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Exposure to per-and poly-fluoroalkyl substances and respiratory and skin effects in children and adolescents: A systematic review and meta-analysis

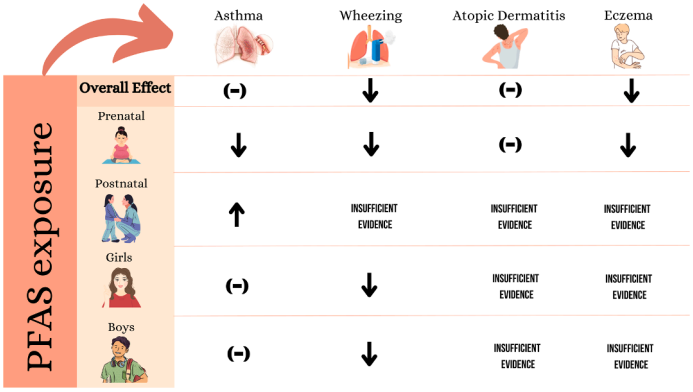
Georges Hatem [a,b,c], Ana Margarida Faria [a,b,c], Mariana Bessa Pinto [a,1], Amina Salamova [d], João Paulo Teixeira [a,b,c], Carla Costa [a,b,c,*], Joana Madureira [a,b,c]

[a] Environmental Health Department, National Institute of Health Dr Ricardo Jorge, Porto 4000-053, Portugal
[b] EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto 4050-600, Portugal
[c] Laboratório para a Investigação Integrativa e Translacional em Saúde Pública (ITR), Porto 4050-600, Portugal
[d] Gangarosa Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA, United States

HIGHLIGHTS

- Prenatal PFAS exposure showed lower asthma odds as opposed to postnatal exposure.
- PFAS exposure decreased wheezing odds by 4 %, with a stronger effect in girls.
- PFAS exposure had no significant impact on atopic dermatitis odds.
- PFAS exposure significantly decreased eczema odds by 8 %.

GRAPHICAL ABSTRACT



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ABSTRACT

Despite being previously banned due to long-term health effects, Per- and polyfluoroalkyl substances (PFAS) remain widespread in the environment, accumulating in animals and humans. This systematic review and meta-analysis explores associations between exposure to PFAS and asthma onset, wheezing, atopic dermatitis, and eczema in children and adolescents while addressing exposure timing and sex-specific differences. After comprehensive search conducted in several databases, including risk of bias, study heterogeneity, and quality of evidence evaluation, the review included 28 observational studies, most with low risk of bias in all domains. PFAS exposure was not significantly associated with asthma onset (OR:1.03, CI:0.99;1.07), but revealed significantly lower association in the prenatal period (OR:0.97, CI:0.94;0.99), higher in the postnatal period (OR:1.20, CI:1.07;1.35), and no differences among sexes. PFAS exposure (mainly prenatal) was associated with 4 % significantly lower odds of wheezing (OR:0.96, CI:0.94;0.98), higher in girls (OR:0.94, CI:0.91;0.98) than in boys (OR:0.97, CI:0.94;1.00). No significant impact was noted on atopic dermatitis (OR:1.04, CI:0.94;1.16), while

* Corresponding author at: Environmental Health Department, National Institute of Health Dr Ricardo Jorge, Porto 4000-053, Portugal.
E-mail address: carla.trindade@insa.min-saude.pt (C. Costa).
[1] Co-author.

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PFAS exposure was associated with 8 % significantly lower eczema odds (OR:0.92, CI:0.89;0.96). Evidence was insufficient to perform sensitivity analyses on atopic dermatitis and eczema. Additional research is needed on the impact of synergistic and co-exposure to other pollutants on children and adolescents' health.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals commonly used in the production of fluoropolymers and stain-resistant fabrics [1], along with other applications due to their ability to repel water and oil [2], and found in many consumer products, such as non-stick cookware, waterproof clothing, food packaging, and fire-fighting foams [3]. The Organisation for Economic Co-operation and Development (OECD) and the United Nations Environment Programme (UNEP) report identified and categorized 4730 PFAS-related CAS numbers [4], of which less than 6 % are commercially relevant [5]. Well-known studied PFAS subgroups include Perfluorooctanoic Acid (PFOA), Perfluorooctanesulfonic Acid (PFOS), Perfluorononanoic Acid (PFNA), Perfluorohexane Sulfonate (PFHxS), and Perfluorobutane Sulfonic Acid (PFBS) [6].

Exposure to widespread PFAS poses serious health and environmental risks since they can persist in the environment and bioaccumulate in living organisms, including humans [7]. The toxicity of PFAS is largely driven by their chemical properties and ability to interact with biological molecules [8], potentially leading to health problems like cancer, liver damage, and impaired immune function [9,10]. Therefore, governments and organizations worldwide, such as the Environmental Protection Agency (EPA), are taking steps to regulate and mitigate the risks associated with exposure to PFAS [11,12]. This includes setting limits for PFAS concentrations in drinking water, phasing out certain PFAS, and developing technologies to remediate PFAS-contaminated sites [13,14].

Children and adolescents are at a higher risk of exposure to PFAS due to a combination of behavioral, environmental, and physiological characteristics. Many toys, baby products, school supplies, and uniforms are treated with PFAS [15]. Household items like carpets, upholstery, and cookware, common in environments where children spend time, may also contain PFAS [3,9], increasing the likelihood of PFAS exposure from settled dust or air. PFAS are also in food commonly consumed by children and adolescents (e.g., fast food, dairy, and meat) [9]. Moreover, due to their higher food and water intake per unit of body weight compared to adults [16], children and adolescents can ingest higher doses of PFAS relative to their body size. Recent research explored the relationship between PFAS exposure and the onset of respiratory diseases and symptoms and immune-related conditions in children and adolescents [17–19]. Among others, several epidemiological studies have found an increased risk of asthma onset and other respiratory diseases in children and adolescents exposed to PFAS during the pre- or post-natal periods [19–21]. Wheezing or whistling sounds while breathing can also result from exposure to environmental pollutants [22], such as PFAS, with studies showing contradictory findings [20,23]. Research also emphasized the immunotoxic effects of PFAS, such as increasing inflammatory biomarkers, immunosuppression, autoimmunity, and allergic responses through disruption of signaling pathways and modulation of cytokine production [24,25]. For example, such exposure can induce or worsen eczema and atopic dermatitis symptoms, which can occur even at an early age [26] by directly irritating the skin, triggering allergic reactions, and contributing to inflammation [27,28].

Asthma, wheezing, atopic dermatitis, and eczema are common childhood conditions that may share overlapping immunological mechanisms, inflammatory pathways, and environmental risk factors, including potential susceptibility to PFAS exposure [29–31]. These conditions are commonly grouped under the term "atopic triad," which represents the typical progression of allergic diseases, often beginning with eczema in infancy and potentially developing into food allergies, asthma, and allergic rhinitis as the child grows [30,32]. Not all studies have found a consistent link between PFAS exposure and the above-mentioned conditions, highlighting the need to evaluate the surrounding evidence systematically. Moreover, research is needed to understand the specific factors, such as the timing of exposure, route, and level of exposure, or population characteristics under which PFAS might increase disease risk. Therefore, this systematic review aims to assess the available evidence on the association between exposure of children and adolescents to PFAS and asthma, wheezing, atopic dermatitis, or eczema. A meta-analysis is conducted to integrate and analyze the available data to provide a comprehensive overview. Moreover, it explores these associations considering the timing of exposure (pre- or postnatal) and the sex of children/adolescents. Findings from this study can help explore published studies, the risk of bias in each study, and draw suggestions based on the results of the meta-analysis and the quality of evidence assessment.

2. Methods

The present systematic review adhered to the established guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [33]. The study was formally registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023495682).

2.1. Literature search strategy and data sources

The following search terms were systematically combined to retrieve published evidence on the review subject: Perfluoroalkyl, perfluorooctane sulfonic acid, perfluorooctane sulfonate, perfluorooctanoic acid, perfluorooctanoate, polyfluoroalkyl, perfluorinated, PFAS, PFOA, PFOS, PFAA, PFNA, PFC, PFHxS, PFOSA, child, children, adolescent, asthma, respiratory sounds, wheezing, dermatitis, atopic, and eczema. Details regarding the search terms employed are provided in Table S1.

Web of Science, PubMed, Scopus, and Cochrane Library databases were used for a systematic literature search from their inception to June 19th, 2024. After exporting data in Research Information Systems (RIS) format, the references were integrated into Endnote Software version 21 for an initial screening to identify and eliminate duplicates. This process was supplemented by manual elimination and then imported into Covidence software for an additional round of duplicate removal before screening.

2.2. Inclusion and exclusion criteria

Studies were included if: 1) The population was children and adolescents up to 18 years; 2) At least one PFAS was quantified in any biological or environmental matrix; 3) PFAS exposure (pre- or postnatal) was assessed in relationship with asthma, wheezing, eczema, or atopic dermatitis prevalence.

