



Review

Association between exposure to airborne endocrine disrupting chemicals and asthma in children or adolescents: A systematic review and meta-analysis[☆]

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ABSTRACT

Various studies have explored the association between Endocrine Disrupting Chemicals (EDCs) exposure and children's and adolescents' respiratory health, showing potential long-term effects and links to asthma. This systematic review explores the association between exposure to seven EDC groups during school age and adolescence and asthma onset or exacerbation while highlighting the predominant compounds underlying these potential associations. PubMed, Web of Science, Scopus, and Cochrane Library databases were searched with no time restriction. The risk of bias and heterogeneity across the included studies were assessed using the Newcastle Ottawa scale and I² test, respectively. Pooled Odds Ratios (OR) and their 95% Confidence Intervals (CI) were calculated using the random effect model, and the quality of evidence for each outcome was measured using the GRADE approach. The review included 64851 children and adolescents from 61 observational studies, most with a low risk of bias in the studied domains. The pooled OR for asthma onset was significant for phthalates in dust samples (OR:1.21, CI:1.02; 1.44). Due to limited studies, the overall pooled effects for the other groups were not computed. Individual compounds demonstrating significant associations with asthma onset included airborne nickel (OR:1.10, CI:1.03; 1.18) and zinc (OR:1.13, CI:1.11; 1.15), urinary Bisphenol S (OR:1.40, CI:1.13; 1.73), Bisphenol A (OR:1.57, CI:1.02; 2.40) and arsenic (OR:2.08, CI:1.33; 3.26), and DiBP (OR:1.41, CI:1.08; 1.82), DEHP (OR:1.89, CI:1.00; 3.57), and TBOEP (OR:2.61, CI:1.08; 6.30) in the dust. Individual compounds with significant associations with greater asthma exacerbation odds comprised airborne nickel (OR:1.08, CI:1.01; 1.16) and zinc (OR:1.09, CI:1.01; 1.17), and urinary MEHHP (OR:1.24, CI:1.02; 1.51), MECPP (OR:1.30, CI:1.07; 1.57), MEOHP (OR:1.30, CI:1.09; 1.55), and MCOP (OR:1.32, CI:1.11; 1.57). Exposure to EDCs was significantly associated with asthma onset and exacerbation in children and adolescents, namely for phthalates, bisphenols A and S, arsenic, nickel, and zinc. Further research is recommended to focus on the impact of synergistic and co-exposure to other indoor air pollutants.

1. Introduction

Endocrine Disrupting Chemicals (EDCs) prevalent as outdoor and indoor pollutants are commonly found in various industrial, cleaning, and personal care products, agricultural practices, vehicle exhaust, urban runoff, waste disposal sites, wildfires, and atmospheric deposition (Rudel and Perovich, 2009). These include widely used plastics in

building materials, medical equipment, food containers, water bottles, and toys (Zhang et al., 2021). Paints, glues, and flame retardants also may incorporate EDCs (Zeng et al., 2023). Among others, phthalates, polycyclic aromatic hydrocarbons (PAHs), flame retardants, volatile organic compounds, heavy metals, and bisphenols have currently been identified and classified by the World Health Organization (WHO) as EDCs (Macedo et al., 2022; TERRI DAMSTRA et al., 2002).

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The presence of EDCs has raised substantial concerns over their impact on human health and the environment. Focusing on air pollutant exposure, the associated pervasive threat poses a critical environmental hazard, significantly impacting human health and standing as a major contributor to the global burden of respiratory diseases, morbidity, and mortality (Velasco and Jarosińska, 2022). Despite extensive research on EDCs, understanding their role in disease onset, particularly in vulnerable populations such as children, remains a significant scientific challenge. Epidemiological research in children and adolescents has identified elevated EDC concentrations detected in different biological matrices (e.g., urine, blood, hair) associated with higher indoor and outdoor airborne contaminant concentrations (Aimuzi et al., 2023; Nafea et al., 2020; Terri Damstra et al., 2002). This can lead to potential acute and chronic adverse respiratory (Aimuzi et al., 2023; Nafea et al., 2020; Robinson and Miller, 2015), neurological (Flaws et al., 2020; Cajachagua-Torres et al., 2024), immune (Robinson and Miller, 2015), and reproductive (Yesildemir and Celik, 2024) health outcomes.

Among children and adolescents, asthma is one of the most common chronic respiratory diseases (Vos et al., 2020), characterized by bronchial hyperresponsiveness and variable airflow obstruction, causing wheezing, breathlessness, coughing, and chest tightness (Franken et al., 2017). Asthma can significantly affect quality of life, decrease academic performance, and reduce well-being (Hsu et al., 2016). The pathophysiology of asthma involves complex interactions between genetic predisposition and environmental factors, with growing evidence linking its onset and exacerbation among humans to exposure to air pollutants (Lee et al., 2023; Chen et al., 2015), including EDCs. Nevertheless, most of the literature has focused on individual compounds (Madrigal et al., 2021; Nafea et al., 2020; Zhang et al., 2021; Zhao et al., 2022), leaving critical gaps in understanding the health effects of chemical mixtures and their interactions.

A recent review reported a significant correlation between EDC exposure during critical developmental windows, such as prenatal and early childhood periods, and subsequent adverse health outcomes later in life, mainly due to the vulnerability of developing organ systems and immature detoxification pathways (Raja et al., 2022). For respiratory health, early exposure to airborne EDCs during periods of rapid lung development can result in long-term implications for lung function and increased susceptibility to respiratory diseases (Vandenberg and Matouskova, 2023). While some studies have explored potential associations between specific EDC groups and asthma-related outcomes, the findings remain fragmented, with limited examination of combined chemical exposures (Jackson-Browne et al., 2023; Paciência et al., 2019; Ortega and Hernandez-Trujillo, 2019). These studies may also involve different environmental and biological matrices, analytical methods, and sampling techniques, with substantial disparities between findings, leading to limitations and disparities in reported exposure data (Hsu et al., 2012). Given these challenges, a systematic and quantitative examination of airborne EDC exposure and its association with the onset and/or aggravation of asthma in school-age children and adolescents is essential for consolidating existing evidence and guiding future research directions.

Humans are exposed to EDCs through various pathways, including ingesting contaminated food and water, inhaling polluted air, and dermal contact with products containing EDCs (Yang et al., 2006). Given that preventing asthma onset involves a combination of strategies aimed at reducing exposure to triggers, in addition to managing the condition effectively and alleviating symptoms among asthmatics (Wang et al., 2016), the WHO (2021) provided updated health-based guideline concentrations for the major health-damaging air pollutants to assist policymakers and the general population. Periodic updates of air quality guidelines are paramount in light of many scientific advances. Therefore, the primary aim of this research is to explore the evidence regarding associations between exposure to EDCs during school age and adolescence and the onset and exacerbation of asthma. It also seeks to explore the predominant groups of EDCs most strongly implicated in

these associations. To achieve these objectives, a systematic review of the existing literature was conducted to assess published evidence on the topic. This approach included identifying and critically appraising relevant studies, evaluating the risk of bias at the individual study level, and synthesizing data through meta-analysis to quantify the strength and direction of the associations. Furthermore, the quality of evidence for each compound was evaluated using established frameworks, enabling an understanding of the reliability and robustness of the findings. By integrating these methods, this review aims to provide a thorough and evidence-based understanding of the role of EDCs in childhood asthma, offering insights that could inform future research and public health interventions.

2. Methods

The present systematic review followed the standards in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Page et al., 2021). It was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under reference CRD42023466637.

2.1. Literature search strategy and data sources

The following search terms were combined to retrieve published evidence on the review subject: “Endocrine disrupting chemicals” OR parabens OR phthalates OR metal OR “flame retardant” OR “alkyl phenol” OR “phenoxy phenol” OR triclosan OR bisphenol OR polycyclic aromatic hydrocarbon) AND (indoor OR “outdoor air”) AND (school-children OR “school age” OR adolescents) AND asthma. Details about the search terms for this systematic review are presented in [Supplementary Table S1](#).

PubMed, Web of Science, Scopus, and Cochrane Library databases were employed for a systematic literature search from their inception to November 1st, 2023. After exporting data in Research Information Systems (RIS) format, references were imported to Endnote Software version 20 for initial duplicate screening and removal, followed by additional manual elimination. In addition to electronic database searches, hand-searching was also employed as a supplementary strategy. This involved manually reviewing the reference lists of pre-existing systematic reviews and relevant articles to identify any additional studies that may have been missed during the initial search. The obtained file was then imported to Covidence software for another duplicate removal round before screening initiation.

2.2. Inclusion and exclusion criteria

Studies were included if: 1) Population was children and adolescents between five and 18 years (or age-adjustment was performed in the multivariate analysis); 2) At least one EDC parent compound or metabolite was detected in air, dust, urine, sputum, hair/nail, or blood; 3) EDC exposure was assessed in relationship with asthma onset or/and 4) asthma exacerbation in asthmatic children/adolescents.

Studies were excluded if: 1) Animal or *in vitro* cell models were used; 2) No quantitative data on EDC exposure were presented; 3) Analyses investigated the associations between prenatal/preschool EDC exposure and asthma in neonates or children; 4) Studies with qualitative endpoints for outcome(s) assessment; 5) Abstracts with unpublished results, reviews, editorials, letter to the editor and case reports and, 6) Studies unavailable in English.

Considering the above, the PECO (Population, Exposure, Comparators, Outcomes) statement was defined as follows. The population included children and adolescents from 5 to 18 years of any nationality, social and educational status; Postnatal EDC exposure was assessed through various biological and/or environmental matrices; the comparator or subgroup analyses included cases (asthmatic children/adolescents) and controls (non-asthmatic healthy children/adolescents)

for asthma onset assessment (outcome one) and only cases when considering asthma exacerbation (outcome two). Children/adolescents were classified as cases if: i) a doctor diagnosed them as asthmatic 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 have asthma?”; or ii) had a positive bronchodilatation (at least a 12% and over 200 mL increase in forced expiratory volume in 1 s (FEV1) after bronchodilation). In cross-sectional studies additional criteria were considered: i) pre-defined timeline of asthma prevalence, ii) recurrence of at least two of the three symptoms: cough, wheeze, and shortness of breath within the previous 12 months or less, iii) asthma medication use in past 12 months or iv) a positive exercise challenge test (a $\geq 10\%$ decrease in forced expiratory volume in 1 s compared with baseline, performed 2–7 days after exposure assessment. Participants with diagnosed asthma were included in the asthma exacerbation assessment if they: i) had two or more episodes of asthma or an asthma attack during the past 12 months; ii) used asthma medication; iii) reported breathing difficulties in the past three months by parents/legal guardians or caregivers; iv) visited an emergency room or urgent care because of asthma during the past year; or v) a pediatric asthma exacerbation severity score was computed. Participants not meeting the above criteria were classified as healthy controls.

