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# The impact of exposure to tobacco smoke and e-cigarettes on asthma-related outcomes: Systematic review informing the EAACI guidelines on environmental science for allergic diseases and asthma

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## Abstract

To inform the clinical practice guidelines' recommendations developed by the European Academy of Allergy and Clinical Immunology systematic reviews (SR) assessed using GRADE on the impact of environmental tobacco smoke (ETS) and active smoking on the risk of new-onset asthma/recurrent wheezing (RW)/low lung function (LF), and on asthma-related outcomes. Only longitudinal studies were included, almost all on combustion cigarettes, only one assessing e-cigarettes and LF. According to the first SR (67 studies), prenatal ETS increases the risk of RW (moderate certainty evidence) and may increase the risk of new-onset asthma and of low LF (low certainty evidence). Postnatal ETS increases the risk of new-onset

**Abbreviations:** ACT, asthma control test; ACQ, asthma control questionnaire; AHR, airway hyper-responsiveness; CI, confidence interval; EAACI, European Academy of Allergy and Clinical Immunology; e-cigarette, electronic cigarette; ED, emergency department; ETS, environmental tobacco smoke; EU, European Union; LF, lung function; FEV1, forced expiratory flow in the first second; FVC, forced vital capacity; GDG, guideline development group; ICS, inhaled corticosteroids; MD, mean difference; OR, odds ratio; PECO, population exposure comparator outcome; PEF, peak expiratory flow; Q, question; QoL, quality of life; RCT, randomized control trial; ROB, risk of bias; ROBINS-E, risk of bias in non-randomized studies of exposure; RR, risk ratio; SMD, standard mean difference; SoF, summary of findings; SR, systematic review; WHO, World Health Organization.

Ioana Agache and Ignacio Ricci-Cabello are co-first equal contribution.

Pablo Alonso-Coello, Marek Jutel, and Cezmi A. Akdis are co-last equal contribution.

For affiliations refer to page 2360.

asthma and of RW (moderate certainty evidence) and may impact LF (low certainty evidence). Combined in utero and postnatal ETS may increase the risk of new-onset asthma (low certainty evidence) and increases the risk of RW (moderate certainty evidence). According to the second SR (24 studies), ETS increases the risk of severe asthma exacerbations and impairs asthma control and LF (moderate certainty evidence). According to the third SR (25 studies), active smoking increases the risk of severe asthma exacerbations and of suboptimal asthma control (moderate certainty evidence) and may impact asthma-related quality-of-life and LF (low certainty evidence).

#### KEYWORDS

asthma, GRADE, guideline, systematic review, tobacco smoke

## 1 | INTRODUCTION

Asthma is a prevalent chronic disease, which poses a significant global public health challenge, impacting worldwide more than 300 million individuals across all age groups.<sup>1,2</sup> In 2019, there were 455,000 reported deaths attributed to asthma, predominantly occurring in low- and middle-income countries due to the difficulties associated with underdiagnosis and undertreatment. These countries also have a high prevalence of active or passive exposure to tobacco smoke.<sup>3-5</sup>

Tobacco consumption is the single largest avoidable health risk, and the most relevant cause of premature death in the European Union (EU), responsible for nearly 700,000 deaths every year. Around 50% of smokers die prematurely (on average 14 years earlier). Despite considerable progress made in recent years, the number of smokers in the EU is still high—26% of the overall population and 29% of young Europeans aged 15–24 smoke.<sup>3-5</sup>

Tobacco smoke comprises a complex mixture of over 6000 chemical compounds, including, potent respiratory irritants and immune modulators like acrolein, acrylamide, formaldehyde, sulfur dioxide, and ammonia, besides nicotine.<sup>6-9</sup> The World Health Organization (WHO) has nominated nine key toxic substances: *N*-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, acetaldehyde, acrolein, benzene, benzo[*a*]pyrene, 1,3-butadiene, carbon monoxide, and formaldehyde.<sup>10</sup>

The prevalence of current and past smoking in adults with asthma is similar to that of the general population. Multiple studies have shown that environmental tobacco smoke (ETS) or active smoking is a major risk factor for new-onset asthma, recurrent wheezing, low lung function and fast lung function decline, asthma exacerbations, impaired asthma control and quality of life (QoL), reduced response to asthma controller medication, especially to inhaled corticosteroids (ICS), and overall increased asthma severity.<sup>11-21</sup> Tobacco smoking increases the risk of lung cancer, cardiovascular diseases, and thus overall mortality in asthmatic patients. Electronic cigarettes (e-cigarettes) seem to have the same detrimental effect on cardiovascular and respiratory health and on patients with asthma.<sup>22,23</sup> Therefore, the avoidance of tobacco exposure may play a critical role in preventing and controlling asthma.

There is relative paucity in mechanistic understanding of how the components of cigarette smoke impact the lung. The mechanisms described until now include epigenetic modifications with transgenerational impact, altered epithelial barrier with overproduction of epithelial derived cytokines, impaired response to infections, mucus hypersecretion, oxidative stress, amplification of the type 2 (T2), and non-T2 chronic airway inflammation.<sup>7,8,24-38</sup> Recognizing that nicotine is a major component in both smoking and vaping products, it is critical to understand the mechanisms by which nicotine impacts airways and boosts lung diseases such as asthma. Nicotine appears to be the responsible component of tobacco smoke that affects lung development.<sup>17</sup> There is now increasing evidence that alpha7 nicotinic acetylcholine receptors are critical players in nicotine effects on airways.<sup>7</sup>

The specific aims of these systematic reviews (SR) and meta-analyses are to synthesize and update the current scientific evidence of the impact of (i) ETS (combustion or e-cigarette) on the risk of new-onset asthma, (ii) ETS (combustion and e-cigarette) on asthma-related outcomes, and (iii) active smoking (combustion and e-cigarette) on asthma-related outcomes. The results of these SRs are meant to inform the recommendations of the Guidelines on Environmental Science for Allergic Diseases and Asthma developed by the European Academy of Allergy and Clinical Immunology (EAACI).

## 2 | METHODS

This systematic review has been conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (registered in PROSPERO CRD42023455368).

### 2.1 | Guideline development group

The EAACI Asthma Voting Panel and Guidelines Steering Committee (henceforth referred as the “guideline development group”—GDG) includes clinicians, researchers, and patient's representatives with different backgrounds (the complete list of experts is available from

the EAACI website) who voluntarily participate in the development of EAACI clinical practice guidelines.

## 2.2 | Structured questions and outcome prioritization

The GDG framed three Population, Exposure, Comparator, and Outcomes (PECO) questions (Q) (Table 1): (i) "Does pre- or postnatal or combined pre- and postnatal ETS (combustion or e-cigarette) increase the risk of new-onset asthma?" (Q1); (ii) "Does ETS (combustion or e-cigarette) impact asthma-related outcomes?" (Q2); and (iii) "Does active smoking (combustion smoking/e-cigarette) impact asthma-related outcomes?" (Q3).

