis). Observed differences by study design may also be due to the timing of blood collection itself. Indeed, van Gerwen et al. (2023) (van Gerwen et al., 2023) showed that the association between measured serum levels of most investigated types of PFAS and thyroid cancer was stronger when including only cases (and matched controls) diagnosed at least one year after blood collection. This highlights the importance of taking into account a possibly long induction period between PFAS exposure and cancer occurrence. However, it may also be due to modifications in serum levels after cancer occurrence, although to our knowledge cancer itself or its treatment have not been shown to modify PFAS levels.

The mechanisms by which PFAS lead to cancer are poorly understood. After ingestion from drinking water or food, or inhalation through contaminated air, PFAS are distributed through plasma proteins mainly to the liver and kidney, although accumulation in other organs, including the lung, has been reported (Pesonen and Vähäkangas, 2024; Lau et al., 2007; Pérez et al., 2013). PFAS are slowly eliminated through bile and urine, while there is no evidence for PFAS metabolism in humans (Pesonen and Vähäkangas, 2024). Since mutagenic effects and DNA damage due to PFAS have not been proven, they are thought to act through non-genotoxic mechanisms. In particular, PFAS may induce cancer through activation of the peroxisome proliferator-activated receptor alpha (PPARα) and the expression of genes involved in apoptosis and cell proliferation (Pesonen and Vähäkangas, 2024). Oxidative stress and epigenetic modifications induced by PFAS may also be involved in their carcinogenicity (Pesonen and Vähäkangas, 2024), as well as chronic inflammation and immunosuppression (Zhang et al., 2023).

To our knowledge, this is the first meta-analysis summarizing available epidemiological evidence on the potential association between PFAS exposure and lung and head and neck cancer in humans. A

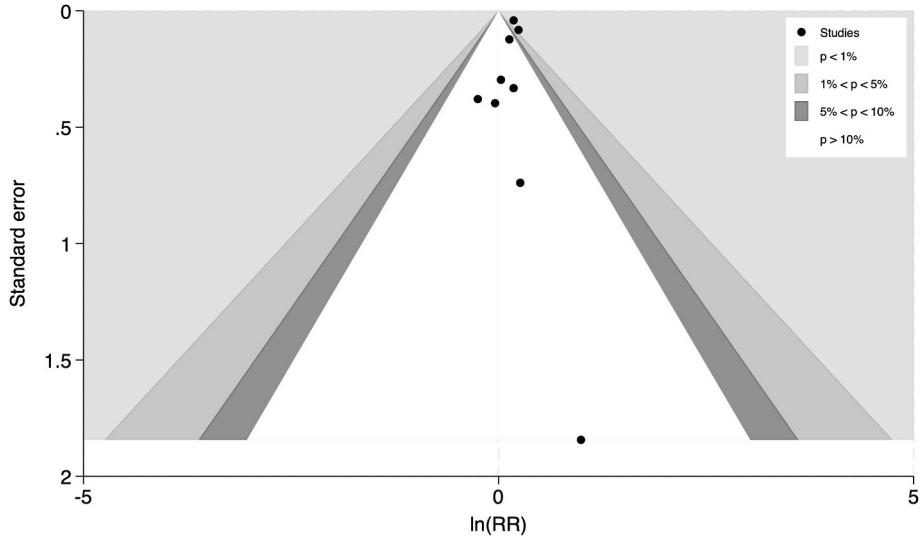

Fig. 3. Contour-enhanced funnel plot to explore the occurrence of the small-study effect in the meta-analysis on the association between environmental or occupational exposure to per- and polyfluoroalkyl substances and lung cancer.