Exclusion criteria encompassed studies meeting the following conditions: 1) Utilization of animal or *in vitro* cell modelsfor outcome or exposure assessment; 2) Lack of quantitative data on PFAS exposure; 3) Incorporation of qualitative endpoints for outcome assessment; 4) Abstracts presenting unpublished results, reviews, editorials, letters to the editor, and case reports; and/or 5) Studies unavailable in English.

Given the above, the PECO (Population, Exposure, Comparators, Outcomes) statement was formulated, where the population included children and adolescents 18 years or less of any nationality, social and educational status; PFAS exposure was assessed through various

biological and/or environmental matrices; the comparator or subgroup analyses included cases and controls. Individuals were classified as cases if i) a doctor diagnosed them during the study period; ii) their parents/legal guardians answered affirmatively to the following question: "Has a doctor or other health professional ever told you that your child/ward has asthma/eczema/atopic dermatitis?"; or iii) reported wheezing or respiratory sounds during the past 12 months. In cross-sectional studies, an additional positive response to the question: "Does your child/ward still have asthma/eczema/atopic dermatitis?" or a set period for the age of disease diagnosis was considered to ensure association with current asthma /eczema/atopic dermatitis. Those not meeting the above criteria were classified as healthy controls.

2.3. Study selection, risk of bias, and data extraction

Three researchers (GH, AMF, and MBP) independently selected studies, assessed bias risk, and extracted data. The titles and abstracts of all records were identified and subjected to an initial screening assessment based on the predefined inclusion criteria. Afterward, full texts were retrieved and screened if quantitative associations between PFAS concentrations and the outcomes of interest were performed. If studies were incomplete or inaccessible, corresponding authors were contacted via email, with a predetermined deadline of two weeks to receive responses. If no answer was received within the stipulated timeframe, studies were excluded. While conducting the systematic review, corresponding authors of two inaccessible studies were contacted, and both successfully provided the required information. Before final approval, at least two authors had to reach a consensus. In case of conflicts or disagreements, a fourth team member was consulted. The reasons for excluding studies were documented.

The bias assessment in the included studies followed the Newcastle Ottawa scale [34]. To ensure inter-rater reliability, three independent reviewers conducted the assessments. The goal was to achieve consistency across all three evaluations. Any discrepancies were resolved through discussion and consensus among the reviewers. Employing three distinct forms tailored to specific study designs, the scale addressed potential biases in population selection (comprising four questions), comparability (comprising two questions), and outcome (for cohorts and cross-sectional studies) or exposure (for case-control studies) (comprising three questions). Each question was assigned a score based on the selected answer.

Regarding selection bias, criteria included the representativeness of the sample, justification of sample size, comparability between respondents and non-respondents, ascertainment of exposure, and the absence of the outcome of interest at the study's commencement (for cohorts). Studies were rated as having low bias if they scored 4 points, unclear if they scored 3–2 points, and high risk if they scored 1–0 points. For comparability bias, the assessment considered how confounding variables (socio-demographic variables) were controlled in the multivariate analyses and were then classified as having a low, unclear, or high risk of bias based on scores of 2, 1, or 0 points, respectively. The outcome/exposure evaluation encompassed the duration and adequacy of follow-up and the statistical tests employed. Studies were characterized as having a low, unclear, or high risk of bias based on scores of 3, 2, or 1 point, respectively.

The features of the incorporated studies, including authorship, publication year, location, study design, and participant details such as age, sample size, and number of cases, were systematically extracted. Information on exposure indicators, encompassing the chemical, matrix, and timing of exposure (pre- or post-natal), was also collected. The outcomes of interest were also documented. The presentation of these details followed a tabular format, incorporating odds ratios with corresponding 95 % confidence intervals (Table S2). This formatting adhered to the guidelines outlined in the NTP/OHAT Handbook for Conducting a Literature-Based Health Assessment [35].

2.4. Heterogeneity and risk of publication bias assessment

The analysis of heterogeneity was conducted using MetaXL version 5.3 software. For each study, the natural logarithm of the Odd Ratios (LnOR) was independently calculated, and subsequently, these values were pooled and weighted using random effects models. To assess the variability among the included studies, the I^2 test was employed. Heterogeneity levels were categorized as follows: minimal/insignificant ($I^2 < 30$ %), moderate ($I^2 = 30$–60 %), substantial ($I^2 = 60$–75 %), or notably significant ($I^2 > 75$ %) [36]. When having substantial or notably significant heterogeneity ($I^2 > 60$ %), sensitivity analyses were conducted to evaluate the robustness of the meta-analysis findings and identify any studies that significantly influenced heterogeneity. This process involved removing one study at a time, rerunning the meta-analyses, and comparing the combined estimates with and without the excluded study to assess the impact of its exclusion. The z-test was used to assess significance, and individual findings are presented in Table S3. The risk of publication bias was assessed through the funnel plots by examining the shape and symmetry of the plot for chemicals explored in at least three studies [37]. Luis Furuya-Kanamori (LFK) index was further used to detect the risk of publication bias, with values between -1 and $+1$ deemed symmetrical and those above $+2$ or below -2 reflecting major asymmetry [38]. Chemicals evaluated in a minimum of two studies were incorporated into the meta-analysis, and those assessed in at least four studies were used to calculate the overall PFAS pooled effects. Sensitivity analyses stratified by sex (girls vs. boys) and timing of exposure (prenatal vs. postnatal) were conducted when applicable. The same set of studies from the main meta-analysis was used, and the same statistical approach was applied by pooling the LnOR and weighting the studies using random-effects models. Heterogeneity among studies was assessed using the I^2 statistic, and publication bias was evaluated through funnel plots complemented by the LFK index.

2.5. Quality of evidence assessment

GH and MBP conducted independent assessments to determine the strength of evidence for each measured outcome. The quality of evidence was categorized into high, moderate, low, or very low, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. This classification was based on four key criteria: study design, precision, heterogeneity, and directness [39]. Factors considered to decrease the quality of evidence included study design limitations (e.g., observational studies prone to selection bias, confounding, and measurement bias), inconsistency of results or unexplained heterogeneity, imprecision reflected in wide confidence intervals or small sample sizes, and elevated risk of bias from methodological flaws. Conversely, factors that increased the quality of evidence included a large effect size with minimal risk of confounding, plausible confounding variables or biases that would likely reduce rather than exaggerate the observed effect, and consistency of results across different subgroups, populations, or settings. When performing subgroup analyses based on the timing of exposure, the same LnOR from the primary analysis was used, resulting in the same quality of evidence. Nevertheless, changes may occur in the comparability domain when performing sensitivity per sex, and therefore, in this case, key confounding factors considered were maternal age at delivery, pre-pregnancy body mass index, maternal education level, parity, smoking during pregnancy, household income, child's breastfeeding status, and exposure to secondhand smoke. The full list of confounding variables considered in each study is available in Table S4. One study [40] presented an adjusted model when stratifying per sex, and its exclusion did not significantly affect the pooled OR ($p > 0.05$).

3. Results

3.1. Study selection

A systematic search across four electronic databases - PubMed, Web of Science, Scopus, and Cochrane Library - yielded 2435 studies. After eliminating duplicate entries, the remaining pool for screening comprised 2269 studies. Based on titles and abstracts, initial screening excluded 2176 articles. The exclusion was based on predefined criteria, including lack of relevance to the research question (e.g., studies not addressing asthma, eczema, or atopic dermatitis), inappropriate study design (e.g., case reports, editorials, reviews), and non-human studies or those involving strictly adults, leaving 93 studies for full-text assessment. Sixty-two studies were excluded, 3 were removed due to overlapping populations, and 28 were deemed eligible for inclusion in the systematic review and meta-analysis. One study [41] was performed in two countries, each considered independently in the meta-analysis. The screening process is depicted in Fig. 1.