According to the GRADE approach, asthma-related outcomes were prioritized by the GDG group using a 9-point scale (7–9 critical, 4–6 important, and 1–3 of limited importance).<sup>39</sup> For Q1, the critical outcomes were new-onset asthma, recurrent wheezing, and low lung function (forced expiratory volume at one second [FEV1]). For Q2 and Q3, the critical outcomes were severe asthma exacerbations,

asthma control, asthma-related quality of life (QoL), and lung function (FEV1, FEV1/forced vital capacity [FVC], and peak expiratory flow [PEF]). Important outcomes for Q2 and Q3 were frequency of asthma well-controlled days and use of asthma controller and/or reliever medication [Table 1].

## 2.3 | Data sources and search methodology

The search for primary studies included MEDLINE (PubMed, July 2022) and EMBASE (Ovid, July 2022). Search algorithms (with use of validated filters on study designs) were adapted to the requirements of each database (Tables S1 and S2). Additional studies provided by the GDG and previous SR were also evaluated.

## 2.4 | Eligibility criteria and selection of studies

The SR included randomized controlled trials (RCTs) and longitudinal prospective non-randomized studies (i.e., cohort studies). Only

TABLE 1 Research questions and prioritization of outcomes for the systematic review.

Research Question	Population	Exposure	Comparator	Outcomes
Q1: Does pre- or postnatal or combined pre- and postnatal ETS (combustion or e-cigarette) increase the risk of new-onset asthma?	Healthy children	Environmental exposure to: <ul style="list-style-type: none"> <li>• Cigarette/pipe/other combustion smoking</li> <li>• E-cigarettes</li> </ul>	No exposure	Critical <ul style="list-style-type: none"> <li>• New-onset asthma</li> <li>• Recurrent wheezing</li> <li>• Low lung function (FEV1)</li> </ul>
Q2: Does ETS (combustion or e-cigarette) impact asthma-related outcomes?	Children or adults with asthma	Environmental exposure to: <ul style="list-style-type: none"> <li>• Cigarette/pipe/other combustion smoking</li> <li>• E-cigarettes</li> </ul>	No exposure	Critical <ul style="list-style-type: none"> <li>• Severe asthma exacerbations (ED visits/hospitalizations or systemic steroid for at least 3 days)</li> <li>• Asthma control (ACT, ACQ)</li> <li>• Asthma-related QoL</li> <li>• Lung function (FEV1, FEV1/FVC, and PEF)</li> </ul> Important <ul style="list-style-type: none"> <li>• Asthma well-controlled days</li> <li>• Asthma rescue and/or controller medication</li> </ul>
Q3: Does active smoking (cigarette/pipe/other combustion/e-cigarette) impact asthma-related outcomes?	Children, adolescents or adults with asthma	Active smoking of: <ul style="list-style-type: none"> <li>• Cigarette/pipe/other combustion smoking</li> <li>• E-cigarettes</li> </ul>	No exposure	Critical <ul style="list-style-type: none"> <li>• Severe asthma exacerbations (ED visits/hospitalizations or systemic steroid for at least 3 days)</li> <li>• Asthma control (ACT, ACQ)</li> <li>• Asthma-related QoL</li> <li>• Lung function (FEV1, FEV1/FVC, and PEF)</li> </ul> Important <ul style="list-style-type: none"> <li>• Asthma well-controlled days</li> <li>• Asthma medication</li> </ul>

Abbreviations: ACQ, asthma control questionnaire; ACT, asthma control test; ED, emergency department; ETS, environmental tobacco smoke; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, Peak expiratory flow.

studies published in English were included. Studies in which smoking was not considered as the primary exposure variable (i.e., studies including “smoking” as part of a wider group of exposures, e.g., alcohol and air pollution) were not included. Abstracts or conference communications not published as full articles in peer-reviewed journals were excluded.

After initial calibration, one reviewer screened the search results based on their titles and abstracts to identify potentially eligible studies. Subsequently, two reviewers independently assessed the eligibility of studies based on the assessment of the full article text. Disagreements were solved by discussion with a third reviewer.

## 2.5 | Data extraction and risk of bias assessment

From each study included in the SR two independent reviewers extracted information on the description of study design, population, setting, follow-up, and results and assessed the risk of bias (ROB). Discrepancies were solved by discussion with a third reviewer. If needed, additional data were requested from the authors of the studies included.

For RCTs, ROB was assessed with the Cochrane ROB tool.<sup>40</sup> The ROB was judged as “low,” “high,” or “unclear” for each domain: random sequence generation, allocation concealment, blinding of participants and personnel, blinding for outcome assessment, incomplete outcome data, and selective reporting. For non-randomized studies, the ROB was assessed by applying the Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E) tool.<sup>41</sup> The seven items included in ROBINS-E are (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of exposures, (4) bias due to departures from intended exposures, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of reported results. For each item, ROB can be judged as “low,” “moderate,” “serious,” or “critical.” Overall, ROB was rated as “not serious,” “serious,” or “very serious.”

For those studies including more than one eligible asthma-related outcome, we conducted outcome-specific assessments of ROB for the domains “blinding of outcomes assessment,” “incomplete outcome data,” or “bias in measurement of outcomes”. For simplicity and clarity of presentation, the results of the outcome-specific assessments are presented as footnotes in the evidence profile tables but not in the ROB tables.

## 2.6 | Data synthesis and analysis

For dichotomous outcomes, results are presented using odds ratio (OR) or risk ratio (RR). For continuous outcomes, results are reported as mean differences (MD) or standardized mean differences (SMD) (the latter calculated when considering scores assessing patient-reported health-related QoL measured using different instruments)

in change from baseline values. For each outcome, we performed random-effects meta-analysis using the DerSimonian and Laird method. For continuous outcomes, we performed meta-analysis for the change from baseline values. Statistical heterogeneity was assessed with the Q-Cochran test and with the  $I^2$  statistic.<sup>42</sup> A  $p$ -value of the Q-Cochran test  $< .10$  and an  $I^2 > 50\%$  were considered to indicate substantial heterogeneity. All statistical analyses were performed using STATA software, v.15.

Data from RCTs and observational longitudinal studies were not pooled together in the same meta-analyses.

For Q2 and Q3, we conducted subgroup analyses by (a) age group (children (below 18 years old) and adults) and by (b) adjustment status of effect size measures of primary studies (effect size measures adjusted vs. unadjusted for confounders). For Q1, we conducted subgroup analyses based on (a) the relatives who were sources of tobacco exposure (mother, father, both parents and other relatives) and by (b) adjustment status of effect size measures of primary studies. For those studies addressing the outcome “recurrent wheezing,” we conducted subgroup analyses depending on the definition of recurrent wheezing as (a) “lifetime wheeze”; (b) “more than three wheezing episodes”; and (c) studies not providing a specific or clear characterization of wheezing. The ICEMAN criteria<sup>43</sup> were applied to evaluate the credibility of subgroup effect.