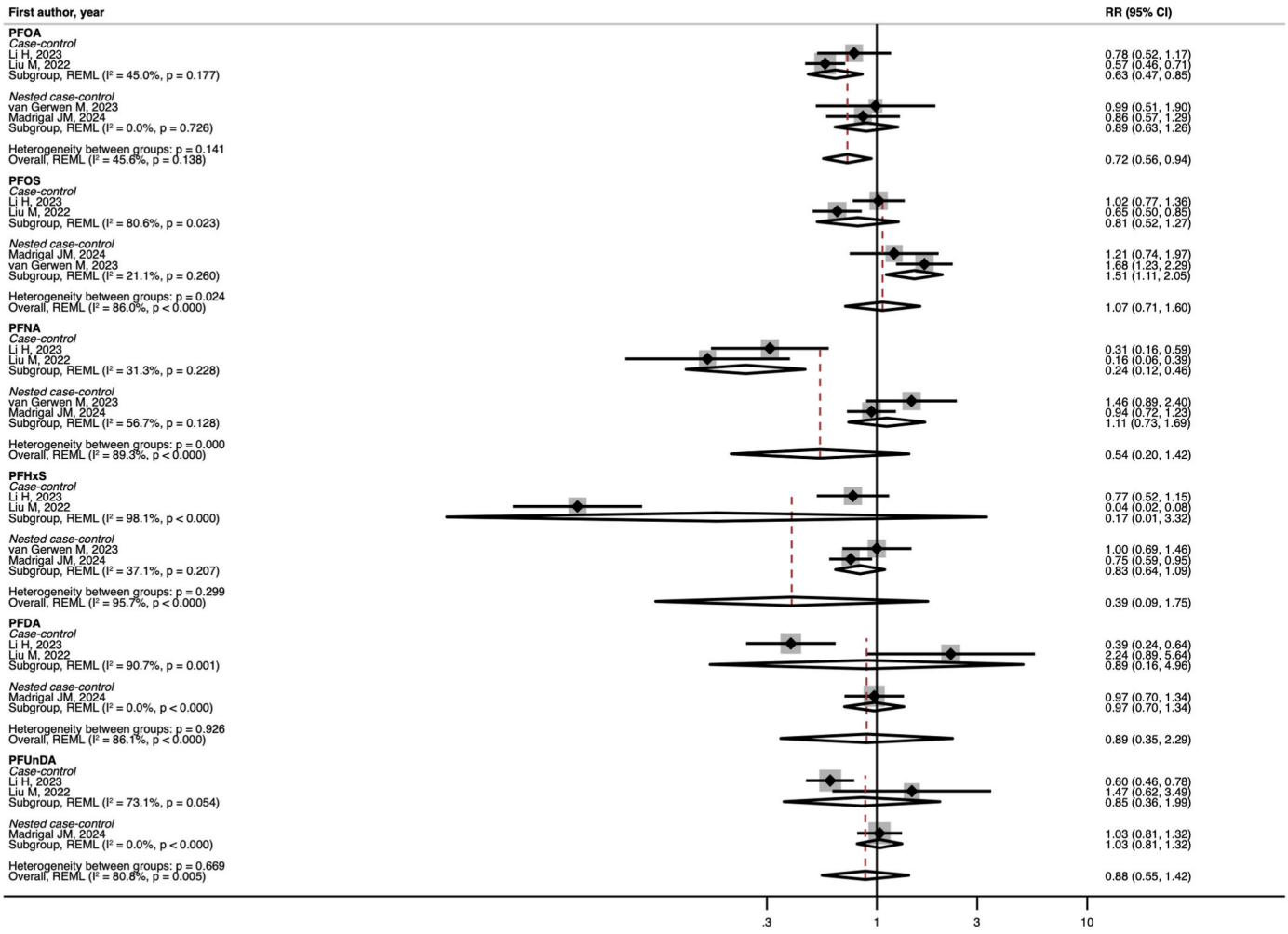

Fig. 4. Pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) for the association between a natural log-unit increase in measured concentrations of per- and polyfluoroalkyl substances and thyroid cancer, overall and by study design.
PFOA: perfluorooctanoic acid, PFOS: perfluorooctanesulfonic acid, PFNA: perfluorononanoic acid, PFHxS: perfluorohexanesulfonic acid, PFDA: perfluorodecanoic acid, PFUnDA: perfluoroundecanoic acid.

previous meta-analysis on thyroid cancer incidence reported no clear associations for different types of PFAS (van Gerwen et al., 2024). Our overall results are in agreement with the previous meta-analysis (van Gerwen et al., 2024), which however did not carry out subgroup analyses by study design.