3.2. Study characteristics

The characteristics of the included studies are detailed in Table S2 (A). These studies span from 2011 to 2024, most performed in 2019 (n = 8). Among them, 13 were conducted in Europe, 10 in Asia, and 6 in

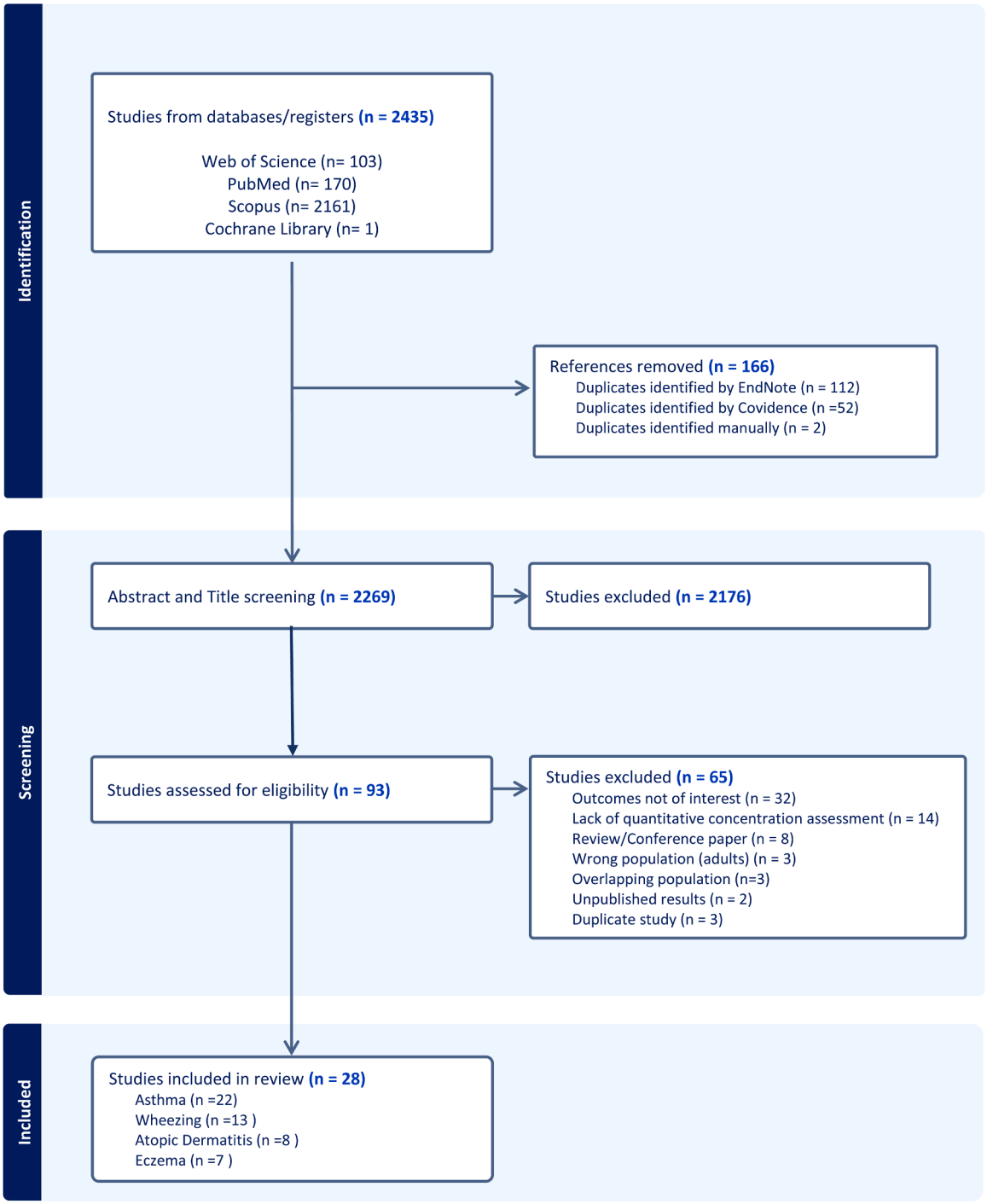

Fig. 1. Flowchart of the study selection procedure.

North America. Most studies (n = 22) were cohorts, and three were case-controls, and three were cross-sectional. PFAS exposure was assessed in the pre-natal period in 19 studies and the post-natal period in 11 studies, and two matrices: blood (n = 26) and food items assessing diet (n = 2). Most studies classified the outcomes of interest based on parent- or self-reported doctor-diagnosed conditions, often utilizing standardized tools such as the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire or medical record linkage. Only one study [42] relied on clinical diagnoses made directly by pediatricians. Sensitivity analyses excluding this study showed no significant impact on the pooled ORs ($p > 0.05$) or the direction of associations.

3.3. Risk of bias assessment

Overall, most of the included studies had a low risk of bias. Regarding the selection domain, eight studies were judged to have an unclear risk of bias, of which three [20,40,43] lacked information about the characteristics of non-respondents, and two studies [44,45] did not confirm that the outcome of interest was absent at the start of the study. One study [46] was rated as having an unclear risk due to the lack of a defined control group and the use of record linkage for defining cases. In contrast, another study [47] received the same rating because it relied on self-reported exposure data. Similarly, one study [48] was deemed to have an unclear risk of bias due to misrepresenting the exposed cohort. In the comparability domain, 25 studies were assessed as having a low risk of bias. In contrast, two studies [21,41] were identified with a high risk of bias due to the lack of control over the main confounding factor, which was sex in this case. One study [49] had an unclear risk of bias because it did not present an adequate multivariate analysis to control for additional confounding factors. Concerning the outcome/exposure domain, only one study [50] showed a high risk of bias due to the lack of duration and adequacy of follow-up of the cohort. Eleven studies were judged to have an unclear risk of bias in this domain: eight because they did not designate or describe the non-response or drop-out rate [42,49,51–56], and three studies due to a short follow-up period [28,45,48].

3.4. Association between exposure to PFAS and asthma onset in children and adolescents

Twenty-two publications explored the relationship between PFAS exposure and asthma onset, of which twenty-one assessed chemicals in the blood [20,21,23,40–46,49,50,53,55,57–62] (Fig. 2 (A, B)) and two [47,54] in the diet (Fig. 2 (C)). Studied chemicals (full names included in Table S2 (B)) included Me-PFOSA-AcOH, PFBS, PFDA, PFDoDA, PFHpA, PFHpS, PFHxA, PFHxPA, PFHxS, PFNA, PFOA, PFOS, PFOSA, PFTrDA, PFTA, PFUnDA, and PFAA-Ge-Li, which included 12 PFAS (PFBS, PFDA, PFDoA, PFHpA, PFHxA, PFHxS, PFNA, PFOA, PFOS, PFTeDA, PFTrDA and PFUnDA). Exposure to PFTA was assessed in two studies [60,62] and was the only PFAS significantly associated with higher odds of asthma onset (OR: 1.14; CI: 1.06–1.22). Minimal heterogeneity (I^2=0 %) was noted, and the quality of evidence was judged as low, which was downgraded due to the observational nature of the included studies and the insufficient evidence. Twenty studies assessed the exposure to PFOS [20,21,23,40–42,44–46,49,50,53,55,57–62], 19 assessed PFOA [20,21,23,40–42,45,46,49,50,53,55,57–62], 19 PFHxS [20,21,23,40–42,44,46,49,50,53,54,57–62], 17 PFNA [20,21,23,40–42,46,49,50,53,57–62], 13 PFDA [21,23,41–43,46,50,57,58,60–62], 10 PFUnDA [21,23,41–43,46,49,50,53], 5 PFDoDA [41,42,50,62], 4 PFBS [42,50,60,62], 4 PFHpA [21,41,47], 3 PFHpS [21,50,53], 2 PFHxA [60,62], and 2 assessed PFOSA [21,49], all showing no significant associations with asthma onset among children/adolescents. After computing the pooled effect size (Fig. 2 (A)), exposure to PFAS was associated with 1.03 times higher odds of asthma onset with no statistically significant differences (OR=1.03;CI:0.99–1.07). Of the above chemicals, studies assessing exposure to PFUnDA, PFDoDA, PFHpA, PFHpS, and PFOSA had minimal heterogeneity (I^2=<30 %), and those assessing the exposure to PFOS, PFNA, PFDA, PFBS and PFHxA had moderate heterogeneity (I^2=30–60 %). Studies investigating PFOA, and PFHxS exposure had substantial heterogeneity (I^2=60–75 %). Sensitivity analyses showed that excluding either of the two studies [60,62], assessing PFOA and PFHxS reduced heterogeneity to a moderate level without significantly affecting the pooled OR ($p > 0.05$). As a result, minimal heterogeneity was noted for the pooled PFAS effect (I^2=0 %). Two studies assessed exposure to PFAA-Ge-Li in diet [47,54], with notably significant heterogeneity (I^2=81 %) between them, and showed no significant association with asthma onset (OR: 0.97; CI: 0.77–1.24) among children/adolescents. Publication bias assessment (Figure S1) showed no asymmetry for studies assessing PFDA and PFBS (LFK=0.12 and 0.02, respectively), and minor asymmetry for those evaluating PFOS (LFK=1.11), PFOA (LFK=1.84), PFNA (LFK=1.45), and PFHpS (LFK=-1.92). Major asymmetry was noted in the funnel plots for PFHpA (LFK=-2.44), PFHxS (LFK=2.96), PFUnDA (LFK=-2.17), and PFDoDA (LFK=5.44), with fewer studies with low precision/small effect.