For all meta-analyses, we report overall effect estimates, except for those cases in which subgroup analyses demonstrated significant differences of pooled meta-analytical results according to the adjustment status of effect size measures of primary studies (in that case, only pooled effects from studies reporting adjusted results are presented).

## 2.7 | Certainty of the evidence

The certainty (quality) of evidence was rated for each outcome using the GRADE approach.<sup>44</sup> Certainty of evidence was rated as “high,” “moderate,” “low,” or “very low,” taking into consideration the ROB, imprecision, inconsistency, indirectness, and publication bias domains. Results are present in the format of summary of findings (SoF) tables.<sup>45</sup>

# 3 | RESULTS

## 3.1 | Selection process

The selection process is summarized in a PRISMA flowchart (Figure 1). The search identified a total of 8478 records, of which 7749 corresponded to unique records. Of those, 7399 records were excluded after title and abstract screening. For the remaining 350 references, 67 studies met eligibility criteria for Q1<sup>26,46-111</sup> (Table S3), 24 publications met the eligibility criteria for Q2<sup>91,112-134</sup> (Table S4), and 25 studies for Q3<sup>122,130,135-157</sup> (Table S5).

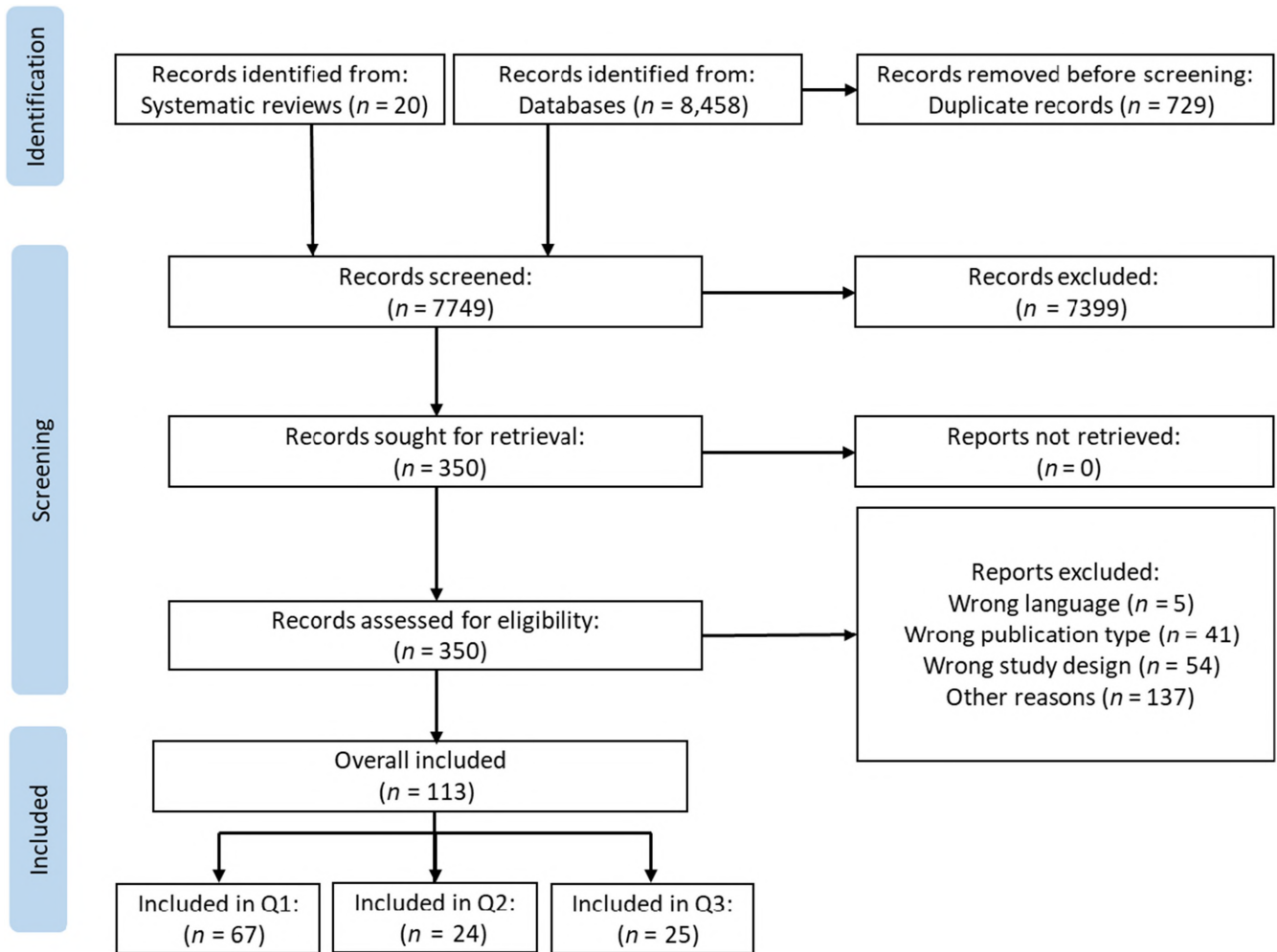


FIGURE 1 PRISMA flowchart illustrating study selection.

### 3.2 | Characteristics of studies included

From the 67 studies evaluated for Q1 (Table S3), 32 (48%) were performed in Europe, 16 (24%) in North America, 9 (13%) in Asia, 5 (7%) in Oceania, 3 (4%) in South America, 1 in Africa, and 1 on multiple continents. Of the 67 studies, 61 were prospective cohort studies, and 6 were retrospective studies. The number of included participants ranged from 101 to 844,003 participants. The mean (range) proportion of female participants was 47.9% (25.6%–55.3%). Of the 67 studies, 12 presented a serious or critical ROB, 53 were at moderate ROB, and 2 had low ROB. The most frequent concerns for bias resulted from reporting the measurement of tobacco exposure (only 15% of the studies with low ROB in this domain), measurement of asthma-related outcomes (low ROB in 34%), and missing data (low ROB in 39%).

From the 24 studies evaluated for Q2 (Table S4), most ( $n=14$ , 58%) were conducted in North America, 7 (29%) in Europe, 2 in Asia (8%), and 1 in Australia (4%). Most studies had an observational design (14 prospective cohort studies and 2 retrospective cohort studies). The remaining studies were either RCTs ( $n=3$ ) or quasi-experimental studies ( $n=5$ ). The number of included participants

ranged from 6 to 5263 participants. The mean (range) proportion of female participants was 53.9% (30%–100%). Nine studies presented a high ROB, 14 a moderate ROB, and 1 had a low ROB. Most frequent sources of high ROC in observational studies were related to confounding bias (2 studies) and bias related to selection of participants (2 studies), whereas in RCTs bias was related to the generation of the random sequence (5 RCTs).