Among the limitations of our meta-analysis is the lack of information on potential confounders in the relationship between PFAS exposure and the cancers included in the analysis. For instance, tobacco smoking is a relevant risk factor for both lung cancer and HNC, yet most occupational studies included in our review did not take it into account in the analysis. In this context, tobacco smoking may be a mediator of socioeconomic status, which may be related to both PFAS exposure and cancer. Indeed, individuals with poor socioeconomic conditions, such as blue-collar workers, may have higher PFAS exposure compared with those with higher socioeconomic status, such as white-collar workers or workers with managerial or organizational tasks. Workers with worse living conditions may also experience higher PFAS exposure outside of work, since socioeconomic and racial disparities have also been reported for environmental exposure through drinking water (Smalling and Bradley, 2024). Also, most studies did not take into account co-exposure with potential carcinogens other than PFAS, which might be relevant both in occupational settings and in communities close to industrial areas. Another limitation stems from the lack of detailed environmental monitoring data in occupational studies included in our review. A similar limitation may affect also studies on environmental or community exposure, since they did not actually measure individuals' PFAS intake, or did only for a limited number of study participants. In both cases, inter-individual differences in PFAS exposure were overlooked, potentially leading to exposure misclassification, likely nondifferentially according to the outcome status, which could be expected to bias estimates towards the null. However, when study-specific estimates were reported according to different levels of intensity of exposure, categorization of an otherwise nondifferentially biased linear exposure (e.g., airborne PFAS levels) could have also led to differential misclassification, which may bias estimates away from the null (Flegal et al., 1991). Furthermore, due to lack of related data, we could not quantitatively assess the role of duration and level of environmental or occupational PFAS exposure. The limited number of studies also did not allow us to conduct subgroup analyses according to study or participants' characteristics for HNC and thyroid cancer. Additionally, although we were able to conduct a meta-analysis on measured serum PFAS levels and thyroid cancer, it included only four studies, and the number of studies in each subgroup in the analysis by study design was thus very low, suggesting the need for confirmation of our findings for PFOS. Also, cross-sectional or case-control studies on measured serum PFAS levels and cancer may be affected by reverse causality, which might have influenced our results. As for lung cancer and HNC, conversely, available data on measured serum PFAS levels did not allow a meta-analysis,

suggesting the need for substantial further research in this area. Additionally, our analysis on incidence and mortality combined may be appropriate for cancers with high case-fatality rates (Hamra et al., 2014), such as lung cancer (5-year survival rate in the USA for the years 2014–2020: 26.7%) (Surveillance Research Program - National Cancer Institute, 2024), while mortality may not be a valid indicator for incidence for cancers with lower rates, such as thyroid cancer and some types of HNC (Surveillance Research Program - National Cancer Institute, 2024). Also, we observed generally high degrees of heterogeneity in the analyses on thyroid cancer, suggesting differences between including studies and limiting generalizability of our findings, albeit observed high heterogeneity may be mainly due to differences in study designs (e.g., case-control study design nested or not within a cohort) or to timing of measurement of serum PFAS levels (e.g., pre- or post-diagnostic). Eventually, another limitation of our review is the limited geographic variability of included studies, with most of them being conducted in the USA. This may potentially limit the generalizability of our findings to other countries or contexts with different PFAS exposure levels and further highlights the need for new studies, especially from developing countries where lung cancer incidence is increasing (Bray et al., 2024; Leiter et al., 2023).

In conclusion, the results of our meta-analysis of available epidemiological studies suggest that PFAS exposure may be associated with lung cancer incidence, while they do not support an association for HNC. As for thyroid cancer, there may be an association with PFOS exposure, based on results from nested case-control studies. These findings, however, should be taken cautiously due to the limited number of available studies on the topic, as well as for their limitations, including potential residual confounding and exposure misclassification. Future research should account for co-exposure with other potential carcinogens and detailed assessment of study participants' exposure, either through environmental monitoring data or through complete serum measurements. As for the latter, in particular, prospective studies are urgently needed to establish the causality of observed associations.

CRediT authorship contribution statement

Michele Sassano: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Monireh Sadat Seyyedsalehi:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Elizabeth Maria Kappil:** Data curation. **Sirui Zhang:** Data curation. **Tongzhang Zheng:** Writing – review & editing, Conceptualization. **Paolo Boffetta:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paolo Boffetta acted as an expert in litigation involving PFAS exposure, unrelated to the present work. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120606.

Data availability

Data will be made available on request.

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