3.4.1. Sensitivity analysis per the timing of exposure

Twelve studies [20,21,40,43–46,55,60–62] associated exposure to PFAS in blood during prenatal (Figure S2) and 11 during postnatal (Figure S3) periods. The two studies [47,54] evaluating dietary samples reflected prenatal exposure (Figure S2 (C)). The studies assessing PFTA exposure [60,62] analyzed samples collected during the postnatal period, and therefore significance was preserved. Exposure to PFHxS during the prenatal period was assessed in 12 studies [23,41,42,45,49,50,53,54,57–59] and was associated with 4 % significantly lower odds of asthma onset (OR: 0.96; CI: 0.91–1.00), with minimal heterogeneity between studies (I^2=0 %). In contrast, PFHxS exposure during the postnatal period (assessed in 8 studies [20,21,40,44,46,60–62]) was associated with 1.31 times significantly higher asthma odds (OR: 1.31; CI: 1.01–1.69), with notably significant heterogeneity between study findings (I^2=85 %). The other chemicals assessed showed no significant association with asthma onset odds during both periods. When calculating the pooled effect size, prenatal exposure to PFAS (Figure S2 (A)) was associated with 3 % significantly lower odds of asthma onset (OR=0.97; CI:0.94–0.99), while postnatal exposure (Figure S3 (A)) was associated with 1.20 times significantly higher asthma onset odds (OR=1.20; CI:1.07–1.35).

3.4.2. Sensitivity analysis per sex

Ten studies [20,21,23,40,42,43,53,57–59] evaluated PFAS exposure by sex and the odds of asthma onset in children and adolescents (Figure S4). Nine studies [20,21,23,40,42,53,57–59] analyzed PFOS, PFOA, PFNA, and PFHxS, finding no significant differences in asthma odds in boys nor girls. Moreover, six studies [21,23,42,43,57,58] examined the aforementioned association with exposure to PFDA, five [21,23,42,43,53] to PFUnDa, and two [21,53] to PFHpS, all reporting no statistically significant differences neither in boys or girls. Minimal heterogeneity (I^2<30 %) was observed between studies assessing both sexes' PFOS, PFOA, PFDA, and PFHpS exposure. For PFNA, minimal heterogeneity was found in girls, while boys showed moderate heterogeneity (I^2 = 39 %). Similarly, PFHxS exhibited minimal heterogeneity in girls but moderate heterogeneity in boys (I^2 = 36 %). In the case of PFUnDA, minimal heterogeneity was observed in girls, whereas boys again showed moderate heterogeneity (I^2 = 59 %). The sex-specific pooled effects of PFAS exposure showed no significant differences in boys (OR=1.00; CI:0.98–1.01; Figure S4 (A)) or girls (OR=0.96; CI:0.91–1.01; Figure S4 (C)).

3.5. Association between exposure to PFAS and wheezing in children and adolescents

Fourteen studies investigated the correlation between PFAS exposure and wheezing, with eleven studies analyzing chemicals in the blood [20,23,41,42,48–50,53,58,59,63] (Fig. 3 (A,B)) and two [47,54] in the diet

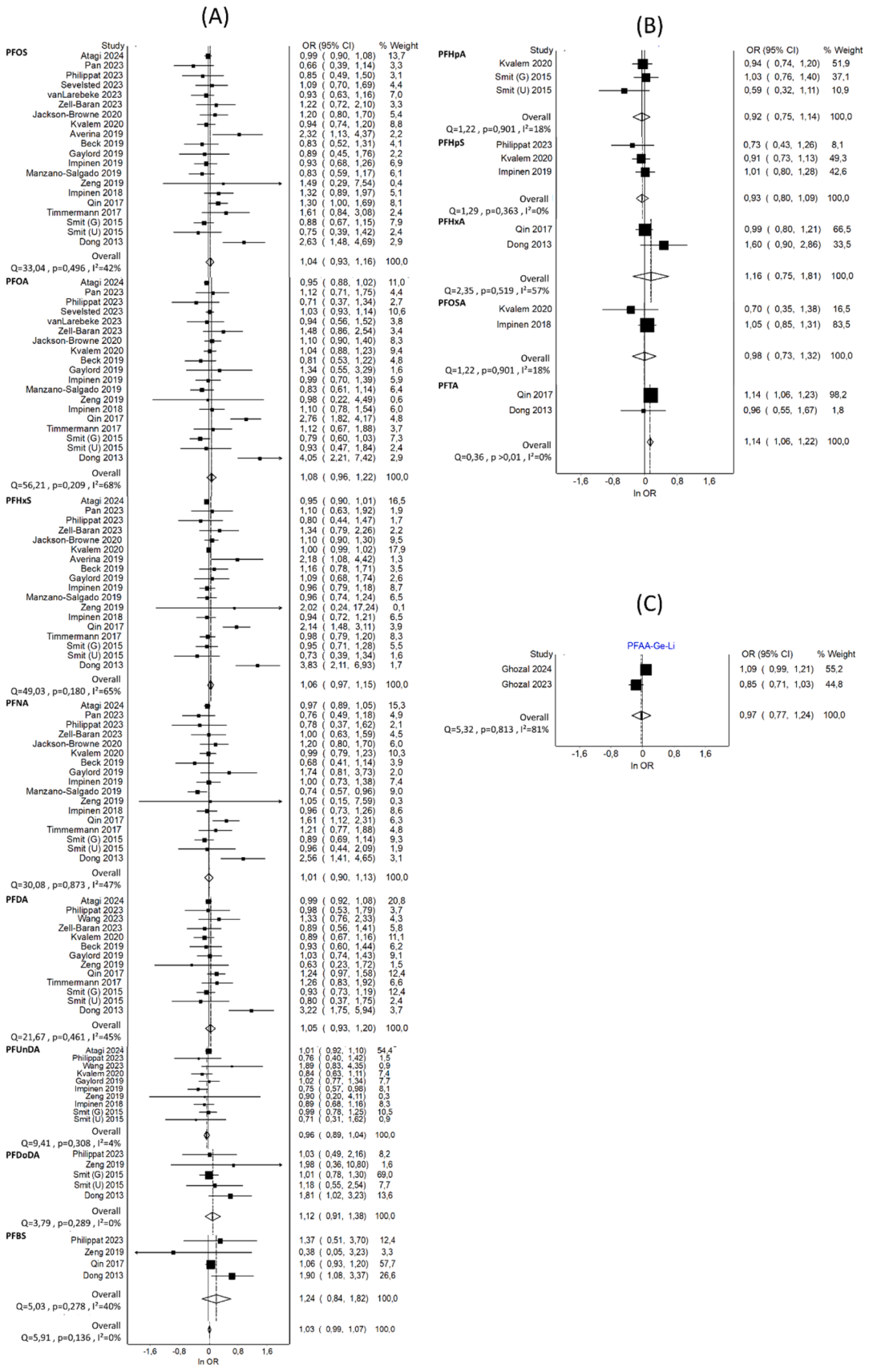

Fig. 2. Associations assessed for ((A) PFAS considered for pooled effect calculation and (B) PFAS assessed in less than four studies) and (C) diet and asthma onset odds among children and adolescents.