Of the 25 studies evaluated for Q3 (Table S5), around two-thirds ( $n=16$ , 64%) were conducted in Europe. The rest were conducted in North America ( $n=4$ ), Asia ( $n=3$ ), and Oceania ( $n=2$ ). Most studies were observational, (19 prospective cohort and 2 retrospective cohort studies); there were also 3 RCTs and 1 quasi-experimental study. The number of included participants included ranged from 10 to 17,480 participants. The mean (range) proportion of females was 62% (15%–100%). Twentynine studies (84%) included both males and females, whereas 3 studies (12%) focused exclusively on pregnant women (the proportion of females was not reported in one study). Nine studies presented high ROB and 16 presented moderate or unclear ROB (no studies with low ROB were identified).

### 3.3 | The impact of ETS (combustion or e-cigarettes) on the risk of new-onset asthma (Q1)

The evidence profiles and certainty of evidence for Q1 are summarized per outcome in [Table 2](#) and detailed in [Figures S1A–L](#). All data refer to ETS to combustion cigarettes as no study examined the impact of ETS to e-cigarettes on the risk of developing asthma.

#### 3.3.1 | New-onset asthma (prenatal exposure)

Thirty-one studies reported on the impact of prenatal exposure to combustion smoking on new-onset asthma ([Table S3A](#)). The pooled analysis from 23 studies ([Figure S1A](#)) showed that prenatal exposure to combustion smoking may result in an increased risk of new-onset asthma (pooled OR=1.28; 95%CI=1.18–1.39;  $I^2=67.1\%$ ; Q Cochran test  $p$ -value < .001) (low certainty evidence). This pooled estimate was consistent with the findings from the other 8 studies not included in the meta-analysis.

Most studies assessed the impact of maternal smoking on new-onset asthma ([Figure S1B](#)), where a positive association was observed (pooled OR=1.30; 95%CI=1.20–1.41), albeit with severe heterogeneity ( $I^2=62.3\%$ ; Q Cochran test  $p$ -value < .001).

#### 3.3.2 | Recurrent wheezing (prenatal exposure)

Twenty-three studies examined the impact of prenatal exposure to combustion smoking on the risk of recurrent wheezing ([Table 3A](#)). Pooled adjusted results from 21 studies ([Figure S1C](#)) showed that prenatal exposure to combustion smoking increases the risk of recurrent wheezing (OR=1.43; 95%CI=1.30–1.56;  $I^2=64.4\%$ ; Q Cochran test  $p$ -value < .001) (moderate certainty evidence). The 2 studies not included in the meta-analysis (due to unavailable data), also suggested that prenatal exposure to combustion smoking could increase the risk of recurring wheezing.<sup>47,70</sup> Most studies assessed the impact of maternal smoking (pooled OR=1.52; 95%CI=1.41–1.64;  $I^2=13.2\%$ ; Q Cochran test  $p$ -value=.283) ([Figure S1D](#)).

#### 3.3.3 | Low lung function (prenatal exposure)

Three studies reported the impact of prenatal exposure to smoking on incident low lung function.<sup>59,64,91</sup> These studies presented results using different effect size measures (mean differences, OR, and percent changes) and lung function measures (FEV1 and FEV1/FVC), which precluded from pooling their results. One study<sup>59</sup> found that in utero exposure was associated with decreased FEV1 in boys (mean difference=−13.6%; 95%CI=−18.9% to −8.2%) and with decreased FEV1/FVC in girls (−9.3%; 95% CI, −12.9% to −5.4%). Another prospective study<sup>64</sup> reported that maternal smoking during pregnancy was negatively associated with maximal mid expiratory

flow (FEF25-75) (−0.05 SD units, 95% CI=−0.07 to −0.03), but no significant changes were observed for FEV1. The third study<sup>91</sup> suggested that prenatal tobacco exposure was associated with decreased FEV1 (adjusted mean difference=−0.07L, 95%CI −0.13 to −0.01L). All the studies provided adjusted estimates. Overall, evidence was considered of low certainty.

#### 3.3.4 | New-onset asthma (postnatal exposure)

The SR identified 16 studies examining the impact of postnatal ETS (combustion smoke) on the risk of new-onset asthma ([Table S3B](#)). The meta-analysis of 13 studies ([Figure S1E](#)) reporting adjusted estimates shows that postnatal ETS increases the risk of new-onset asthma (OR=1.12; 95%CI=1.01–1.24;  $I^2=47.9\%$ ; Q Cochran test  $p$ -value=.007) (moderate certainty evidence). Stronger associations were observed when both parents smoked (OR=1.20; 95%CI=1.09–1.32;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.956) compared to the risk provided by only the mother smoking (OR=1.07; 95%CI=0.83–1.38;  $I^2=62\%$ ; Q-Cochran test  $p$ -value=.006) or the father smoking (OR=1.05; 95%CI=0.96–1.14;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.775) ([Figure S1F](#)).

#### 3.3.5 | Recurrent wheezing (postnatal exposure)

Seventeen studies examined the impact of postnatal ETS (combustion smoke) on the risk of recurrent wheezing ([Table S3B](#)). Pooled data from 10 studies providing adjusted estimates ([Figure S1G](#)) showed that postnatal ETS increases the risk of recurrent wheezing (OR=1.15; 95%CI 1.04–1.27;  $I^2=29.7\%$ ; Q-Cochran test  $p$ -value=.155) (moderate certainty evidence). The pooled estimate was consistent with the findings from the other 2 studies not included in the meta-analysis.<sup>57,70</sup> A significant association was observed when both parents smoked (OR=1.19; 95%CI=1.11–1.29;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.820) or when only the mother smoked (OR=1.36; 95%CI=1.06–1.74;  $I^2=56.8\%$ ; Q-Cochran test  $p$ -value=.031) ([Figure S1H](#)).

#### 3.3.6 | Low lung function (postnatal exposure)

Four studies examined the impact of ETS (combustion smoke) on the risk of low lung function. These studies used different effect size measures (MD, OR, and percent changes) and lung function parameters (FEV1; FEV1/FVC), which precluded from pooling their results. One prospective cohort study<sup>57</sup> observed that, for each person smoking indoors, ETS was associated with an average decrease in FEV1 of 0.30% (6.8mL). Another study<sup>59</sup> reported no significant detrimental effects on lung function from ETS (effect estimates not reported). A third study<sup>87</sup> claimed that ETS had no significant detrimental effects for absolute FEV1 or FVC in either sex. Parental smoking was, however, reported to be associated with persistent, but mild and

TABLE 2 Summary of findings for the impact of ETS (combustion smoke) pre- or postnatal or combined on the risk of new-onset asthma.