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

Selection of studies, risk of bias assessment, and data extraction were conducted independently by two researchers (GH and AMF). Titles and abstracts of all records were identified, and a preliminary screening assessment was performed based on predetermined inclusion criteria. After the title/abstract screen was completed, full texts were retrieved and screened according to the selection criteria. If full texts were missing or inaccessible, the corresponding authors were contacted by email, with a pre-defined deadline of two weeks to receive answers. If no answer was obtained, studies were excluded. The two authors had to reach a consensus before final approval. If conflicts/disagreements arose, a third team member was consulted until agreement. All exclusions were listed with a brief justification of the exclusion rationale, including duplicate data, an outcome not of interest, different exposure timing, lack of quantitative exposure assessment, unpublished results, wrong population, full text unavailable, another language than English, and studies with no primary data. Where multiple publications used the same population, only the most complete was included.

The risk of bias in the included studies was assessed using the Newcastle Ottawa scale (Wells et al., 2000). Depending on the study design, three different forms were employed to address potential biases in the following domains: selection (four questions), comparability (two questions), and outcome (cohorts and cross-sectional) or exposure (in case-control studies) (three questions). Each question was assigned one point based on the answer chosen. Selection bias assessed sample representation, the definition of cases, information on non-respondents characteristics, the selection/definition of controls (hospital or non-description provided), and information on the outcome of interest at baseline (in cohorts). As for comparability, it evaluated how confounding variables were controlled, considering age as the most important factor, while additional factors included, among others, sex, body mass index, maternal age, parental education, and household income. Outcome/exposure evaluation included the indication of the non-response rate or description of the drop-out rate, the duration and adequacy of follow-up, and the use of similar methods of outcome ascertainment for cases and controls. Regarding selection bias, studies received a low bias rating if they scored 4, unclear (3–2 points), or high risk (0–1 points). For comparability bias, studies were deemed to have low, unclear, or high risk of bias if they scored 2, 1, or 0 points, respectively. As for outcome/exposure bias, studies were categorized as having a low, unclear, or high risk of bias based on their 3, 2, or 1-point

scores, respectively.

The characteristics of the included studies (author, year of publication, location, and study design), the participants (age, number, and ratio cases: controls when possible), exposure indicators (EDC group, compound/metabolites analyzed, matrix), outcome (asthma onset or/and exacerbation of asthma) and associations between the exposure and outcome indicators were extracted and presented in a table format (Table S3) in addition to odds ratios (OR) with 95% confidence intervals (CI) and/or geometric means with standard deviations following the guidelines established in NTP/OHAT Handbook for Conducting a Literature-Based Health Assessment (Rooney et al., 2014). To preserve objectivity and increase the findings' reliability and accuracy, two reviewers (GM and AMF) extracted the data independently using the data extraction form to ensure all relevant information was included while considering coherence between them.

2.4. Statistical analysis

For the meta-analysis, only chemicals assessed in at least two different studies were considered (n° studies = 44). MetaXL version 5.3 software was used for effect size calculation, forest plot generation, and heterogeneity assessment. The natural logarithm of the OR (LnOR) was employed independently for each study and then pooled and weighted using random effects models. Weighted geometric mean (WGM) difference was computed if data were available. The pooled effect was calculated for EDC groups, including only those compounds evaluated in at least four studies. Sensitivity analyses were conducted to evaluate the robustness of the meta-analysis findings and identify any studies that significantly influenced the results. 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 S2. The I2 test was employed to evaluate the heterogeneity among the included studies. Heterogeneity was categorized as minimal/insignificant ($I^2 < 30\%$), moderate ($I^2 = 30\text{--}60\%$), substantial ($I^2 = 60\text{--}75\%$), or notably significant ($I^2 > 75\%$) (Higgins and Thompson, 2002). Publication bias was evaluated using DOI plots, which offer greater sensitivity and specificity than funnel plots (Cheema et al., 2022; Furuya-Kanamori et al., 2018). This method was applied to compounds investigated in at least three studies. The Luis Furuya-Kanamori (LFK) index was employed to assess the risk of publication bias, with values between -1 and $+1$ indicating symmetry, while values above $+2$ or below -2 signifying major asymmetry (Furuya-Kanamori et al., 2018).

2.5. Quality of evidence assessment

Two researchers individually evaluated the strength of evidence for each outcome measured. They categorized the quality of evidence into one of four levels (high, moderate, low, or very low) based on the four criteria from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework: study design, precision, heterogeneity, and directness (Granholt et al., 2019). Factors considered to decrease the quality of evidence included an observational study design, inconsistency of results/heterogeneity, and increased risk of bias, while factors increasing it included plausible confounding/biases.

3. Results

3.1. Study selection

In total, 1664 studies were identified through four electronic databases: PubMed, Web of Science, Scopus, and Cochrane Library. After removing duplicates, 1218 studies were left for screening. Following initial title and abstract screening, 1019 articles were discarded, and 199 studies underwent full-text screening. One hundred thirty-eight studies

were excluded, of which nine assessed the same compounds in the same population, leading to overlaps. Finally, 61 studies were included in the systematic review. The screening flow chart is displayed in Fig. 1.

3.2. Study characteristics

The basic characteristics of the included studies are shown in Table S3. Screened studies deemed eligible for this systematic review were performed from 2001 to 2023, with the highest frequency in 2022 ($n = 9$). Regarding geographical distribution, 25 studies were conducted in Asia, 23 in America (22 in North America and one in South America), nine in Europe, and four in Africa. Forty-one studies were performed in a high-income country, fifteen studies were performed in upper-middle-

income countries, five were performed in lower-middle-income countries, and no study was performed in a low-income country. More studies were performed in the United States ($n = 22$), China ($n = 8$) and Taiwan ($n = 7$). A total of 64851 children/adolescents were included in this systematic review. Study designs included cross-sectional ($n = 26$), case-control ($n = 17$), and cohorts ($n = 18$). EDC parent compounds or their metabolites were investigated in children's urine ($n = 35$), blood ($n = 11$), and toenail ($n = 1$), or in environmental matrices, such as the air ($n = 8$), and dust ($n = 8$). Sixty-one studies focused on the seven EDC groups: five on flame retardants, 17 on phthalates, 15 on PAHs, 13 on heavy metals, seven on bisphenols, one on paraben, and three on triclosan. The number of studies investigating the associations between EDC exposure and asthma onset was 51, while asthma exacerbation was

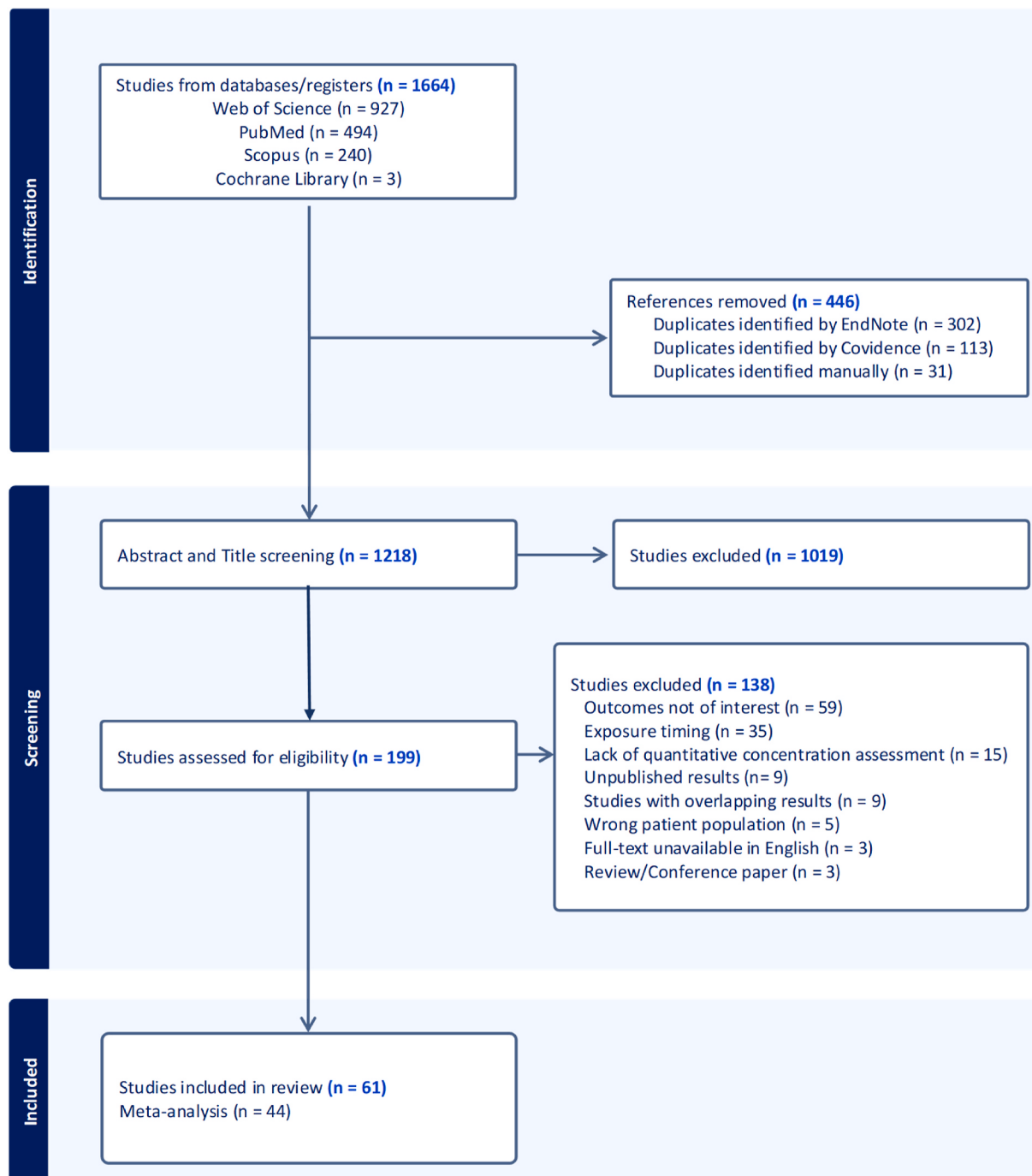


Fig. 1. Flowchart of the study selection procedure.

assessed in 18 studies.