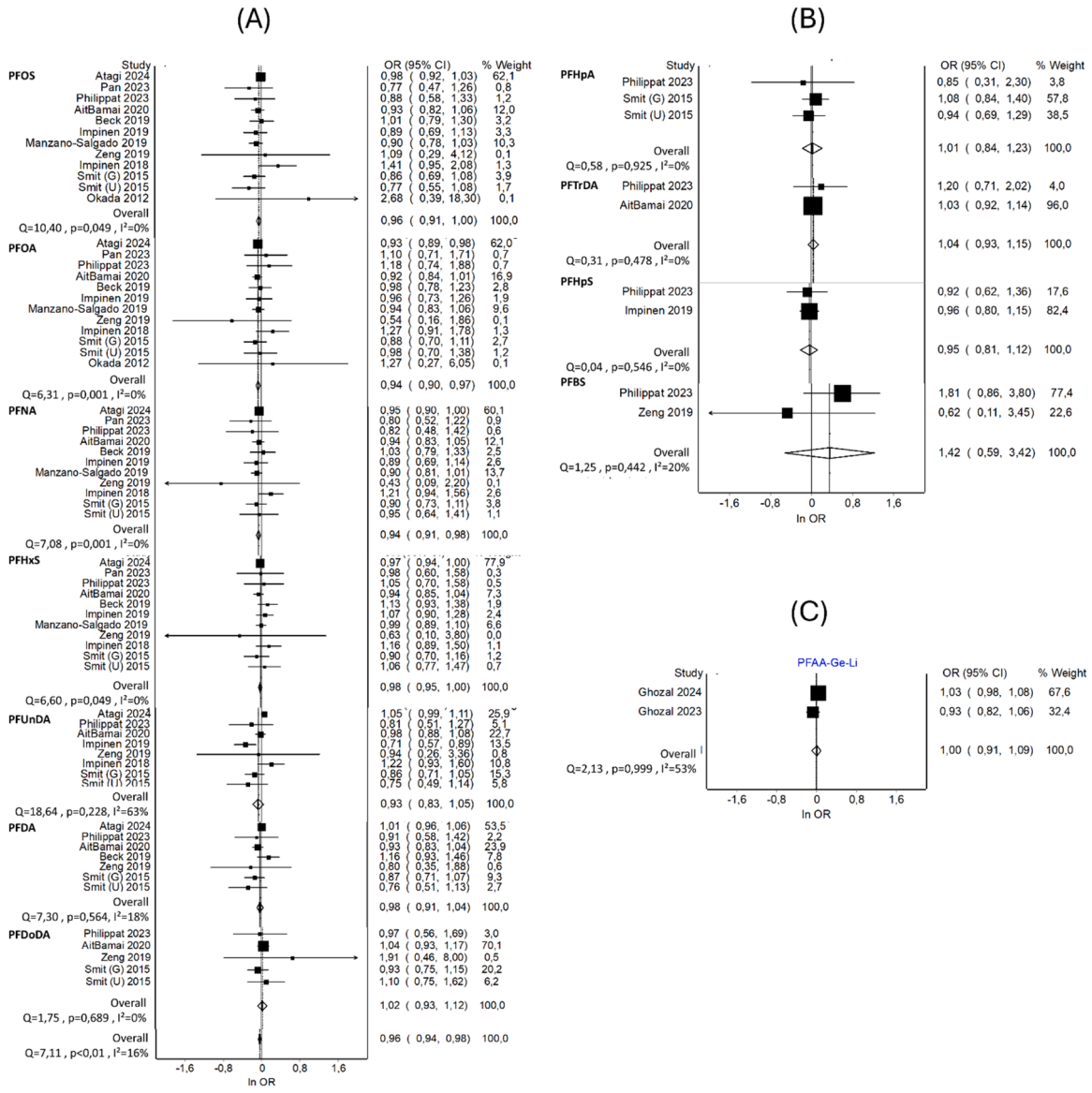

Fig. 3. Associations assessed for ((A) PFAS considered for pooled effect calculation and (B) PFAS assessed in less than four studies) and (C) diet and wheezing odds among children and adolescents.

(Fig. 3 (C). Assessment included PFAA-Ge-Li (as a mixture of PFAS), and PFBS, PFDA, PFDoDA, PFHpA, PFHpS, PFHxPA, PFHxS, PFNA, PFOA, PFOS, PFOSA, PFTrDA and PFUnDA. Exposure to PFOS and PFOA was evaluated in twelve studies [20,23,41,42,48–50,53,58,59,63], revealing a significant association with 4 % and 6 % lower odds of wheezing, respectively (PFOS: OR 0.96, 95 % CI 0.91–1.00; PFOA: OR 0.94, 95 % CI 0.90–0.97). Similarly, exposure to PFNA and PFHxS was assessed in the same twelve studies, indicating significantly lower odds of wheezing in children and adolescents (PFNA: OR 0.94, 95 % CI 0.91–0.98; PFHxS: OR 0.98, 95 % CI 0.95–1.00). Minimal heterogeneity (I^2 = 0 %) was observed among all the mentioned studies, indicating consistency in the results. The quality of evidence was assessed as moderate but was downgraded due to the observational nature of the included studies. Eight studies assessed the exposure through blood sample analysis to PFUnDA [23,41,49,50,53,63], 7 assessed PFDA [23,41,42,50,58,63], 5 PFDoDA [41,42,50,63], 4 PFHpA [41,47,50], 2 PFTrDA [50,63], 2 PFHpS [50,53] and 2 PFBS [42,50], while dietary exposure to PFAA-Ge-Li was assessed in two studies [47,54]. All these chemicals showed no significant associations with wheezing odds among children and adolescents. After computing the pooled effect (Fig. 3 (A)), exposure to PFAS was associated with 4 % significantly lower odds of wheezing in children and adolescents (OR=0.96; CI:0.94–0.98). Minimal heterogeneity (I^2<30 %) was found between studies assessing PFDA, PFDoDA, PFHpA, PFTrDA, PFHpS, and PFBS moderate heterogeneity (I^2=53 %) between studies assessing PFAA-Ge-Li and substantial heterogeneity between those examining PFUnDA (I^2=63 %). Excluding one study [53], assessing PFUnDA reduced heterogeneity to a moderate level without significantly impacting the pooled OR (p = 0.399). As a result, minimal heterogeneity was noted for the pooled PFAS effect (I^2=16 %). The quality of evidence for PFOS, PFOA, PFNA, PFHxS, PFDA, and PFDoDA was assessed as moderate, primarily due to the observational nature of the studies. The evidence for PFHpA, PFTrDA, PFHpS, PFBS, and PFAA-Ge-Li was rated low, with further downgrade because of insufficient supporting evidence. Similarly, the evidence for PFUnDA was rated as low, with an additional downgrade due to substantial heterogeneity between study findings. The assessment of publication bias (Figure S5) showed no asymmetry for studies assessing PFOS (LFK=0.46) and minor asymmetry for those evaluating PFHxS (LFK=1.09). Major asymmetry was noted in the funnel plots for PFOA (LFK=2.46), PFNA (LFK=-3.20), PFUnDA (LFK=-4.81), PFDA

(LFK=-5.23), PFDoDA (LFK=2.77), and PFHpA (LFK=-5.37) with fewer studies with low precision/small effect.

3.5.1. Sensitivity analysis per the timing of exposure

Among the studies mentioned in Section 3.5, only one [20] assessed PFAS exposure during the postnatal period, while the rest focused on prenatal exposure. The two studies [47,54] that evaluated dietary samples also reflected prenatal exposure. This study [20] assessed PFOA, PFOS, PFHxS, and PFNA with a weight of less than 1 %, while the analysis of the other chemicals exclusively represented the prenatal period. Excluding this study from the analysis (Figure S6) preserved the significant association between exposure and lower odds of wheezing in children and adolescents. Thus, the pooled effect size was only calculated using studies reflecting prenatal exposure to PFAS (Figure S6 (A)), which was also associated with 4 % significantly lower odds of wheezing (OR=0.96; CI:0.94–0.98).

3.5.2. Sensitivity analysis per sex

Seven studies [20,23,42,48,53,58,59] evaluated PFAS exposure by sex and wheezing odds in children and adolescents (Figure S7). All seven studies analyzed PFOS and PFOA, 6 [20,23,42,53,58,59] assessed PFNA and PFHxS, and 3 assessed PFUnDA [23,42,53] and PFDA [23,42,58]. Exposure to PFOA was associated with 8 % significantly lower odds of wheezing in girls (OR: 0.92; CI: 0.86–0.98), with no significant alteration found in boys (OR: 0.96; CI: 0.90–1.04). No significant associations were found between exposure to other chemicals and wheezing odds in both sexes. The sex-specific pooled effects of PFAS exposure showed 3 % and 6 % significantly lower wheezing odds in boys (OR=0.97; CI:0.94–1.00; Figure S7 (A)) and girls (OR=0.94; CI:0.91–0.98; Figure S7 (C)), respectively. Minimal heterogeneity (I^2<30 %) was found between studies in both sexes except in those assessing PFNA and PFUnDA in girls (moderate heterogeneity) and studies examining PFUnDA in boys (substantial with an I^2=74 %). The quality of evidence was judged as moderate for PFOS, PFOA, PFNA, and PFHxS (downgraded due to the observational nature of the studies), low for PFDA (additional downgrade due to insufficient supporting evidence), and very low for PFUnDA (downgraded due to the high heterogeneity between study findings).

3.6. Association between exposure to PFAS and atopic dermatitis in children and adolescents

Eight publications explored the association between PFAS exposure and atopic dermatitis (Fig. 4), all assessing exposure in blood [21,27,28,49,53,56,61,64]. The PFAS included PFBS, PFDA, PFDoDA, PFHpA, PFHpS, PFHxS, PFNA, PFOA, PFOS, PFOSA, and PFUnDA. Six studies explored the exposure to PFHxS [21,27,28,49,53,61], which exhibited significant association with 1.15 times higher odds of atopic dermatitis (OR: 1.15; CI: 1.02–1.30). Minimal heterogeneity (I^2=0 %) was noted between these studies, and the quality of evidence was judged as moderate (downgraded due to the observational nature of the studies). Seven studies [21,27,28,49,53,56,61] assessed the exposure to PFNA, PFOA and PFOS, 5 assessed the exposure to PFUnDA [21,27,28,49,53], 3 to PFDA [21,28,61], 2 to PFDoDA [27,28], and 2 to PFHpS and PFOSA, respectively [21,53] all showing no significant associations with atopic dermatitis. After computing the pooled effect size (Fig. 4 (A)), exposure to PFAS was associated with 1.04 times higher odds of atopic dermatitis in children and adolescents with no statistical significance (OR=1.04 CI:0.94, 1.16). Minimal heterogeneity between study findings was noted in those assessing PFNA, PFOS, PFHpS, and PFOSA (I^2<30 %), moderate heterogeneity between those analyzing PFOA, PFDA and PFDoDA (I^2=30–60 %), and substantial heterogeneity for those assessing PFUnDA (I^2=60–75 %). Consequently, moderate heterogeneity was noted for the pooled PFAS effect (I^2=39 %). Excluding one study assessing PFUnDA [53], reduced heterogeneity to a moderate level, while the pooled OR was not statistically significantly impacted