Outcomes	No. of studies [Follow-up; years]	Certainty of evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk compared with no exposure*	Risk difference in the exposed group
New-onset asthma (in utero exposure)	23 [median: 7; range: 1–22]	⊕⊕○○ <sup>a,b</sup> Low	OR 1.28 (1.18 to 1.39)	11.1%	+27 per 1000 (+17 to +37)
Recurrent wheezing (in utero exposure)	21 [median: 6; range: 1–24]	⊕⊕○○ <sup>c</sup> Moderate	OR 1.43 (1.30 to 1.56)	19.2%	+62 per 1000 (+ 44 to +78)
Low lung function (in utero exposure)	3 [median: 6; range: 1–24] [median: 7; range: 7–8]	⊕⊕○○ <sup>d</sup> Low			
					<ul style="list-style-type: none"> <li>• Gilliland et al. examined in 5933 children longitudinal medical history, tobacco smoke exposure, and lung function data and found that in utero exposure was associated with decrease in FEV1 (–13.6%; 95%CI: –18.9 to –8.2%) among boys and decrease in FEV1/FVC (–9.3%; 95% CI: –12.9 to –5.4%) among girls.</li> <li>• Henderson et al. observed in 6606 children that maternal smoking during pregnancy was negatively associated with maximal mid expiratory flow (FEF25-75) (–0.05 SD units, 95%CI: –0.07 to –0.03), but no significant declines were observed for FEV1.</li> <li>• Sunde et al. examined prenatal tobacco exposure by maternal smoking during the third trimester in 411 children enrolled in the Copenhagen Prospective Studies on Asthma in Childhood 2000 birth cohort followed-up to the age of 7 years. The study reported that prenatal tobacco exposure was associated with decreased FEV1 (adjusted mean difference = –0.07 L, 95%CI: –0.13 to –0.005 L).</li> </ul>
New-onset asthma (postnatal exposure)	13 [median: 8; range: 2–18]	⊕⊕○○ <sup>e</sup> Moderate	aOR 1.12 (1.01 to 1.24)	8.3%	+9 per 1000 (+1 to +18)
Recurrent wheezing (postnatal exposure)	10 [median: 2; range: 1–8]	⊕⊕○○ <sup>f</sup> Moderate	aOR 1.15 (1.04 to 1.27)	21.0%	+24 per 1000 (+7 to +42)
Low lung function (postnatal exposure)	4 [median: 8; range: 6–15]	⊕⊕○○ <sup>g</sup> Low			
					<ul style="list-style-type: none"> <li>• Fernández-Plata et al. evaluated a prospective cohort study of 1632 boys and 1555 girls aged 8–17 years from Mexico City and observed that for each person smoking indoors ETS was associated with a decrease in FEV1 of 0.30% (6.8 mL). The decrease was 0.41% (9.2 mL) for girls, and 0.17% (4.1 mL) for boys.</li> <li>• Gilliland et al. assessed 5933 children and found no evidence for impact of ETS on lung function (effect estimates not reported).</li> <li>• Sherrill et al. examined in a cohort of New Zealand children from 9 to 15 years of age the impact of ETS on lung function and reported no association with significant detrimental effects for absolute FEV1 or FVC in either sex. Parental smoking was, however, associated with persistent but mild and nonprogressive impairment of the FEV1/FVC ratio in males but not in females.</li> <li>• Tashkin et al. analyzed respiratory questionnaires and lung function results obtained during field testing of residents in the Los Angeles area and found that, among younger boys, residual values were significantly lower in the maternal smoking category than in the other 2 household categories (only father smokes, and neither parent smokes). No differences were noted between the paternal-smoking only and non-smoking household categories. A trend toward similar results was found in older boys. Among older girls, the FEF during the middle half of the FVC and maximal flow after exhalation of 75% of FVC were significantly lower in relation to maternal smoking.</li> </ul>

TABLE 2 (Continued)

Outcomes	No. of studies [Follow-up; years]	Certainty of evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk compared with no exposure*	Risk difference in the exposed group
New-onset asthma (in utero and postnatal exposure)	6 [median: 4.2; range: 1.8–8]	⊕⊕○○ <sup>h,j</sup> Low	aOR 1.49 (1.12 to 1.99)	6.0%	+27 per 1000 (+7 to +53)
Recurrent wheezing (in utero and postnatal exposure)	8 [median: 6; range: 1.5–11]	⊕⊕○○ <sup>j</sup> Moderate	aOR 1.46 (1.28 to 1.66)	23.5%	+75 per 1000 (+47 to +103)

Note: Results are presented per the outcomes of interest (new-onset asthma, recurrent wheezing, and low lung function).

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; FEF, forced expiratory flow; FEV1, forced vital capacity; OR, odds ratio.

<sup>a</sup>Serious risk of bias: of the 23 studies included, one presented a very high risk of bias, 3 high risk, 18 had some concerns, and 1 low risk. Most frequent sources of bias were related to the measurement of the ETS (self-reported in 32 of the studies), bias due to missing data (some concerns in 19 studies and high/very high risk in 2 studies), and bias in the measurement of the outcomes (some concerns in 24 studies that used self-reported measures). Only 2 studies (Wu 2014, and Wu 2019) did not adjust by confounding.

<sup>b</sup>Serious inconsistency: large, unexplained heterogeneity ( $I^2 = 67.5\%$ ).

<sup>c</sup>Serious risk of bias: of the 21 studies, 4 presented a high risk of bias, and 17 had some concerns. The most frequent reasons for bias were: bias in the measurement of the outcomes (some concerns in 18 studies due to the use of self-reported data), bias due to missing data (some concerns in 12 studies), bias in the selection of participants into the study (some concerns in 6 studies, high risk in one study), and bias in the measurement of the exposure (some concerns in 18 studies due to use of self-reported data). In 8 studies recurrent wheezing was defined as lifetime wheeze of more than three episodes; whereas in 13 studies the definition of recurrent wheezing was unclear. Subgroup analysis indicated no effect differences between both types of studies (defining recurrent wheezing as lifetime wheeze of more than three episodes vs. unclear definition).

<sup>d</sup>Very serious risk of bias: two of the studies (Gilliland 2003, Sunde 2022) presented some concerns, and one (Henderson 2010) high risk of bias. The most common sources of bias were related to missing data (some concerns in all three studies), selection of participants (some concerns in Gilliland 2003 and Sunde 2022), and bias due to potential confounding (high risk of bias in Henderson 2010 and some concerns in Sunde 2022).