3.3. Risk of bias assessment

In the current review, most studies had a low or unclear risk of bias in the three analyzed domains (Table S3). Regarding the selection domain, 29 studies on establishing the differentiation between respondents' and non-respondents characteristics found an unclear risk of bias. Only four studies had a high risk of potential bias in the abovementioned domain due to sample misrepresentation (Bortey-Sam et al., 2018; Youssef et al., 2018; Mitsui-Iwama et al., 2019; Madrigal et al., 2021), missing information on non-respondents characteristics (Bortey-Sam et al., 2018; Madrigal et al., 2021; Mitsui-Iwama et al., 2019), and unclear definition of controls (hospital or non-description provided) (Youssef et al., 2018). Concerning the comparability domain, most studies had a low risk of bias ($n = 36$), while 17 had an unclear risk and eight had a high risk of bias. The high risk was attributed to the lack of control over the main confounding factor (age in this case) (Wang et al., 2016; Wu et al., 2019; Bertelsen et al., 2013; Gehring et al., 2015; Mitsui-Iwama et al., 2019; Chang et al., 2022; Jung et al., 2014; Jung et al., 2012; Kim et al., 2014; Kim et al., 2015b; Ku et al., 2015; Mener et al., 2015; Meng et al., 2016; Lin et al., 2018; Lin et al., 2022; Navaranjan et al., 2021b), or the presentation of non-adjusted multi-variable analysis (Liu et al., 2019; Kuang et al., 2020; Hosny et al., 2001; Gale et al., 2012; Al-Daghri et al., 2013; Kim et al., 2005; Suresh et al., 2009; Youssef et al., 2018). No study had a high risk of bias in the outcome/exposure domain, while 16 had an unclear risk of bias, of which 14 did not designate the non-response rate or drop-out rate (Suresh et al., 2009; Gehring et al., 2015; Wang et al., 2016; Choi et al., 2017; Franken et al., 2017; Youssef et al., 2018; Liu et al., 2019; Kuang et al., 2020; Nafea et al., 2020; Quirós-Alcalá et al., 2021; Lin et al., 2022; Louis et al., 2023; Hu et al., 2022; Zhu et al., 2022), one had a short follow-up period for outcomes of interest and another one used different methods of outcome ascertainment for cases and controls (Kim et al., 2005).

3.4. Associations between EDC exposure and asthma onset or exacerbation

3.4.1. Associations between exposure to phthalates and asthma onset

Fifteen publications on the relationship between phthalates exposure and asthma onset were enrolled, of which six (Zhu et al., 2022; Sun et al., 2017; Bamai et al., 2014; Bornehag et al., 2004; Hsu et al., 2012; Navaranjan et al., 2021a) assessed compounds in dust and ten (Chang et al., 2022; Lin et al., 2018; Franken et al., 2017; Ku et al., 2015; Bertelsen et al., 2013; Hoppin et al., 2013; Zhao et al., 2022; Lee et al., 2021b; Odebeatu et al., 2019; Hsu et al., 2012) in children's/adolescents' urine. Studied compounds comprised: di(2-ethylhexyl) phthalate (DEHP), benzylbutyl phthalate (BBP), dibutyl phthalate (DBP), diethyl phthalate (DEP), di-isobutylphthalate (DiBP), dinonyl phthalate (DNP) which were analyzed in dust and monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP), mono-isobutyl phthalate (MiBP), mono(2-ethylhexyl) phthalate (MEHP), monocarboxynonyl phthalate (MCNP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), monocarboxyoctyl phthalate (MCOP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), monomethyl phthalate (MMP), and mono (3-carboxy propyl) phthalate (MCPP) and sum DEHP metabolites (MECPP, MEHHP, and MEOHP) in urine.

When testing phthalates concentrations in the dust (Fig. 2), exposure to DEHP was associated with significantly higher odds of asthma onset ($OR = 1.89$; $CI: 1.00, 3.57$; $p = 0.049$), in addition to DiBP ($OR = 1.41$; $CI: 1.08, 1.82$; $p = 0.009$). After computing the pooled effect size, exposure to phthalates was associated with 1.21 times significantly higher odds of asthma onset ($OR = 1.21$; $CI: 1.02, 1.44$; $p = 0.029$). Three phthalates (DBP, DiBP, and DNP) had minimal heterogeneity, while BBP, DEHP, and DEP had a substantial one. As a result, minimal

heterogeneity was noted for the pooled phthalates effect ($I^2 = 29\%$). Publication bias assessment (Fig. S1) showed minor asymmetry for studies evaluating DEP ($LFK = 1.66$) only, while major asymmetry was noted for the other compounds: BBP ($LFK = 3.34$), DEHP ($LFK = 5.64$), DBP ($LFK = 6.56$), DiBP ($LFK = 6.52$) and DNP ($LFK = -2.99$). The quality of evidence of this outcome was judged based on moderate OR (downgraded by one level because of the observational design of the included studies). Excluding any of the studies assessing DEHP, except one (Zhu et al., 2022), led to a loss of significance in the pooled effect. Excluding one study assessing DiBP (Navaranjan et al., 2021a), also led to a loss of significance in the pooled effect, despite an 18.4% increase in the OR. Sensitivity analyses of other compounds maintained non-significance, and no statistically significant differences were noted between the original and new OR in all compounds ($p > 0.05$). Thirteen phthalates or their metabolites were tested in urine (Fig. 3). No significant association was found between metabolite concentrations and asthma onset odds. Non-significant pooled effect was noted ($OR = 1.06$; $CI: 0.97, 1.15$; $p = 0.180$). Minimal heterogeneity was found between studies for MBzP, MEP, MiBP, MEHP, MCP, and MECP; moderate for MBP, MEOHP, and MCOP; and substantial for MCNP, MEHHP, and MMP. In summary, minimal heterogeneity was found between the studied metabolites ($I^2 = 0\%$). Publication bias assessment (Fig. S2) showed no asymmetry for studies assessing MBP ($LFK = -0.78$), MEP ($LFK = -0.13$), MEHP ($LFK = 0.92$), $\sum$ DEHP ($LFK = -0.40$), MEOHP ($LFK = -0.97$), MEHHP ($LFK = -0.76$) and MCOP ($LFK = -0.30$). Minor asymmetry was reported in studies investigating MBzP ($LFK = 1.04$), MCP ($LFK = -1.13$), and MCNP ($LFK = -1.86$), while major asymmetry was noted in two compounds: MiBP ($LFK = -2.49$) and MECP ($LFK = -2.73$). The strength of the evidence was low, primarily due to the observational nature and the heightened heterogeneity observed in the studies, resulting in a two-level downgrade. Weighted GM was assessed in two studies through different matrices: dust (Bornehag et al., 2004), and urine (Chang et al., 2022); Therefore were not included in the meta-analysis. Excluding any of the studies had no notable impact on the pooled effect for any of the compounds, with no statistically significant differences between original and post-sensitivity analysis ORs ($p > 0.05$).

3.4.2. Associations between exposure to phthalates and asthma exacerbation

Three studies (Babadi et al., 2022; Fandiño-Del-Rio et al., 2022; Lee et al., 2021b) examining the association between phthalates and asthma exacerbation were included in the analysis. The metabolites considered in these studies included MBzP, MCNP, MCOP, MCP, MECP, MEHHP, MEHP, MEOHP, MEP, MiBP, MBP, the sum of DEHP metabolites, all assessed through urine samples. Among asthmatic children, higher concentrations of MCOP ($OR = 1.32$; $CI: 1.11, 1.57$; $p = 0.001$), MECP ($OR = 1.30$; $CI: 1.07, 1.57$; $p = 0.007$), MEHHP ($OR = 1.24$; $CI: 1.02, 1.51$; $p = 0.031$), MEOHP ($OR = 1.30$; $CI: 1.09, 1.55$; $p = 0.003$), and sum DEHP metabolites (MECP, MEHHP, and MEOHP) ($OR = 1.34$; $CI: 1.10, 1.62$; $p = 0.003$) were associated with significantly higher odds of asthma exacerbation (Fig. 4). Due to insufficient available evidence, the pooled effect size was not computed. Minimal/insignificant heterogeneity was observed for the different metabolites, except for MBzP, MEHP, MEP, and MiBP (moderate). Publication bias assessment (Fig. S3) showed no asymmetry for studies assessing MBP ($LFK = -0.50$), MBzP ($LFK = -0.90$), MCOP ($LFK = 0.93$), MCP ($LFK = 0.27$), MEHHP ($LFK = 0.01$) and $\sum$ DEHP ($LFK = -0.51$). Minor asymmetry was reported in studies investigating the three remaining compounds: MCNP ($LFK = 1.13$), MECP ($LFK = 1.42$), and MEOHP ($LFK = -1.36$). The strength of the evidence was judged as low because of the observational nature of the studies and insufficient supporting evidence (most metabolites were only assessed in two studies). Sensitivity analyses showed that excluding one study (Babadi et al., 2022) for MCOP, another (Fandiño-Del-Rio et al., 2022) for MECP, and one of the two studies (Fandiño-Del-Rio et al., 2022; Lee et al., 2021b) for MEHHP and