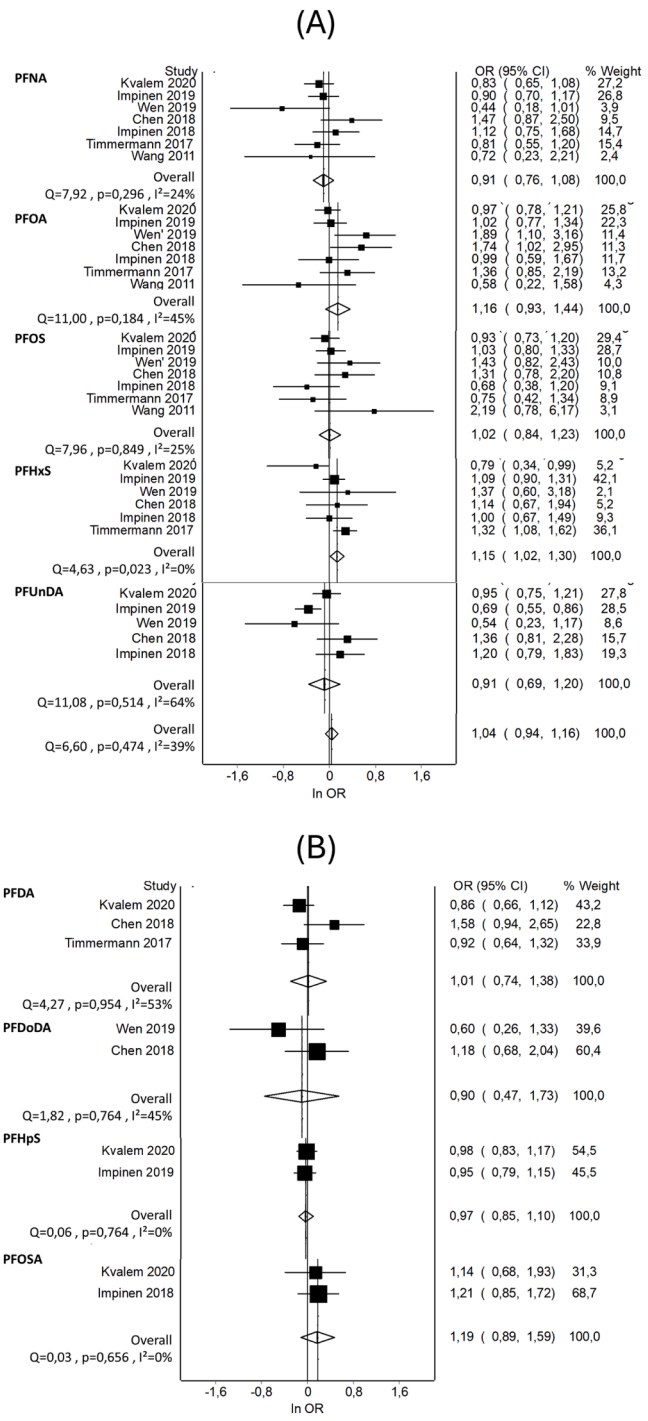

Fig. 4. Associations assessed for ((A) PFAS considered for pooled effect calculation and (B) PFAS assessed in less than four studies) and atopic dermatitis odds among children and adolescents.

(p = 0.523). The quality of evidence was judged as moderate for PFNA, PFOA, and PFOS, downgraded due to the observational nature of the studies, and low for PFUnDA, PFDA, PFDoDA, PFHpS, and PFOSA, with additional downgrade due to the increased heterogeneity between studies (for PFUnDA and PFDA) and due the insufficient supporting evidence for the other chemicals. The assessment of publication bias (Figure S8) showed no asymmetry for studies assessing PFHxS (LFK=-0.78) and PFUnDA (LFK=-0.78) and minor asymmetry for those evaluating PFNA (LFK=-1.35), PFOA (LFK=1.66) and PFOS (LFK=1.25). In contrast, major asymmetry was reported for PFDA

(LFK=2.49), with fewer studies with low precision.

3.6.1. Sensitivity analysis per the timing of exposure

Out of the eight studies mentioned in Section 3.6, six [27,28,49,53,56,61,64,65] associated PFAS exposure during the prenatal period with atopic dermatitis odds and two [21,61] during the postnatal period. During the prenatal period, exposure to PFHxS was associated with 1.17 times significantly higher odds of atopic dermatitis odds (OR: 1.17; CI: 1.03–1.33), and no significant associations were noted for the other assessed compounds (Figure S9). The corresponding pooled effect (Figure S9 (A)) showed that prenatal exposure to PFAS was associated with 1.10 times significantly higher atopic dermatitis odds (OR: 1.10; CI: 1.00–1.22). Postnatal exposure to analyzed PFAS showed no significant associations with atopic dermatitis odds (Figure S10). Less than four studies examined this exposure; therefore, the associated pooled effect was not calculated.

3.6.2. Sensitivity analysis per sex

Three studies [21,28,53] evaluated PFAS exposure by sex and atopic dermatitis odds in children and adolescents (Figure S11). All three studies associated PFOS, PFOA, PFNA, and PFHxS exposure with atopic dermatitis, while two examined PFHpS and PFUnDA [21,53], and PFDA [21,28]. No significant differences were noted for the compounds assessed in both boys and girls. Minimal heterogeneity (I^2<30 %) was found between these studies in both sexes for PFOS and PFHpS, moderate heterogeneity in studies assessing PFOA in girls (I^2=31 % vs. minimal with I^2=0 % in boys) and PFHxS in boys (I^2=51 % vs. substantial with I^2=69 % in girls) and notably significant heterogeneity between studies assessing PFNA in girls (I^2=82 % vs. minimal with I^2=0 % in boys), PFUnDA in boys (I^2= 78 % vs. minimal with I^2=10 % in girls) and PFDA in girls (I^2=86 % vs. minimal with I^2=0 % in boys). The quality of evidence was judged as low for PFOS and PFHpS (downgraded due to the observational nature of the studies and the insufficient supporting evidence) and very low for the remaining chemicals (additionally downgraded due to the increased heterogeneity between study findings. Given that only three studies assessed sex-specific PFAS exposure, pooled effects were not calculated.

3.7. Association between exposure to PFAS and eczema in children and adolescents

The correlation between PFAS exposure and eczema was evaluated in seven studies, of which five evaluated chemicals in blood [41,45,48,59,63] (Fig. 5 (A,B)) and two [47,54] in the diet (Fig. 5 (C)). PFAA-Ge-Li was assessed as a mixture of PFAS in addition to other PFAS, including PFDA, PFDoDA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFTrDA, and PFUnDA. Exposure to PFOA and PFOS was assessed in five studies [41,45,48,59,63] and was significantly associated with 9 % and 12 % significantly lower odds of eczema (OR: 0.91; CI: 0.84–0.97 and OR: 0.88; CI: 0.81–0.96, respectively). Exposure to PFNA was assessed in four studies [41,63,66], also showing significantly lower eczema odds in children and adolescents (OR: 0.93; CI: 0.86–1.00). The exposures to PFDA, PFDoDA, and PFUnDA were examined in three studies [41,63], all showing significantly lower odds of eczema (OR: 0.89; CI: 0.81–0.99, OR: 0.89; CI: 0.80–0.98 and OR: 0.88; CI: 0.81–0.96, respectively). The corresponding overall pooled effect (Fig. 5 (A)) showed that PFAS exposure was associated with 8 % significantly lower eczema odds (OR: 0.92; CI: 0.89–0.96) in children and adolescents. Minimal heterogeneity (I^2=0 %) was noted between all the mentioned studies, leading to minimal heterogeneity in the pooled effect (I^2=0 %). The quality of evidence was judged as moderate for PFOS, PFOA, and PFNA, which was downgraded due to the observational nature of the included studies, and low for PFDA, PFDoDA, and PFUnDA, with supplemental downgrade due to the insufficient evidence. Three studies assessed the exposure through blood sample analysis to PFHxS [41,59,63], and two assessed PFHpA [41]. In comparison, dietary exposure to PFAA-Ge-Li was assessed in two studies [47,54], all showing no significant associations with eczema among children/adolescents, with minimal heterogeneity between these studies. Nevertheless, the corresponding quality of evidence was judged as low due to the observational nature of the studies and the insufficient supporting evidence. The assessment of publication