<sup>e</sup>Serious risk of bias: of the 13 studies, one presented a high risk of bias, and the rest presented some concerns. Most frequent sources of bias were related to the measurement of the outcomes (some concerns in 12 of the studies), missing data (some concerns in 12 studies), selection of participants (some concerns in five studies), and measurement of the exposure (some concerns in 12 studies due to use of self-reported data).

<sup>f</sup>Serious risk of bias: of the 10 studies, one presented a high risk of bias, one low risk of bias, and the rest had some concerns. The most frequent risk of bias were related to bias in the measurement of the outcomes (some concerns in 8 studies), missing data (some concerns in 6 studies), selection of participants (potential selection bias in 2 studies with some concerns and 1 with a high risk of bias), and measuring the ETS (some concerns in 9 studies due to use of self-reported data). Only 6 studies provided a clear and valid definition of recurrent wheezing, but the results were consistent with those from the studies not providing a clear definition.

<sup>g</sup>Very serious risk of bias: of the 4 studies, one presented a very high risk of bias, (Sherrill 1992) one high risk of bias (Fernández-Plata 2016), and 2 some concerns (Gilliland 2003, Tashkin 1984). The most frequent sources of bias were related to missing data (two studies with a high risk of bias – Fernández-Plata 2016; Sherrill 1992), and risk of bias measuring the exposure (self-reported in the four studies). In addition, Sherrill (1982) presented some concerns in bias due to confounding.

<sup>h</sup>Serious risk of bias: 6 studies presented some concerns. The most frequent sources of bias were related to measurement of the outcomes, missing data, and measurement of exposure.

<sup>i</sup>Serious inconsistency: large unexplained heterogeneity ( $I^2 = 95\%$ ).

<sup>j</sup>Serious risk of bias: the 8 studies presented some concerns. The most frequent reasons were related to measurement of the outcome and of the exposure (self-reported in the 8 studies), and missing data (some concerns in four 4 studies). Only 3 studies provided a valid definition of recurrent wheezing, but the results were consistent with those from studies not providing a clear definition.

\*Basal risk computed based on the mean proportion of events in the nonexposed group.

TABLE 3 Summary of findings for the impact of postnatal ETS (combustion smoke) on asthma-related outcomes in children and in adults with asthma.

Outcomes	No. of studies [Follow-up]	Certainty of the evidence (GRADE)	Anticipated absolute effects	
			Relative effect (95% CI)	Risk compared with no exposure*
Severe asthma exacerbations (hospital admissions)	2 [12 months]	⊕⊕○○ <sup>a,b</sup> Low	aOR 2.83 (0.84 to 9.41)	6.1% +94 per 1000 (-9 to +318)
Severe asthma exacerbations (ED visits)	2 [12 months]	⊕⊕○○ <sup>c</sup> Moderate	OR 3.06 (1.65 to 5.68)	11.5% +170 per 1000 (+62 to +310)
Asthma exacerbations with no clear definition	3 [median: 12 months; 3 months to 7 years]	⊕⊕○○ <sup>d</sup> Moderate	aOR 1.75 (1.46 to 2.10)	39.3% +138 per 1000 (+93 to +183)
Asthma control	5 [median: 12 months; 2 weeks to 3 years]	⊕⊕○○ <sup>e</sup> Moderate	aOR 2.24 (1.56 to 3.23)	Not reported
Quality of life	3 [median: 12 months; 24 weeks to 4 years]	⊕○○○ <sup>f,g,h</sup> Very low	-	MD -0.9 (-4.32 to +2.52)
Lung function (acute exposure)	3 [median: 2 h; 54 min to 3 h]	⊕○○○ <sup>h,i</sup> Very low	-	FEV1 MD -0.08 liters (-0.17 to +0.02)
Lung function (long-term exposure)	3 [median: 36 months; 3 months to 6 years]	⊕⊕○○ <sup>j</sup> Moderate	-	FEV1% predicted aMD -5.94 (-7.81 to -4.07 lower)
Asthma medication use (rescue and controller)	3 [median: 3 years; 2 years to 5 years]	⊕○○○ <sup>k,l</sup> Very low	<ul style="list-style-type: none"> <li>• Boskabady 2022: No significant differences in the amount of asthma medication use between children with asthma from smoker parents and children from non-smoker parents.</li> <li>• Eisner 2001: Significant extra bronchodilator use among those exposed to ETS (OR = 8.1; 95%CI = 1.3-50.0)</li> <li>• Eisner 2002: After acute exposure to ETS during travels, 55% of the subjects indicated extra inhaled asthma medication use. There were no differences in asthma medication use by regular ETS exposure status</li> </ul>	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ETS, environmental tobacco smoke; FEV1, forced expiratory volume in the first second; MD, mean difference; OR: odds ratio.

<sup>a</sup>Serious risk of bias: two studies presented "some concerns" due to bias arising from missing data and lost to follow-up (Eisner 2005), and from self-reported ETS exposure and self-reported outcome (Eisner 2002).

<sup>b</sup>Serious imprecision: wide confidence intervals.

<sup>c</sup>Serious ROB: 2 studies presented "some concerns" due to self-reported ETS exposure, and self-reported outcome (Eisner 2002). One study presented a low ROB (Gerald 2009).

<sup>d</sup>Serious risk of bias: all 3 studies presented "some concerns" due to missing data, self-reported outcomes (Sunde 2022), confounding and selection bias (Sutaryono 2019), selection bias and bias related to missing data (Chilmonczyk 1993).

<sup>e</sup>Only one study (Gerald 2009) presented a low risk of bias. Jassal 2020 and Butz 2011 presented a high risk of bias due to issues with randomization and blinding. The overall risk of bias in the rest of the studies was rated as "some concerns," mainly due to missing data (all), and self-reported outcome measurement (Eisner 2002 and Eisner 2005).

<sup>f</sup>Very serious risk of bias: nonresponse bias is concerning in Eisner 2005. Bias arising from self-reported exposure status is high in Eisner 2002.

<sup>g</sup>Serious inconsistency: inconsistent results observed across studies.

<sup>h</sup>Wide confidence intervals due to inconsistent results.

<sup>i</sup>Very serious risk of bias: high risk of bias in Keogan 2020 and Magnussen 1993 due to problems with randomization. Moderate risk of bias for Nowak 1997 due to unclear reporting.

<sup>j</sup>Serious risk of bias: the studies presented "some concerns" due to measures of exposition and outcomes being based on self-reported information. Additionally, Chilmonczyk 1993 and Granup 2014 were at risk of selection bias.

<sup>k</sup>Extremely serious risk of bias: Boskabady 2022 presented a high risk of bias due to a lack of adjustment for confounding factors and potential selection bias. Eisner 2001 presented a high risk of bias due to selection bias and Eisner 2002 due to recall bias and missing data.

<sup>l</sup>Serious inconsistency: inconsistent results were observed across studies, with one observing an effect, another one reporting lack of effect, and the third one focusing on acute exposure.