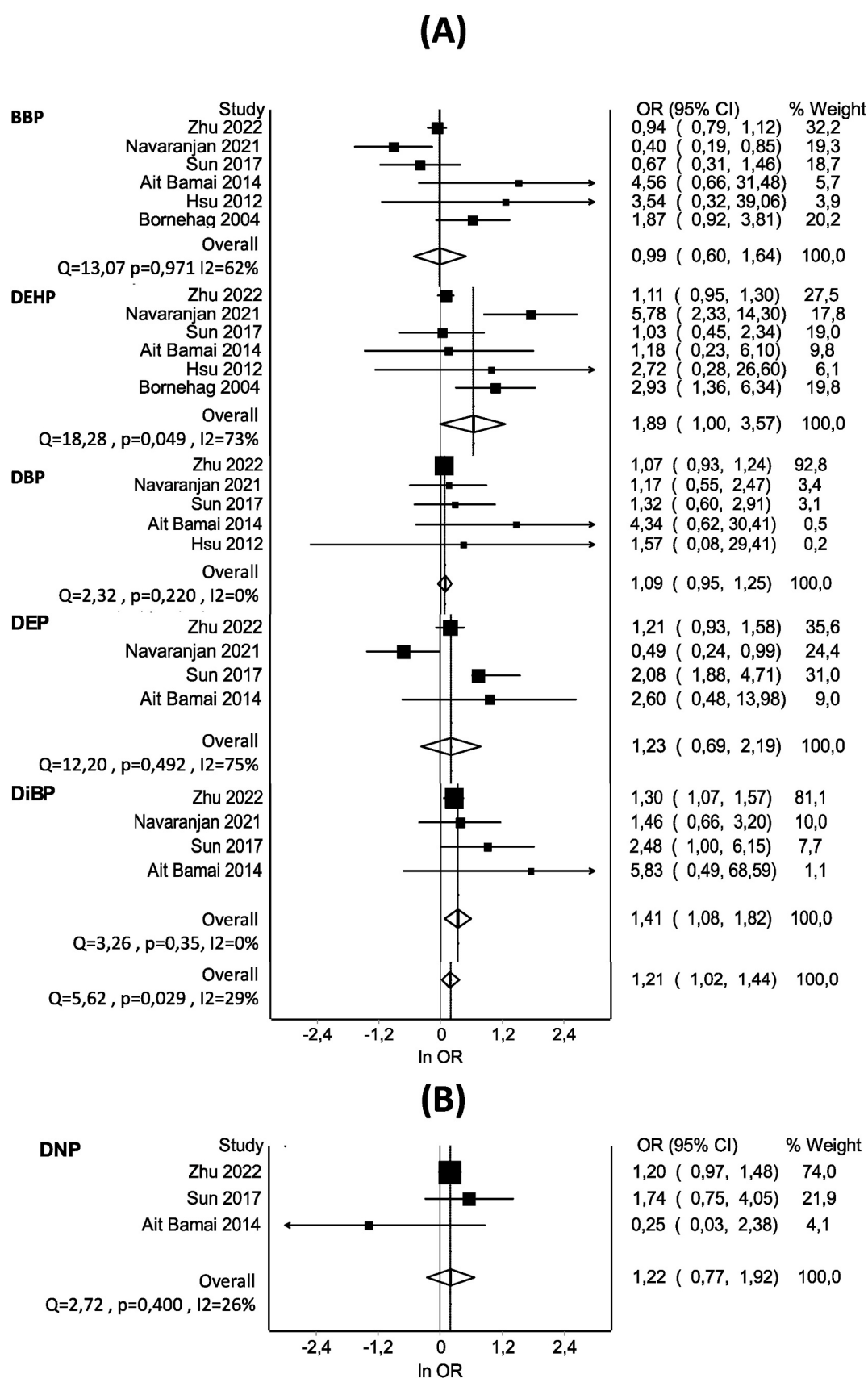


Fig. 2. Association between exposure to phthalates assessed in dust ((A) compounds used for pooled effect calculation and (B) compounds assessed in less than four studies) and asthma onset in school-age children and adolescents. OR: Odds Ratio; Q: Cochran' Q; p: p-value; I2: Higgins' I-squared index.

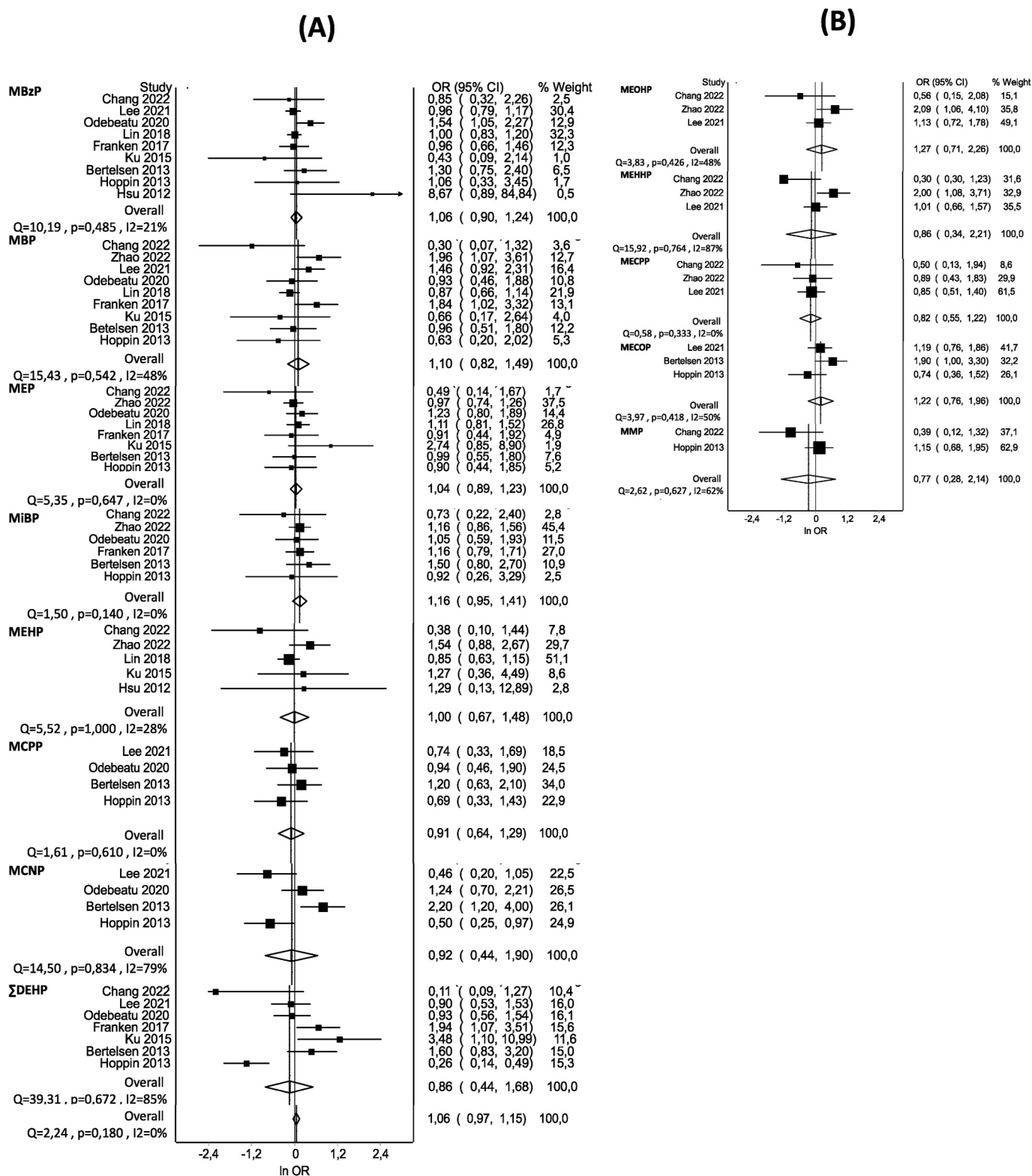


Fig. 3. Association between exposure to phthalates assessed in urine ((A) compounds used for pooled effect calculation and (B) compounds assessed in less than four studies) and asthma onset in school-age children and adolescents. OR: Odds Ratio; Q: Cochran' Q; p: p-value; I²: Higgins' I-squared index.

MEOHP, resulted in a loss in significance in the pooled effect with no statistically significant changes ($p > 0.05$).

3.4.3. Association between exposure to polycyclic aromatic hydrocarbons and asthma onset or exacerbation

Twelve studies investigated the association between PAH exposure

and asthma onset. Among these, two (Hu et al., 2022; Uong et al., 2023) evaluated the urinary concentrations of 1-hydroxypyrene and another two (Paciência et al., 2019; Liu et al., 2019) assessed the concentrations of formaldehyde and the remaining (Han et al., 2018; Paciência et al., 2019; Liu et al., 2016; Al-Daghri et al., 2013; Choi et al., 2017; Jung et al., 2014; Kim et al., 2005; Kuang et al., 2020) assessed other PAHs'