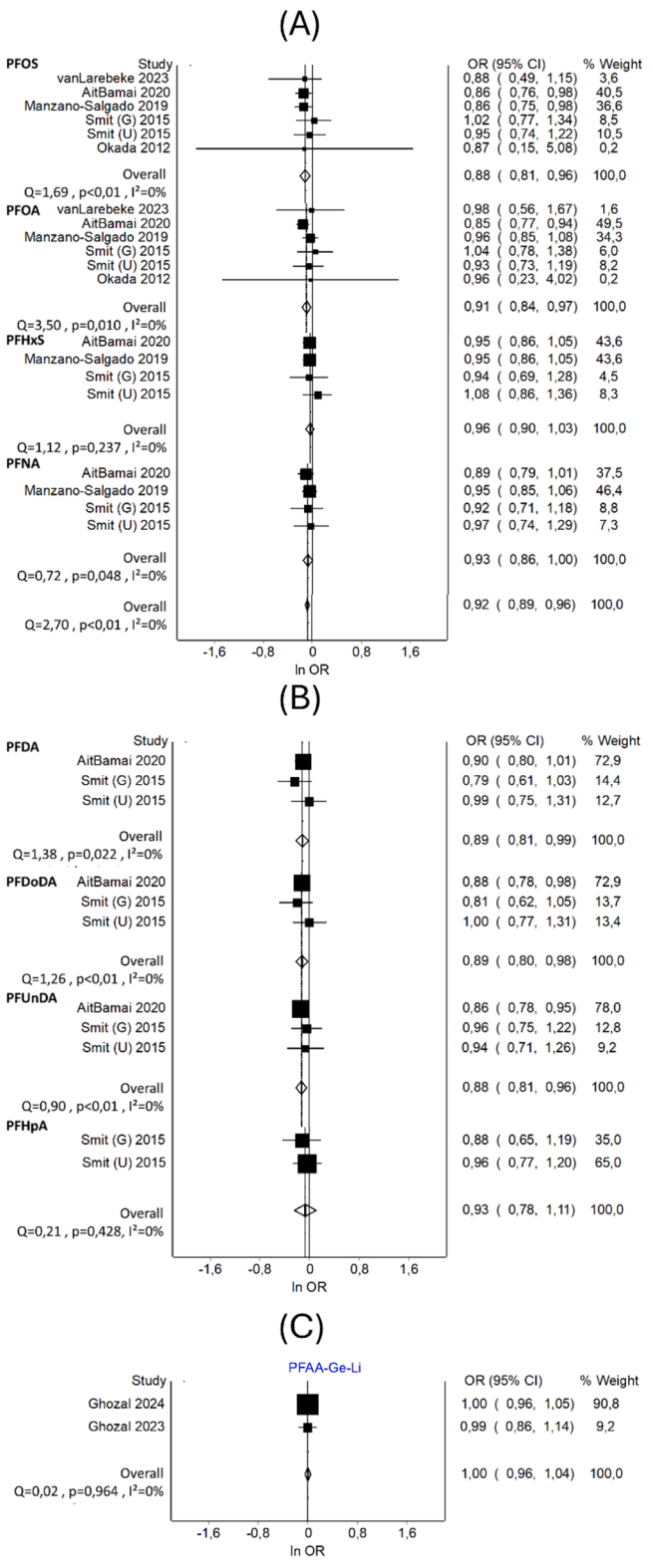

Fig. 5. Associations assessed for ((A) PFAS considered for pooled effect calculation and (B) PFAS assessed in less than four studies) and (C) diet and eczema odds among children and adolescents.

bias (Figure S12) showed no asymmetry for studies assessing PFDA (LFK=-0.33) and PFDoDA (LFK=0.53) and minor asymmetry for those evaluating PFNA (LFK=1.76) and PFHxS (LFK=1.74). In contrast, major asymmetry was noted in the funnel plots for PFOA (LFK=2.25), PFOS (LFK=3.47) with fewer studies with low precision, and PFUnDA (LFK=4.53) with fewer studies with higher precision.

3.7.1. Sensitivity analysis per the timing of exposure

Among the seven studies mentioned in Section 3.7, only one [45] assessed PFAS exposure during the postnatal period, while the remaining assessed samples reflected prenatal exposure. This study [45] assessed PFOA and PFOS with a weight of 1.6 % and 3.6 %, while the analysis of the other chemicals exclusively represents the prenatal period. Excluding it (Figure S13) did not affect the association between exposure to PFOA and PFOS and eczema odds compared to including studies despite the timing of exposure (OR: 0.91; CI: 0.84–0.97 and OR: 0.88; CI: 0.81–0.96, respectively). The pooled effect of prenatal PFAS exposure (Figure S13 (A)) showed 8 % significantly lower eczema odds (OR: 0.92; CI: 0.89–0.96). The pooled effect from postnatal PFAS exposure was not computed due to insufficient evidence.

3.7.2. Sensitivity analysis per sex

Two studies [48,59] evaluated PFAS exposure by sex and the odds of eczema in children and adolescents (Figure S14). Two chemicals were assessed (PFOS and PFOA), of which exposure to PFOS was associated with 23 % significantly lower odds of eczema in girls (OR: 0.77; CI: 0.64–0.93), with no significant alterations in boys (OR: 0.91; CI: 0.75–1.10). There were no significant associations between PFOA exposure and eczema odds in both girls and boys. The corresponding pooled effect was not calculated due to insufficient available evidence. Minimal heterogeneity (I^2=0 %) was found between these studies in both sexes, and the quality of evidence was judged as low (downgraded due to the observational nature of the studies and the insufficient supporting evidence).

4. Discussion

This systematic review and meta-analysis provides a comprehensive overview of research on PFAS exposure and its associations with asthma, wheezing, atopic dermatitis, and eczema in children and adolescents. However, significant geographical and socioeconomic disparities in study representation may limit the global applicability of the findings. Of the 28 studies analyzed, most were conducted in high-income countries, with no representation from low-income regions. This imbalance can create critical data gaps, as children in low-income countries may face distinct environmental exposures [67,68], healthcare barriers [69], and risk factors that remain unexplored. Most studies employed cohort designs, which are valuable for capturing the longitudinal effects of environmental exposures but often focus primarily on prenatal exposure, leaving the postnatal impact underexamined and limiting causal interpretations. Despite a generally low risk of bias across studies, the asymmetry in reported findings for many PFAS chemicals may raise concerns about potential publication bias. Additionally, the review largely focused on legacy PFAS, such as PFOA and PFOS, which are well-documented for their persistence and toxicity. In contrast, emergent PFAS, introduced as safer alternatives, remain understudied despite growing evidence of their potential environmental persistence and health risks. To close these gaps, future research should involve low-income regions, account for postnatal exposure, and include unpublished and negative findings to better capture the global burden of PFAS-related health outcomes and ensure more equitable health outcomes.

4.1. Association between PFAS exposure and asthma onset in children and adolescents

Although the pooled effect did not indicate a significant association with asthma onset, the sensitivity analysis based on the timing of exposure revealed contradictory results: prenatal PFAS exposure was significantly associated with lower odds of asthma onset, whereas postnatal exposure was linked to higher odds. Research has reported a shorter half-life (up to 5 years) of some PFAS among women during their fertile age [70]. This suggests a reduced impact on asthma diagnosis, typically at a mean age of 4.7 ± 1.5 years [71]. Moreover, PFAS exposure during the postnatal period may involve different pathways and routes, with higher exposure to allergens or co-exposure to other chemicals that can trigger asthma development. PFTA, in particular, has a longer carbon chain (14 perfluorinated carbons) than some other PFAS [72] and can non-competitively inhibit carboxylesterases [73], resulting in greater bioaccumulation within the human body and higher internal exposure levels over time, potentially amplifying its impact on the immune system and respiratory health. Sulfonic acid properties of PFHxS also contribute to its hydrosolubility and persistence and result in higher accumulation in the respiratory tract, thereby increasing the risk of asthma and inflammatory responses [74]. Prenatally, the direct exposure of the fetus to PFAS may be reduced by the blood-placental barrier and the potential binding ability to mothers' serum albumin [75]. In addition, PFAS containing a functional sulfonic acid group, such as PFHxS [76], may influence the fetus' immune cell development or function, making immune responses less prone to asthma triggers. Sensitivity analysis by sex revealed no significant differences among girls nor boys, suggesting similar biological pathways for asthma development. This finding is consistent with a previous report highlighting the amplification of the association between PFAS and asthma in both sexes due to reproductive hormones [77].