<sup>m</sup>Basal risk computed based on the mean proportion of events in the not exposed group.

non-progressive impairment of the FEV1/FVC ratio in males, but not in females. The fourth study observed that maternal smoking (but not paternal smoking alone) produced a decline in FEF 25–75 of  $-0.083$  in younger boys.<sup>98</sup> Overall, the certainty of evidence was considered low.

### 3.3.7 | New-onset asthma (combined pre- and postnatal exposure)

Ten studies examined the impact of pre- and postnatal ETS (combustion smoke) on the risk of new-onset asthma (Table 3C). The meta-analysis of 6 studies reporting adjusted data (Figure S1I) shows that ETS may increase the risk for new-onset asthma (pooled OR=1.49; 95%CI=1.12–1.99;  $I^2=95.1\%$ ; Q-Cochran test  $p$ -value < .001) (low certainty evidence). Consistent results were observed when considering studies assessing the impact of maternal smoking (OR=1.23; 95%CI=1.08–1.39;  $I^2=55.9\%$ ; Q-Cochran test  $p$ -value=.026) but not for paternal smoking (OR=1.52; 95%CI=0.73–3.16;  $I^2=98\%$ ; Q-Cochran test  $p$ -value < .001) (Figure S1J).

### 3.3.8 | Recurrent wheezing (combine pre- and postnatal exposure)

Nine studies examined the impact of pre- and postnatal exposure to ETS (combustion smoke) on the risk of recurrent wheezing (Table 3C). Pooled data from 8 studies (Figure S1K) suggest that pre- and postnatal exposure to ETS to combustion smoke increases the risk of recurrent wheezing (pooled OR=1.46; 95%CI=1.28–1.66;  $I^2=64\%$ ; Q-Cochran test  $p$ -value=.007) (moderate certainty evidence). Consistent results were observed in those studies assessing the impact of maternal smoking only (pooled OR=1.42; 95%CI=1.26–1.60;  $I^2=28\%$ ; Q-Cochran test  $p$ -value=.232) (Figure S1L).

## 3.4 | The impact of ETS (combustion smoke or e-cigarettes) on asthma-related outcomes (Q2)

The evidence profiles and certainty of evidence for Q2 are summarized per outcome in Table 3 and detailed in Figures S2A–I. All data refer to ETS to combustion cigarettes as no study examined the impact of ETS to e-cigarettes on asthma-related outcomes.

### 3.4.1 | Severe asthma exacerbations

Four studies reported on severe asthma exacerbations defined as hospital admissions (Figure S2A). Three studies reported hospital admissions during the previous 12 months,<sup>116,117,121</sup> while one study examined hospital admissions during pregnancy.<sup>130</sup> Pooled data from the 2 studies providing adjusted estimates (Figure S2B) shows that ETS may increase hospital admissions for asthma (OR=2.83; 95%CI=0.84–9.41;  $I^2=50\%$ ; Q-Cochran test  $p$ -value=.158) (low

certainty evidence). Consistent results were observed for children and adults in the age subgroup analyses (Figure S2A).

Two studies reported on severe asthma exacerbations defined as one or more emergency department (ED) visits over 12 months.<sup>118,121</sup> Both studies (Figure S2D) show that ETS increases the risk for asthma-related ED visits (OR=3.06; 95%CI=1.65–5.68) (moderate certainty evidence). Consistent results were observed for children and adults in the age subgroup analyses (Figure S2C).

### 3.4.2 | Asthma exacerbations (any definition)

Five studies<sup>91,115,116,126,134</sup> reported on asthma exacerbations defined in one study based on the pulmonary index (oxygen saturation on room air, accessory muscle use, inspiratory-to-expiratory flow ratio, degree of wheezing, and heart and respiratory rate), in another as a combined composite index (the need for oral prednisone or high dose ICS, or need for hospitalization), while the other 3 studies provided no definition for asthma exacerbations. Pooled data from the 3 studies reporting adjusted estimates (Figure S2E) suggests that exposure to ETS increases the risk of asthma exacerbations (OR=1.75; 95%CI=1.46–2.10;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.728) (moderate certainty evidence).

### 3.4.3 | Asthma control

Ten studies examined the impact of exposure to ETS on asthma control (Table S4). Asthma control was measured in most of the studies based on self-reported data, using available Patient-Reported Outcome Measures. Pooled data from five studies (Figure S2F) showed that exposure to ETS increases the risk of uncontrolled asthma (OR=2.24; 95%CI=1.56–3.23;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.800) (moderate certainty of evidence). The pooled estimate was supported by the findings from the other 5 studies<sup>82,83,87,95,98</sup> not included in the meta-analysis. Consistent results were obtained for children and adults in separate pooled analyses according to participants' age (Figure S2F).

### 3.4.4 | Quality of life

Three studies assessed the impact of ETS on asthma-related QoL.<sup>117,118,126</sup> Pooled data from these 3 studies (Figure S2G, Table 3) suggest that ETS may have an impact on asthma-related QoL (pooled MD= $-0.90$ ; 95%CI= $-4.32$ ; 2.52;  $I^2=47\%$ ; Q-Cochran test  $p$ -value=.153) (very low certainty evidence).

### 3.4.5 | Lung function (acute exposure)

Six experimental studies<sup>120,124,125,128,131,132</sup> evaluated the immediate impact of ETS on lung function. A limited number of asthma

patients were exposed in closed rooms to tobacco smoke during 1–24 h. Pooled data from 3 studies (Figure S2H) suggest that acute exposure to ETS may have an impact on mean FEV1 (MD=−0.08 L; 95%CI=−0.17; 0.02;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.861) (very low certainty evidence). The other 3 studies not included in the meta-analysis reported inconsistent results (Table 3).

### 3.4.6 | Lung function (long-term exposure)

Eight studies<sup>112,115,122,126,127,129,130,133</sup> examined the impact of long-term ETS on lung function (Figure S2I, Table 3). Pooled data from 3 studies reporting adjusted estimates indicates that long-term exposure to ETS reduces mean predicted FEV1% (pooled MD=−5.94%; 95%CI=−7.81; −4.07%;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.427) (moderate certainty evidence). Three of the five studies not included in the meta-analysis revealed similar decreases in FEV1 after long exposure to ETS, whereas a fourth study<sup>127</sup> did not find a significant effect.

### 3.4.7 | Asthma well-controlled days

No study on the impact of ETS on asthma well-controlled days was identified.

### 3.4.8 | Asthma medication

Three studies<sup>112,116,117</sup> examined the impact of ETS on asthma rescue and controller medication use. Outcomes were too heterogeneous to be pooled in a meta-analysis, with evidence certainty being classified as “very low” (Table 3).