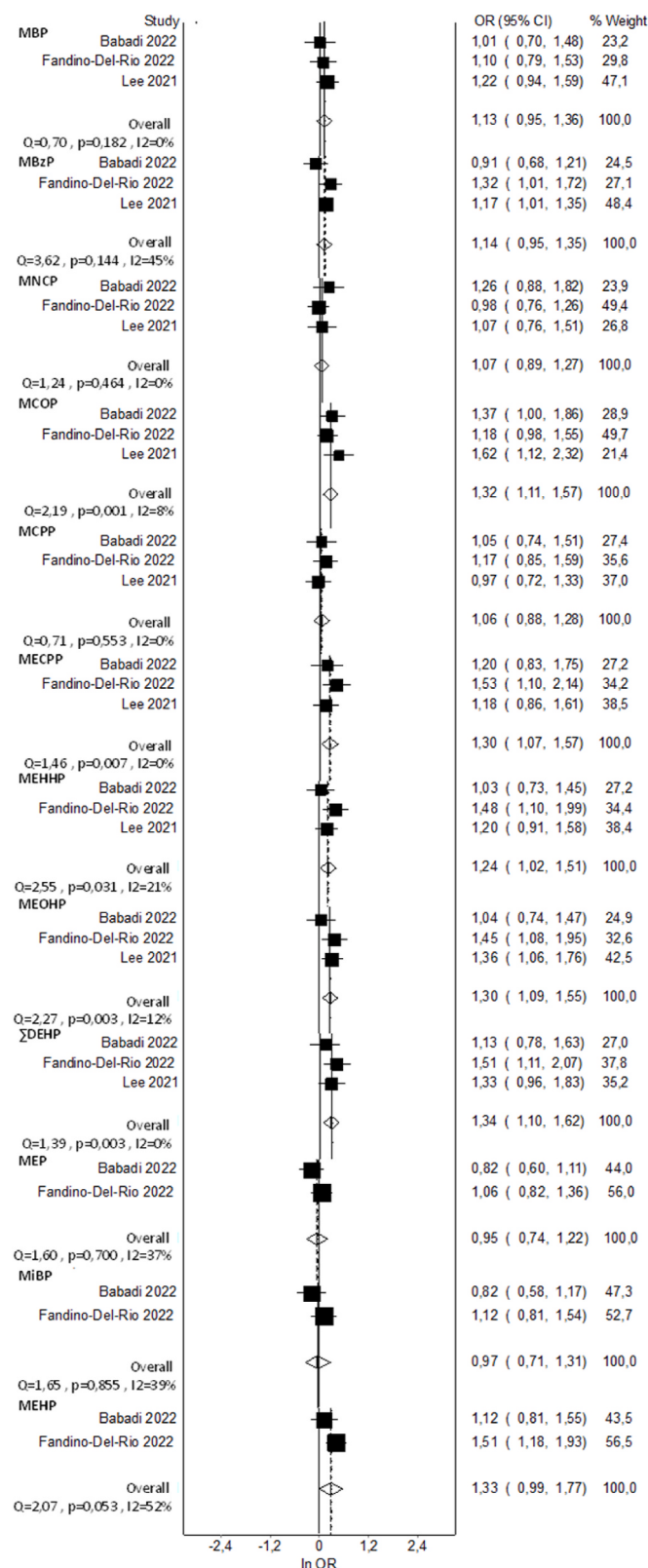


Fig. 4. Association between exposure to phthalates and asthma exacerbation in school-age children and adolescents. OR: Odds Ratio; Q: Cochran's Q; p: p-value; I²: Higgins' I-squared index.

individual compounds. When testing PAHs in urine (Fig. 5), higher hydroxypyrene concentrations were associated with 2.15 times higher odds of asthma onset with no statistically significant differences between asthmatics and non-asthmatics (OR = 2.15; CI:0.35, 12.98; $p = 0.413$). Substantial heterogeneity was noted ($I^2 = 73\%$), and the strength of the evidence was determined to be low, primarily due to the observational nature of the studies and the high level of observed heterogeneity. No statistically significant differences were observed regarding airborne formaldehyde levels (OR = 1.52; CI:0.57, 4.06; $p = 0.410$), with substantial heterogeneity ($I^2 = 84\%$). The strength of evidence was considered low, mainly due to the observational nature of the studies and the insufficient supporting evidence. Three studies were not evaluated since they investigated either distinctive compounds (Han et al., 2018; Liu et al., 2016) or sampling matrix (Paciência et al., 2019). Effects of exposure to five PAHs were assessed using GM (Fig. S4) in two studies (Al-Daghri et al., 2013; Suresh et al., 2009), and showed a positive association between higher concentrations of fluoranthene, naphthalene, and pyrene with asthma onset with minimal heterogeneity between studies ($I^2 = 0\%$). Five studies (Paciência et al., 2019; Uong et al., 2023; Cilluffo et al., 2022; Gale et al., 2012; Jung et al., 2012) explored the association between PAH exposure and asthma exacerbation by assessing different compounds in different matrices: urine (Cilluffo et al., 2022; Uong et al., 2023) and air (Gale et al., 2012; Jung et al., 2012; Paciência et al., 2019), and none of the compounds were assessed in at least two studies and, therefore, were not included in the meta-analysis.

3.4.4. Association between exposure to flame retardants and asthma onset or exacerbation

Five studies investigated the association between exposure to flame retardants and asthma onset (Araki et al., 2014; Meng et al., 2016; Navaranjan et al., 2021a; Aimuzi et al., 2023). The compounds considered in the analysis were tris(2-chloroethyl)phosphate (TCEP); tris(1-chloro-2-propyl)phosphate (TCIPP); tri(n-butyl)phosphate (TnBP); tris(2-butoxyethyl)phosphate (TBOEP); and triphenyl phosphate (TPhP). Two studies (Araki et al., 2014; Navaranjan et al., 2021a) evaluated flame retardants in dust, while two (Aimuzi et al., 2023; Louis et al., 2023) focused on metabolites in urine, and only one (Meng et al., 2016) assessed flame retardants in blood. When testing for flame retardants in dust (Fig. 6), no significant differences were observed between asthmatic children and the control group for TCEP, TCIPP, TnBP, and TPhP. Nevertheless, higher concentrations of TBOEP were associated with 2.61 times significantly higher odds of asthma onset (OR = 2.61; CI:1.08, 6.30; $p = 0.032$). The pooled effect was not computed due to insufficient evidence. Insignificant heterogeneity between studies was noted for TCEP, TCIPP, and TPhP; a moderate heterogeneity for TBOEP ($I^2 = 55\%$) and substantial for TnBP ($I^2 = 86\%$). Moderate strength of evidence was considered and downgraded due to the observational nature of the studies. The analysis of the association between asthma exacerbation and exposure to flame retardants was limited to two studies (Meng et al., 2016; Louis et al., 2023) analyzing distinct compounds in different matrices, and therefore, were not included in the meta-analysis.

3.4.5. Association between exposure to bisphenols and asthma onset or exacerbation

Bisphenol A (BPA) and bisphenol S (BPS) were investigated in urine samples in five (Donohue et al., 2013; Kim et al., 2014; Mendy et al., 2020; Wang et al., 2016; Youssef et al., 2018) and two studies (Mendy et al., 2020; Kiouk et al., 2021), respectively. The exposure to higher concentrations of both compounds (Fig. 7 (A)) was associated with significantly higher odds of asthma onset among children: BPA (OR = 1.57; CI:1.02, 2.40; $p = 0.038$) and BPS (OR = 1.40; CI:1.13, 1.73; $p = 0.002$). Given that only BPA was assessed in more than four studies, the pooled effect size reflected BPA findings. Substantial heterogeneity was observed for BPA ($I^2 = 65\%$), and minimal heterogeneity was found for

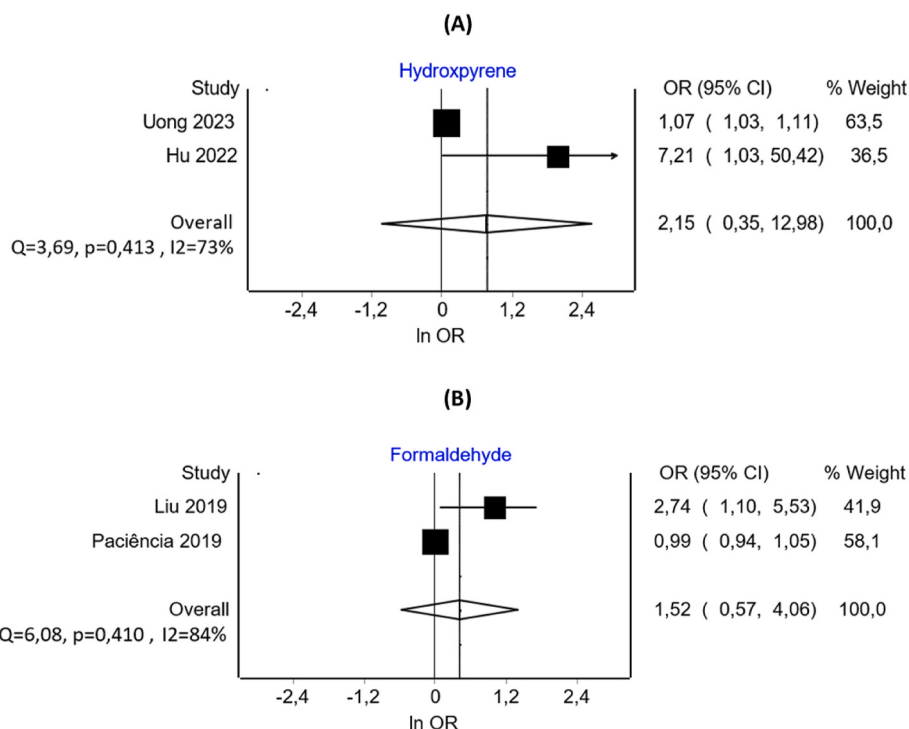


Fig. 5. Association between exposure to polycyclic aromatic hydrocarbons (hydroxypyrene in urine and formaldehyde in air samples) and asthma onset in school-age children and adolescents. OR: Odds Ratio; Q: Cochran' Q; p: p-value; I²: Higgins' I-squared index.

BPS (I² = 0%). Publication bias assessment (Fig. S5) showed major asymmetry for studies assessing BPA (LFK = 2.31). The strength of the evidence was judged as low due to the observational nature of the studies and the significant heterogeneity detected for BPA. Two studies (Mendy et al., 2020; Youssef et al., 2018) tested associations of BPA concentrations using GM (Fig. S4). When computing the pooled effect, a significantly positive relationship was found with asthma onset (Weighted Mean Difference (WMD) = 0.03 CI: 0.02, 0.04). Although non-significant changes were noted between ORs before and after sensitivity analyses ($p > 0.05$), excluding one of three studies assessing BPA (Wang et al., 2016; Kim et al., 2014; Donohue et al., 2013), led to a loss of statistical significance in the pooled effect. Only one study (Quirós-Alcalá et al., 2021) associated bisphenol exposure with asthma exacerbation and, therefore, was not included in the meta-analysis.

3.4.6. Association between exposure to triclosan and asthma onset or exacerbation

Three studies have examined the association between triclosan exposure, which was evaluated in urine, and asthma onset (Spanier et al., 2014; Mitsui-Iwama et al., 2019; Lin et al., 2022). When calculating the pooled effect (Fig. 7 (B)), there was no significant association between triclosan concentrations and asthma odds (OR = 1.36; CI: 0.79, 2.33; $p = 0.268$). A moderate level of heterogeneity was observed among the studies (I² = 35%). Publication bias assessment (Fig. S5) showed no asymmetry in studies' effect sizes (LFK = -0.58). The strength of evidence was judged as low for triclosan due to the observational nature of the studies and the level of overall heterogeneity. Sensitivity analyses preserved the non-significance of the associations ($p > 0.05$). No studies evaluated the association between triclosan concentration and asthma exacerbation.