4.2. Association between PFAS exposure and wheezing in children and adolescents

Exposure to PFOS, PFOA, PFHxS, and PFNA, as well as the pooled effect of PFAS exposure, particularly during the prenatal period, was associated with significantly lower odds of wheezing in children and adolescents. This was also reported in another study [78] targeting children and adolescents, in contrast to a previous systematic review showing null associations with early-life wheezing odds [79]. Prior research also associated prenatal exposure to PFAS with a higher risk of respiratory tract infections later in life [49,80], with no impact on asthma and allergy-related outcomes [49]. Prenatal exposure to PFAS can promote epigenetic modifications that influence the regulation of genes involved in inflammation and lung function [81,82] or induce changes in the structural and functional aspects of the lungs, with inverse associations previously reported with some forms of allergy [45]. These modulations can produce a more balanced inflammatory response after birth, making children and adolescents less prone to the overactive responses that cause wheezing. Furthermore, prenatal exposure to PFAS could alter the body's response to pollutants, allergens, and other environmental triggers after birth, potentially decreasing the likelihood of wheezing, often exacerbated by such factors [83]. Moreover, the Agency for Toxic Substances and Disease Registry associated PFOA exposure with increased serum liver enzymes and lipids [84], which may reflect systematic inflammation, metabolic syndrome, and oxidative stress. The possible implication of PFAS exposure with changes in hormone levels and functions can explain this finding in both sexes [50,85], creating a developmental environment that promotes stronger lung function and a more regulated immune response, thereby reducing the risk of wheezing. Estrogen in girls can regulate such an impact [86], which may explain their significantly lower wheezing odds than boys.

4.3. Association between PFAS exposure and atopic dermatitis in children and adolescents

Exposure to PFHxS was associated with significantly higher odds of atopic dermatitis in children and adolescents, possibly due to its immunomodulatory and immunotoxicity properties [25,87]. PFHxS can modulate the immune system, potentially leading to altered cytokine production and an imbalance in T-helper cells (Th1/Th2), which promotes the overactive immune responses seen in atopic dermatitis [88]. Moreover, PFHxS can interfere with thyroid hormones and glucocorticoid pathways [87], causing hormonal imbalances that compromise skin barrier integrity and immune regulation. Genetic predispositions and epigenetic changes induced by PFHxS exposure may further contribute to developing or exacerbating atopic dermatitis by altering gene expression patterns related to immune function and skin health [89]. This association was only observed for exposures during the prenatal period, possibly due to the association between higher prenatal PFHxS concentrations and a lower percentage of fat mass after birth [90], which can disrupt lipid metabolism and protein functions essential for maintaining the skin barrier [91], increasing its permeability and susceptibility to allergens and irritants. When computing the overall effect, no statistically significant associations with atopic dermatitis odds in children and adolescents were noted, suggesting that the impact of other chemicals alleviated PFHxS impact. No significant differences were noted among the sexes in any of the chemicals assessed, suggesting a similar impact on boys and girls, especially since most studies reflected mothers' exposure. Given that insufficient evidence is available to compute the overall effect postnatally and among sexes, further postnatal PFAS exposure and sex-specific assessments and link to atopic dermatitis can help better validate those findings since a recent gender-age study showed lower PFOS, PFOA, PFNA, and PFHxS concentrations in girls starting at the early beginning of adolescence [92].

4.4. Association between PFAS exposure and eczema in children and adolescents

Different forms of eczema can have different primary triggers, including contact with irritants or allergens [93]. Since eczema is a broad category, studies might find a general reduction in non-specific cases due to reporting biases or diagnostic challenges [94]. Prior research performed during early childhood showed no significant association between PFOA, PFOS, or PFNA and eczema [48,95], in contrast to findings from this meta-analysis. Given that the calculated pooled effect showed a significantly lower eczema odds after exposure to PFAS, this suggests that *in utero* PFAS exposure may have a potential long-lasting impact in late childhood and adolescence health since most samples were examined during the prenatal period. This can be associated with interference with the immune responses or skin barrier functions in ways that reduce the likelihood of developing certain types of eczema, particularly those more irritant-based rather than immunologically driven forms. Despite the inability to compute the pooled effect due to insufficient evidence, the sensitivity analysis per sex per individual chemical showed significantly reduced eczema odds in girls associated with PFOS exposure during the prenatal period, with no significant impact in boys. PFOS might interact with estrogen pathways [96], which can lead to different developmental outcomes in female fetuses that could reduce eczema risk. Moreover, there might be sex-specific differences in the mechanism of PFOS trans-placental transfer or metabolism [97], resulting in different levels of exposure and subsequent health effects in male and female fetuses, which was previously reported in mice [98].

4.5. Strengths and limitations of this study

This systematic review has several strengths. A comprehensive search was conducted across four prominent databases to identify eligible articles. To ensure the reliability of the review, three authors independently performed all stages of the process, resolving any discrepancies through discussion and achieving consensus among at least two of them. This approach minimized the likelihood of researcher bias. Furthermore, minimal heterogeneity was observed among most studies, enhancing the reliability of the findings. However, this systematic review also has certain limitations. The classification of PFAS exposure (e.g., quartile increase, Q4 vs. Q1, log unit increase) is confined to the PFAS concentrations reported in the included studies. As a result, extending the associations observed to a broader spectrum of concentration ranges or ensuring comparability is challenging. To improve comparability across studies and support the implementation of adequate protective measures, it is recommended that uniform cut-off points for PFAS concentration classification should be established. Additionally, the evaluation of specific PFAS did not account for other co-exposures or co-pollutants that might influence the outcomes, making it difficult to isolate the effects of individual chemicals. Moreover, despite the limited number of studies with a high risk of bias, the overall quality of evidence has been downgraded due to the observational nature of these studies. This issue is further compounded by varying exposure durations and differing methods and timings of outcome assessments, which may introduce inaccuracies. The combined data from children and adolescents, despite differences in their physical development and disease susceptibility, may limit the ability to detect age-specific associations. Future research should consider age-stratified analyses to better account for these developmental differences. One potential limitation of this study is the geographical heterogeneity of the included studies, as variations in environmental, cultural, and regulatory factors may influence the consistency and generalizability of the observed associations between PFAS exposure and health outcomes. Moreover, different geographical regions may be associated with cultural dietary habits, lifestyle factors, and environmental conditions that may contribute to differences in health outcomes, which could modulate the impact of PFAS exposure. Hence, it is recommended that future research consider and control local environmental and cultural factors, which would help further understand the global impact of PFAS exposure on health. Most studies examined samples during the prenatal period and outcomes later in childhood and adolescence, during which different exposure patterns could have arisen. While the combination of funnel plots and the LFK index provided complementary visual and quantitative assessments of publication bias, their reliability remains limited, particularly in a small number of studies and potential heterogeneity, which may have influenced the accuracy of bias detection. The assessment of publication bias showed increased likelihood in some chemicals, suggesting the lack of small effect or unpublished studies with null association. Therefore, conducting more studies in future research is crucial for more robust and reliable findings.

5. Conclusion

The present systematic review and meta-analysis suggest that overall PFAS exposure is associated with lower odds of wheezing and eczema among children and adolescents. Prenatal PFAS exposure was associated with lower asthma onset, wheezing, and eczema odds, while postnatal exposure was linked to higher asthma onset odds with insufficient evidence for other outcomes. PFAS exposure had significantly lower odds of wheezing in both sexes, no sex-specific influence on asthma onset, and insufficient evidence for the other outcomes. Without considering the timing of exposure, asthma odds were significantly affected by PFTA exposure, wheezing odds by PFOA, PFOS, PFNA, PFHxS, and PFHpA exposure, atopic dermatitis odds by PFHxS and eczema odds by PFOA, PFOS, PFNA, PFDA, PFDoDA, and PFUnDA. The pooled effect of the various chemicals generally exhibited moderate to low-quality evidence. Most studies analyzed blood samples primarily focusing on prenatal exposures (namely for wheezing and eczema). Sensitivity analyses considering the timing of exposure revealed a contradictory impact of

PFHxS on asthma onset odds between the prenatal and postnatal periods and a significant impact on atopic dermatitis odds only during the prenatal period. In girls, PFOA exposure was significantly associated with wheezing, PFUnDA with atopic dermatitis, and PFOS with eczema, with no significance among boys. These findings highlight the influence of specific PFAS exposures, the timing of these exposures, and sex differences on the health outcomes studied and can provide evidence-based insights for environmental health monitoring. To gain a comprehensive and reliable understanding of these associations and to investigate the underlying mechanisms, it is essential to conduct and publish more studies, regardless of their effect sizes, to mitigate potential publication bias.

Environmental Implication

Per- and poly-fluoroalkyl substances (PFAS) are persistent organic pollutants widely used in industrial and consumer products, leading to long-lasting water, soil, food, and air contamination. PFAS can accumulate in the environment, and exposure may pose significant risks to human health, particularly to vulnerable populations such as children and adolescents. By synthesizing evidence on the association between PFAS exposure and respiratory or skin conditions like asthma, wheezing, atopic dermatitis, and eczema, this study emphasizes the importance of implementing measures that could reduce PFAS environmental burden and protect future generations' health, contributing to safer ecosystems and sustainable public health outcomes.

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CRediT authorship contribution statement

Hatem Georges: Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Faria Ana Margarida:** Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Bessa Pinto Mariana:** Writing – original draft, Resources, Formal analysis, Data curation, Conceptualization. **Salamova Amina:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Teixeira João Paulo:** Writing – review & editing, Visualization, Resources, Project administration, Investigation, Conceptualization. **Costa Carla:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization. **Madureira Joana:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2025.137978.

Data availability

Data will be made available on request.

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