3.4.7. Association between exposure to paraben and asthma onset or exacerbation

Only one study (Quirós-Alcalá et al., 2019) analyzed paraben and associated exposure to asthma onset and, therefore, was not included in the meta-analysis. Parabens, examined in urine, included butylparaben

(But-paraben), ethylparaben (Eth-paraben), methylparaben (Met-paraben) and propylparaben (Prop-paraben). The same study (Quirós-Alcalá et al., 2019) associated the exposure to paraben in urine samples and asthma exacerbation (same metabolites), and therefore, was not included in the meta-analysis.

3.4.8. Association between exposure to metals and asthma onset

Two studies (Gehring et al., 2015; Rosa et al., 2016) investigated the association between metal exposure from airborne/dust particulate matter, namely Iron (Fe), Nickel (Ni), Zinc (Zn), and asthma onset (Fig. 8 (A)). Higher concentrations of Ni (OR = 1.10; CI: 1.03, 1.18; $p = 0.006$) and Zn (OR = 1.13; CI: 1.11, 1.15; $p < 0.001$) were associated with significantly higher odds of asthma onset. The heterogeneity between the studies was minimal for all the metals analyzed (I² < 30%). Due to the observational nature of the studies and insufficient evidence available, the strength of the evidence was considered low.

Ten studies also investigated the association between asthma onset and exposure to metals assessed in biological matrices, of which eight were included in the meta-analysis (Fig. 6 (A)). Three studied mercury (Hg) in blood (Heinrich et al., 2017; Kim et al., 2015a; Wu et al., 2019), four assessed lead (Pb) in blood (Mener and Lin, 2015; Wang et al., 2017; Zeng et al., 2016; Wu et al., 2019), and two evaluated arsenic (As) in urine (Bortey-Sam et al., 2018; Muñoz et al., 2022). Significant differences were only detected for As, where higher urinary concentrations were associated with 2.08 times higher odds of asthma onset (OR = 2.08; CI: 1.33, 3.26; $p = 0.001$). The heterogeneity between the studies for the metals Hg and Pb was substantial (I² > 60%) and minimal (I² = 0%) for As. Publication bias assessment (Fig. S6) showed minor asymmetry for Hg (LFK = 1.76) and major asymmetry for Pb (LFK = 7.50). The strength of evidence was judged as low for all heavy metals due to the observational nature of the studies, additionally downgraded for As due to insufficient supporting evidence, and for Pb and Zn due to the substantial heterogeneity observed. Two studies were not included since they associated distinct metals (Cadmium, Cd (Hossny et al., 2001) and Aluminium, Al (Nafea et al., 2020) in the blood) using GM. Sensitivity analyses preserved non-significance in the pooled effect for Hg and Pb,

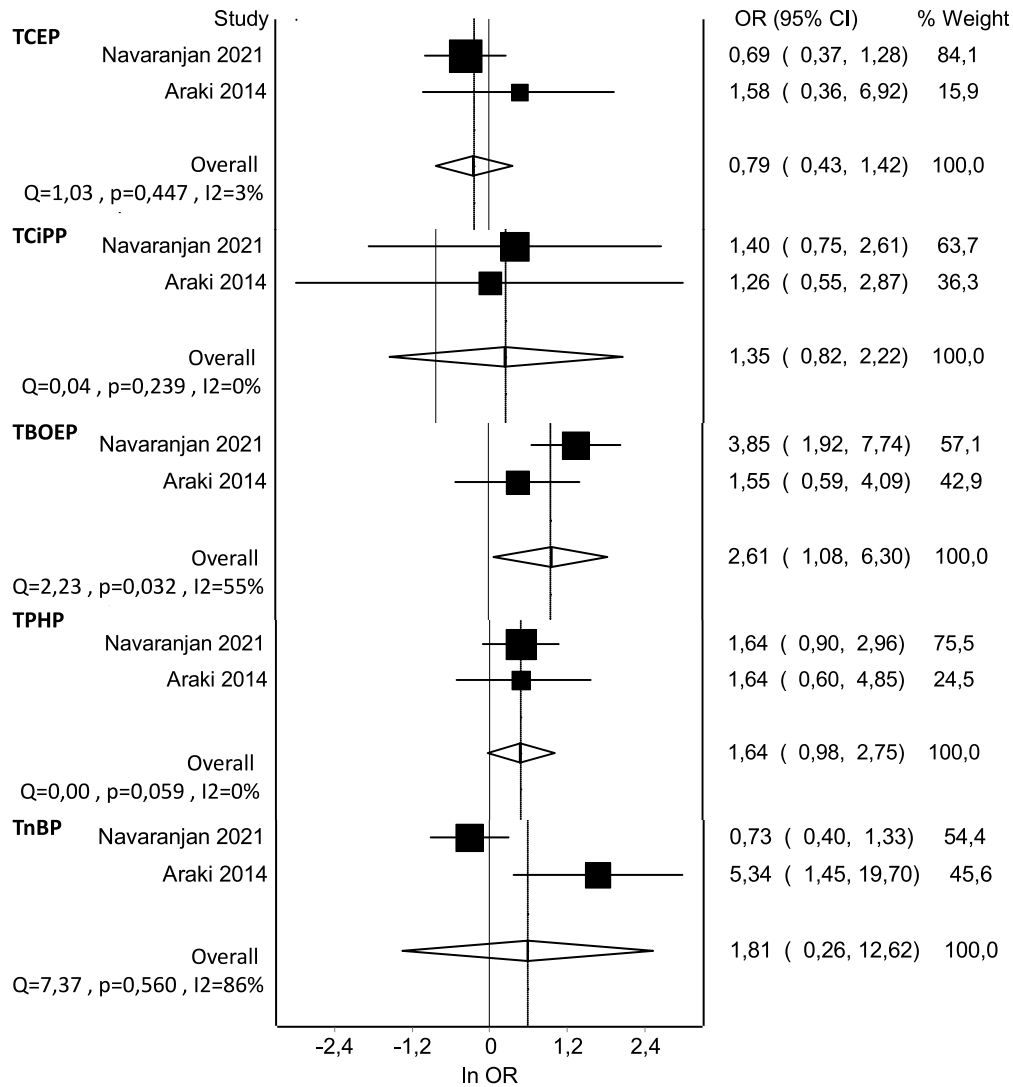


Fig. 6. Association between exposure to flame retardants in dust and asthma onset in school-age children and adolescents. OR: Odds Ratio; Q: Cochran' Q; p: p-value; I2: Higgins' I-squared index.

with no statistically significant changes in the ORs ($p > 0.05$).

3.4.9. Association between exposure to metals and asthma exacerbation

The association between exposure to metals and asthma exacerbation among school-age children/adolescents is presented in Fig. 8 (B). The correlation between Hg concentrations in blood and asthma exacerbation was assessed in two studies (Kim et al., 2015a; Wu et al., 2019), but showed no statistically significant differences. A substantial heterogeneity level was observed between these studies ($I^2 = 73\%$). The strength of evidence was judged as very low, primarily due to the observational nature of the studies, the substantial level of observed heterogeneity, and the lack of supporting evidence. The association between metals found in air samples and asthma exacerbation was assessed in two studies (Gehring et al., 2015; Rosa et al., 2016) for iron (Fe), Ni, and Zn. Higher concentrations of Ni (OR = 1.08; CI:1.01, 1.16; $p = 0.029$) and Zn (OR = 1.09; CI:1.01, 1.17; $p = 0.021$) were significantly associated with higher odds of asthma exacerbation. Minimal heterogeneity was noted for Ni and Zn ($I^2 = 0\%$) and substantial for Fe ($I^2 = 66\%$). The strength of evidence was judged as low for Fe, Ni, and Zn, primarily because of the observational nature of the studies. An additional downgrade for Fe was due to the moderate level of heterogeneity, while for Ni and Zn, it was due to the insufficiency of supporting evidence. A single study evaluated EDC exposure in toenails (Madrigal

et al., 2021) and one AI in the blood (Nafea et al., 2020); therefore, were not employed in the analysis.

4. Discussion

4.1. Summary of the main findings

Previous epidemiological studies suggest that exposure to EDCs may result in disrupted respiratory function (Franken et al., 2017; Nafea et al., 2020; Spanier et al., 2014; Donohue et al., 2013; Rosa et al., 2016), but no comprehensive and quantitative investigations have been carried out to analyze the associations between the various EDC groups and the occurrence and/or exacerbation of asthma. The present systematic review and meta-analysis reviewed 61 studies assessing school-age children's and adolescents' exposure to 7 EDC groups. Most findings from the different EDC groups showed moderate or low-quality evidence, downgraded due to the studies' observational nature or their high heterogeneity level. Major asymmetry was noted in the doi plots in the findings from five phthalate compounds assessed in the dust (83.3%), two urinary phthalate compounds (15.4%), urinary BPA and Pb assessed in the blood. Our findings suggested that exposure to phthalates tested in dust was positively associated with higher odds of asthma onset, while no statistically significant differences were noted

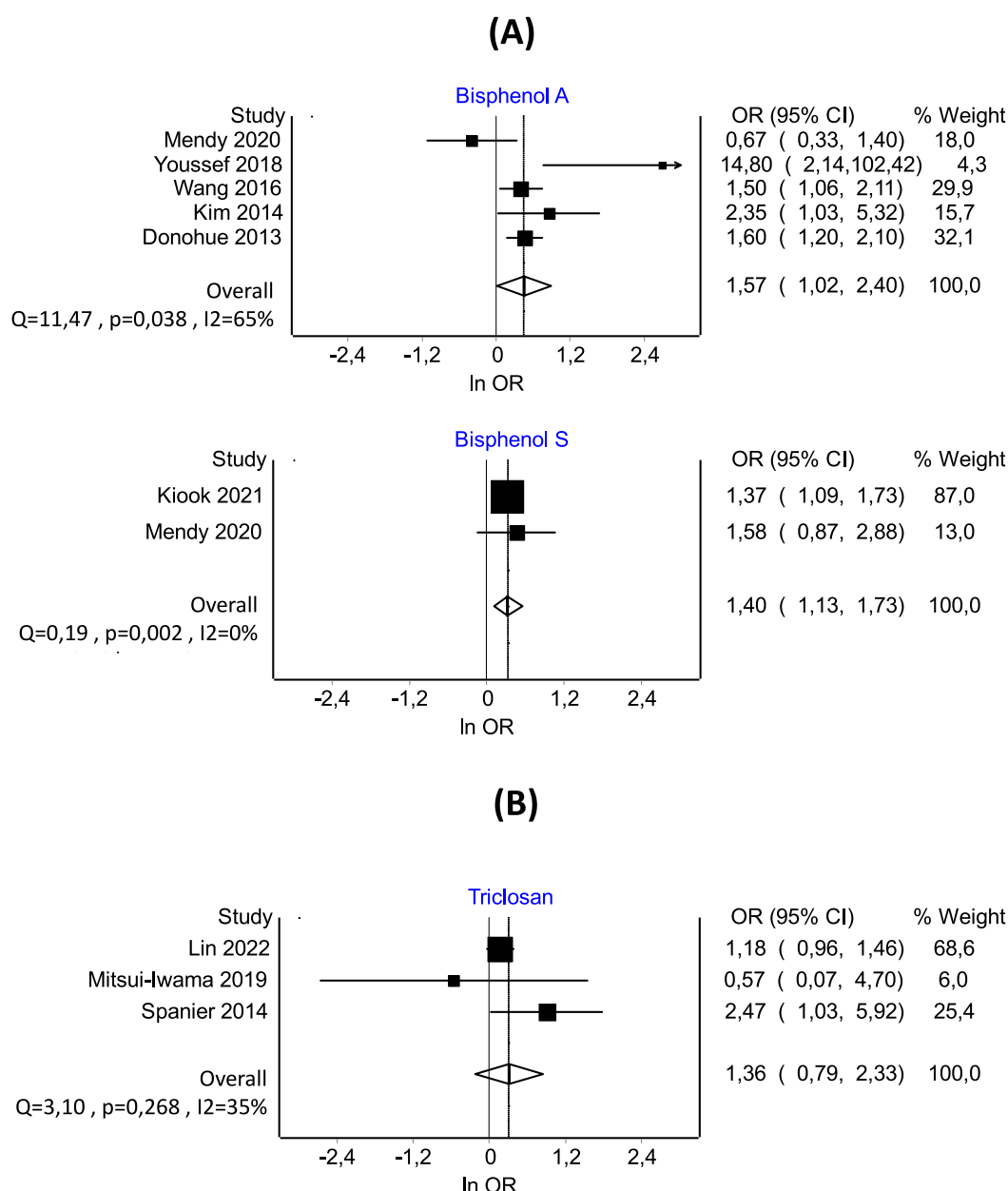


Fig. 7. Association between exposure to (A) bisphenols (A and S) and (B) triclosan and asthma onset in school-age children and adolescents. OR: Odds Ratio; Q: Cochran' Q; p: p-value; I2: Higgins' I-squared index.

when tested in urine. When evaluating phthalates exposure, subgroup analyses found that two compounds' concentrations in dust (DEHP and DiBP) were positively correlated with higher odds of asthma onset, while none of the metabolites studied in urine showed statistically significant differences. Higher urinary concentrations of DNP metabolites (MCOP) and DEHP metabolites (MECPP, MEHHP, MEOHP, and Σ DEHP) were associated with greater odds of asthma exacerbation. No significant association was found between exposure to PAH compounds (tested in air or urine) or triclosan and asthma onset. Among flame retardants, only TBOEP showed a significant association with asthma onset odds. Nonetheless, significantly higher asthma onset odds were associated with urinary bisphenol concentrations (both bisphenol A and S). Higher Ni and Zn concentrations in particulate matter and As in urine were significantly associated with higher odds of asthma onset. When investigating this impact solely among asthmatic children/adolescents, Ni and Zn concentrations were also substantially higher among those with disease exacerbation. The pooled effect size was only computed for

phthalates due to insufficient studies, suggesting the need for further studies for other EDC groups to validate their overall impact on asthma onset or exacerbation in children and adolescents.

4.2. Discussion of the review results

Studies included in this systematic review and meta-analysis provide a broad overview of research on EDC exposure and asthma onset and exacerbation in children and adolescents. Yet, the geographical and socioeconomic representation is skewed, which may limit the global applicability of the findings. Of the 61 studies reviewed, the majority were conducted in high-income countries and none in low-income countries. This imbalance may create data gaps from regions with specific environmental exposures, healthcare infrastructures (Peters et al., 2008), and asthma risk factors (Soto-Martínez et al., 2020). Children in low-income countries may experience different environmental triggers (Ogunsola and Mehtar, 2020) and face barriers to diagnosis and

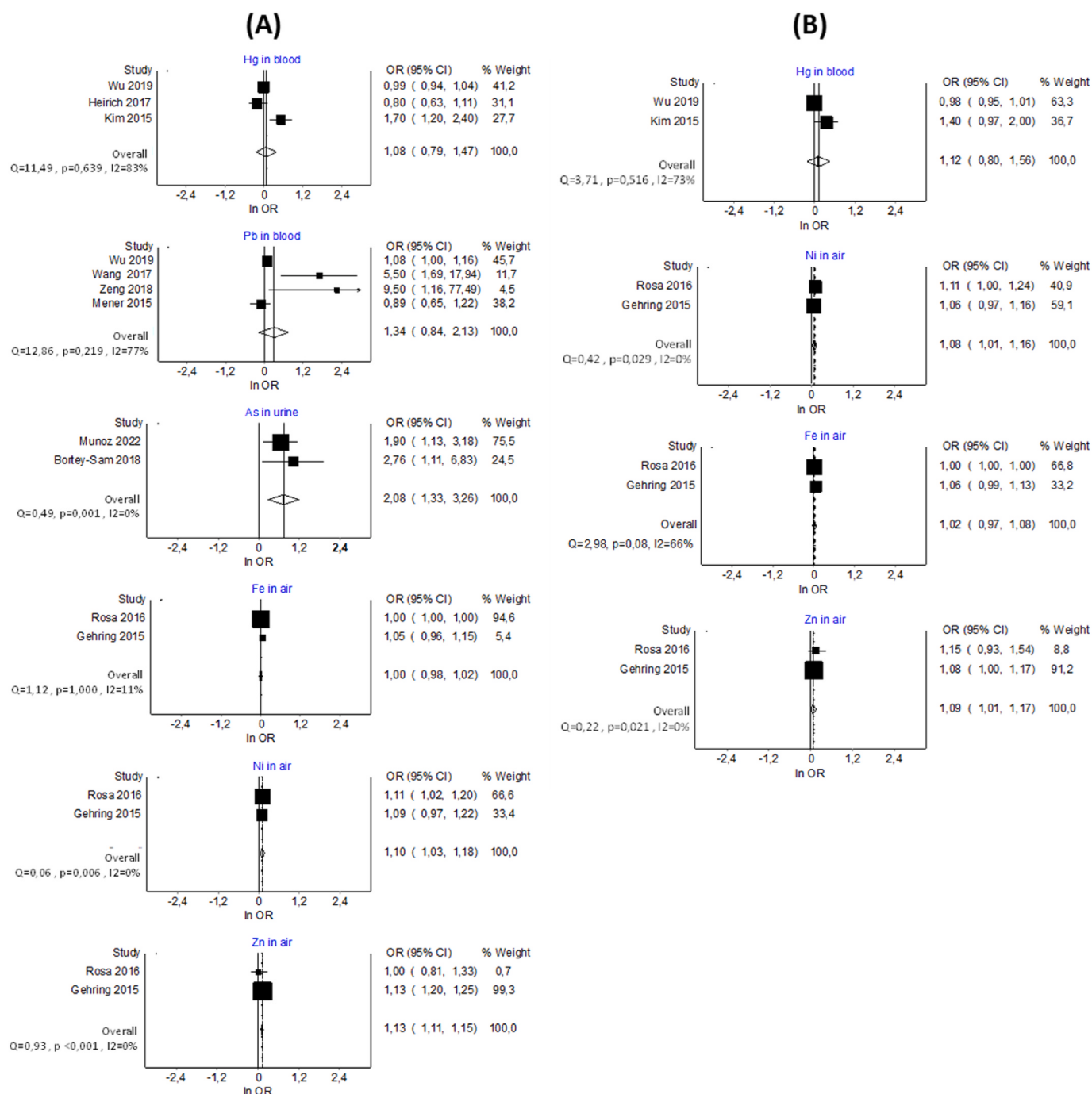


Fig. 8. Association between exposure to metals and (A) asthma onset or (B) asthma exacerbation in school-age children and adolescents. OR: Odds Ratio; Q: Cochran' Q; p: p-value; I2: Higgins' I-squared index.

treatment (Peters et al., 2008) that are not captured in studies from wealthier nations. Most studies employed cross-sectional study design, which, while valuable, has limitations in capturing the longitudinal impacts of environmental exposures on asthma onset and exacerbation, potentially limiting the ability to draw definitive conclusions about causality. Although most studies had a low risk of bias in the different domains, many compounds showed major asymmetry of findings, suggesting potential publication bias. Expanding research to include low-income countries, as well as unpublished and negative results, can provide a more comprehensive understanding of the global contribution of EDCs to the asthma burden and ensure more equitable health outcomes.

One key lesson from this review process is the complexity and

variability in accurately measuring EDC exposures in children, particularly with asthma onset and exacerbation. Traditional exposure assessments often rely on biomonitoring data, but these can only provide snapshots of exposure concentrations, failing to capture the chronic, low-dose, and cumulative nature of EDC exposure, which is critical in understanding long-term health outcomes. Future research should prioritize longitudinal exposure measurements to define critical windows of susceptibility beyond early childhood. Additionally, differentiating between exposures contributing to the onset versus those exacerbating pre-existing conditions requires more refined methodologies, including integrating personal exposure data with environmental monitoring.

4.2.1. Phthalates exposure and asthma onset and exacerbation

Phthalates are plasticizers that enhance the flexibility and reduce the brittleness of plastic materials. They are commonly encountered in contaminated food, building materials, cosmetics, and personal care products (Franken et al., 2017). The release of phthalates from pharmaceuticals and medical plastic delivery devices might also contribute to phthalates exposure, though it is believed that their impact on overall exposure is minimal (Fandiño-Del-Rio et al., 2022). Higher phthalate exposure was reported to be associated with dysregulated respiratory function (Lee et al., 2021b) and higher biomarkers of inflammation (Babadi et al., 2022), possibly burdening the exhalation of such chemicals, which may exacerbate existing health conditions. A previous systematic review of observational studies found that prenatal exposure to DEHP and BBP was strongly associated with childhood asthma onset (Li et al., 2017). The present study found positive associations between total phthalates in dust and asthma onset. Research suggested a possible modulatory effect of such exposure on the peroxisome proliferation-activated receptors, a mechanism that can explain this finding involving a partial antagonist effect or cross-talk with other signaling pathways (Bølling et al., 2013). Findings reported that DEHP in dust was also significantly associated with asthma onset, in addition to DiBP, with no direct relationship with BBP concentrations. Research performed in rats reported lung alveolar development inhibition after exposure to DEHP (Camacho et al., 2020) and increased lung interstitial tissue proportion, leading to alteration of gene expression due to decreased gas-exchange space (Liang et al., 2018), which may possibly explain this association. Previous research on children reported a significant association between BBP concentrations and atopic dermatitis, with no impact on bronchial asthma (Bamai et al., 2014). This may suggest that pregnancy is the most relevant window of susceptibility for exposure to BBP since its primary urinary metabolite (MBzP), which was tested in children/adolescents, had no significant correlation with asthma onset. While DiBP metabolites are typically excreted within 24 h, research indicates the potential for storage in lipid or dermal depots prior to gradual release into the bloodstream (Lorber and Koch, 2013). This process may vary among subgroups due to enzymatic variations and medication interactions (Anderson, 2002).

Considering the pooled effect of phthalates exposure, significant associations were noticed in the dust compared to urine, possibly due to the increased stability of EDC concentrations within the dust, while interindividual disparities or variations in the timing of urine collection might influence their detected concentrations in urine. The above-mentioned finding was also noted for asthma exacerbation, where despite the higher urinary concentrations of MBzP among children/adolescents with increased disease severity, no significant differences were noted between the subgroups. These discrepancies could be related to the formation of a binary complex by MBzP and human serum albumin (Li et al., 2021), discommoding its detection in urine, which cannot rule out its possible correlation with asthma onset and exacerbation. Nonetheless, significantly higher concentrations of DEHP metabolites, MECP, MEHP, and MEOHP, individually or summed, in addition to higher MCOP concentrations, were associated with asthma exacerbation. Considering that these metabolites are biomarkers of parent compounds (DEHP and DNP in this case), these results emphasize the need for additional biomonitoring and pharmacokinetic studies analyzing phthalates exposure to dust and asthma exacerbation. A recent systematic review reported a significant association between MCOP concentrations and metabolic syndrome, a condition marked by heightened oxidative stress, obesity, and dysregulated adipokines, all of which can impact asthma control (Mérída et al., 2023).

4.2.2. Polycyclic aromatic hydrocarbons exposure and asthma onset

PAHs are environmental pollutants primarily originating from the burning of fossil fuels in activities such as heat and power generation, waste incineration, coke ovens, and the operation of motor vehicles (Jung et al., 2014; Cilluffo et al., 2022). Despite the notably elevated

concentrations of urinary hydroxypyrene in asthmatic children/adolescents in both studies (Uong et al., 2023; Hu et al., 2022), no statistically significant differences were noted, highlighting the need for more research and directing attention to other PAH metabolites, namely since research in adults showed a significant association with asthma onset odds without affecting the expression of plasma cytokines (Huang et al., 2018). Moreover, further research is crucial due to the ability of PAH metabolites to enhance the severity of allergic lung inflammation in mice by modulating dendritic cells' function (Wong et al., 2018).

4.2.3. Flame retardant exposure and asthma onset

Flame retardants and plasticizers are used in various applications, such as upholstered furniture, electronics, building insulation, and plastic products (Navaranjan et al., 2021b; Araki et al., 2014). Although early life exposure to these compounds was associated with greater asthma onset risk (Navaranjan et al., 2021b), school-age exposure showed no significant correlation with asthma onset, except TBOEP. As most immune-regulated respiratory diseases generally manifest in early childhood, studies conducted among school-aged children or adolescents involving dust collection and metabolite measurement cannot be used to infer causality (Morawska and Salthammer, 2006; Salthammer et al., 2018) or assess the risk of allergy development (Salthammer et al., 2018). Moreover, while the exact mechanism by which TBOEP can contribute to asthma development is not fully understood, the current findings suggest minimizing exposure levels and the need for additional research to validate its impact on asthma-related outcomes.

4.2.4. Bisphenols exposure and asthma onset

Bisphenols are used to manufacture epoxy resins and polycarbonate plastics in toys, food and beverage containers, and personal care products (Donohue et al., 2013). This systematic review found substantially higher urinary concentrations of BPA and BPS among asthmatic children/adolescents. The pro-inflammatory effect of BPA through Toll-like receptor 4 stimulation (Karunarathne et al., 2021) was reported to be associated with an elevated likelihood of developing respiratory conditions such as wheezing and asthma development (Quirós-Alcalá et al., 2021), which might explain this result.

4.2.5. Triclosan and paraben exposure and asthma onset

Triclosan and paraben are synthetic antimicrobial agents used in several household goods such as soaps, detergents, and toothpaste and added as preservatives to some foods and pharmaceuticals (Mitsui-Iwama et al., 2019; Spanier et al., 2014). Despite the evidence of aggravation of asthma airway responses with triclosan in mice (Hirota et al., 2019), while it significantly impacted aeroallergen and food sensitization in children (Spanier et al., 2014), no significant associations with asthma onset were found in this study. Only one study assessed paraben, showing no significant association with asthma onset, although research showed increased emergency department visits among asthmatics following paraben exposure (Quirós-Alcalá et al., 2019). Nevertheless, these findings are inconclusive since changes in the microbiome and acquired antibiotic resistance could have mediated these correlations (Zhang and Lu, 2023).

4.2.6. Metal exposure and asthma onset and exacerbation

When assessing metals from air samples, significantly increased odds of asthma onset and disease exacerbation were associated with higher concentrations of Ni and Zn. Ni was also associated with asthma onset in the literature (Rosa et al., 2016), while significantly lower serum concentrations were detected among asthmatics (Al-Fartusie et al., 2021). Since pulmonary absorption is the major route of exposure, greater respiratory toxicity could be expected (Lee et al., 2021a), which can explain this finding. Similarly, high concentrations of airborne Zn, in opposition to serum (Al-Fartusie et al., 2021), were associated with higher asthma onset and exacerbation odds, possibly attributed to the role of Zn in the synthesis of antioxidants produced during

pro-inflammatory responses. Asthmatic children had significantly higher urinary As concentrations (Muñoz et al., 2022; Bortey-Sam et al., 2018), likely related to the fact that As exerts an immunomodulatory effect (Haque et al., 2017), resulting in the release of histamine, prostaglandins, and leukotrienes, which might have induced asthma symptoms in children (Arora and Ansari, 2019).

4.3. Strengths, limitations, and potential bias

This systematic review presents strengths. A comprehensive search across four prominent databases was conducted to identify eligible articles. To ensure the reliability of the present systematic review, two authors independently carried out all stages of the review process, and any discrepancies or disagreements were effectively resolved through discussion. As a result, the likelihood of introduced bias was minimal. Nevertheless, this systematic review also possesses certain limitations. The classification of EDC exposure groups (e.g., quartile increase, Q4 vs. Q1, log unit increase) is limited to the EDC concentrations in the included studies, as detailed in Table S2. Consequently, extending the associations observed in our study may be challenging in encompassing a broader spectrum of concentration ranges or ensuring comparability. Furthermore, only one group of EDC was evaluated among the study participants. In real-world situations, individuals are often exposed to multiple EDCs and other pollutants concurrently, making it challenging to isolate the effects of individual EDCs. Given that various EDCs can share common biological mechanisms that may contribute to asthma onset and exacerbation, such as immune system modulation, oxidative stress, endocrine disruption, and epigenetic changes, particularly during critical periods like early childhood and adolescence, future research should be directed towards cumulative and combined EDC exposures role in asthma. Significant heterogeneity exists within certain subgroups, potentially stemming from variations in study populations and differences in the sources and methods used to detect EDCs. This variability could impact the study outcomes. Additionally, despite having only a limited number of studies with a high risk of bias, the overall quality of evidence from these studies has been downgraded due to their observational nature. This is compounded by varying exposure durations and additional exposure pathways other than inhalation (e.g., ingestion and dermal absorption), which may introduce inaccurate results. The studies used varying criteria for outcome assessment, including cases of asthma diagnosed before the study period and possibly associated with other exposures or risk factors. Therefore, findings from this meta-analysis reflect potential associations and cannot be used to establish causality. Moreover, studies did not distinguish between different asthma subtypes, which is an important consideration given the heterogeneous nature of asthma and its varying etiologies. As EDCs may contribute to some subtypes this limitation may affect the interpretation of findings. Consequently, it is imperative to incorporate more eligible studies, while considering asthma subtypes in future research to obtain more robust and reliable findings.

5. Conclusion

Exposure to airborne EDCs is closely associated with asthma onset and exacerbation among school-age children and adolescents, with phthalates, bisphenols, As, Ni Zn, and TBOEP identified as key contributors. No significant associations were noted for PAHs, triclosan, and parabens. Most studies were cross-sectional, and concentrated in high-income countries, particularly the United States, China, and Taiwan, highlighting a geographic and socioeconomic bias. The quality of evidence ranged from moderate to low, with limited data on several EDC groups. Considering the underlying mechanisms, more inclusive research in low-income regions and further exploration of synergetic exposure and co-exposure to other air pollutants, are recommended for a comprehensive understanding of EDC's impact on asthma.

CRedit authorship contribution statement

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

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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. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2025.125830>.

Data availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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