## 3.5 | The impact of active smoking (combustion or e-cigarettes) on asthma-related outcomes (Q3)

The evidence profiles and certainty of evidence for Q3 are summarized per outcome in Table 4A,B and detailed in Figures S3A–F.

### 3.5.1 | Severe asthma exacerbations (combustion cigarette smoking)

The SR identified 4 studies<sup>99,137,149,156</sup> assessing severe asthma exacerbations (defined as hospital admissions, ED visits, or number of urgent clinic visits). Pooled data from the 3 studies providing adjusted estimates (Figure S3A) show that active smoking increases the risk of severe asthma exacerbations (pooled RR=1.44, 95%CI=1.02–2.03;  $I^2=0\%$ ; Q-Cochran test  $p$ -value=.734) (moderate certainty evidence).

One study<sup>150</sup> reported severe asthma exacerbations defined as a worsening of respiratory symptoms for more than 24 h and

requiring treatment with systemic corticosteroids for at least 3 days. This prospective cohort study followed 176 adults with asthma and observed that more than half of current smokers (56%) had at least one exacerbation per year requiring systemic corticosteroids, compared to 22% of nonsmokers. The mean number of exacerbations per year was also significantly different between the groups, with current smokers group having significantly more exacerbations per year compared to nonsmokers (1.3 vs. 0.5, respectively) (low certainty evidence).

### 3.5.2 | Asthma control (combustion cigarette smoking)

Nine studies assessed the impact of active smoking on asthma control (Table S5). Pooled data from 4 studies reporting adjusted estimates (Figure S3B) show that active smoking increases the risk of uncontrolled asthma (OR=2.67, 95%CI =1.51–4.70;  $I^2=82.6\%$ ; Q-Cochran test  $p$ -value < .001) (moderate certainty evidence). The observed increased risk is supported by the findings of 5 studies not included in the meta-analysis.<sup>122,142,146,148,152</sup>

### 3.5.3 | Quality of Life (combustion cigarette smoking)

Four studies examined the impact of smoking asthma-related QoL.<sup>139,144,145,152</sup> Pooled data from 2 of these studies (Figure S3C,D) indicated no significant impact of active smoking on asthma-related QoL (pooled SMD=−2.53; 95%CI=−6.19; 1.13;  $I^2=96\%$ ; Q-Cochran test  $p$ -value < .001) (moderate certainty evidence). The results were broadly consistent with the results reported by the other 2 studies not included in the meta-analysis.

### 3.5.4 | Lung function (combustion cigarette smoking)

Eighteen studies examined the impact of active smoking on lung function (Table S4). One study<sup>157</sup> provided adjusted estimates (Figure S3E) and suggested that active smoking may decrease mean FEV1% (pooled MD=−6.23; 95%CI=−11.28; −1.19) (low certainty evidence), with this finding being broadly consistent with the results from the studies not included in the meta-analysis.

### 3.5.5 | Lung function (electronic cigarette smoking)

A crossover placebo-controlled RCT examined the impact of a 1-h acute vaping session of nicotine-free contaminant-free mixture of propylene glycol and glycerol using a commercially available electronic cigarette on the pulmonary function and respiratory mechanic of 10 patients with asthma.<sup>135</sup> The experiment found no significant

TABLE 4 (A) Summary of findings for impact of active smoking (combustion) on asthma-related outcomes in adolescents or adults with asthma. (B) Summary of findings for impact of active smoking (e-cigarette) on asthma-related outcomes in adults with asthma.

Outcomes	No. of studies [Follow-up]	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk compared with no exposure*	Risk difference in the exposed group
<b>(A)</b>					
Severe asthma exacerbation (hospitalization or ED visit for asthma)	3 [median: 4 years; 1 to 15 years]	⊕⊕⊕○ <sup>a</sup> Moderate	aRR 1.44 (1.02 to 2.03)	28.4%	+125 per 1000 (+6 to +293)
Severe asthma exacerbation (systemic corticosteroids for at least 3 days)	1 [not reported]	⊕⊕○○ <sup>b,c</sup> Low	Tiotiu et al reported a higher frequency of exacerbations in current smokers (56%) than in non-smokers (22%) [RR 2.53; 95%CI 1.60 to 4.01], as well as a higher mean number of exacerbations during the previous year in current smokers (1.3; SD: 0.2) than in former (0.6; SD: 0.8) and nonsmokers (0.5; SD: 0.1).		
Asthma control	4 [median: 2 years; 3 months to 10 years]	⊕⊕⊕○ <sup>d</sup> Moderate	aOR 2.67 (1.51 to 4.70)	27.0%	+227 per 1000 (+88 to +365 more)
Quality of Life	2 [3 and 4 months]	⊕⊕⊕○ <sup>e</sup> Moderate	-	-	SMD -2.53 (-6.19 to +1.13)
Lung function	4 [median: 6 months; 3 months to 12 years]	⊕⊕○○ <sup>f,g</sup> Low	-	-	MD -6.23 (-11.28 to -1.19)
Asthma well-controlled days	1 [not reported]	⊕⊕○○ <sup>h</sup> Low	In 2010 pregnant women with asthma, Newman et al observed significant differences between smokers and non-smokers in: <ul style="list-style-type: none"> <li>• Mean total number of symptomatic days (78.8 vs. 69.3)</li> <li>• Mean total number of nights with sleep disturbance (48.4 vs. 39.2)</li> <li>• Mean total number of days with restricted activity (23.4 vs. 26.8).</li> </ul>		
Asthma medication (rescue and controller)	1 [12 months]	⊕⊕○○ <sup>i</sup> Low	In a prospective cohort study involving 519 patients with asthma, no significant differences were observed at 12 months follow-up between non-smokers and smokers in the proportion of patients using controller medication (73.5% vs. 79.5%) or reliever medication (83.3% vs. 85.3%).		
<b>(B)</b>					
Lung function (electronic cigarette smoking)	1 [1h]	⊕⊕○○ <sup>j,k</sup> Low	A placebo-controlled crossover trial investigating the impact of a 1-h acute vaping session of nicotine-free and flavor-free e-liquid on the pulmonary function of 10 asthmatic individuals found no significant differences in any of the lung function outcomes examined: <ul style="list-style-type: none"> <li>• FEV1: pre-post difference of 0.014 (0.013 to 0.015) in the intervention group versus -0.01 (-0.01 to -0.01) in the placebo group;</li> <li>• FVC: pre-post difference of -0.069 (-0.070 to -0.068) in the intervention group versus -0.05 (-0.05 to -0.05) in the placebo group</li> <li>• FEV1/FVC: pre-post difference of 1.550 (1.516 to 1.584) in the intervention group versus -1.10 (-1.13 to -1.11) in the placebo group.</li> </ul>		

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; MD, mean difference; OR, odds ratio; RR, risk ratio; SMD, standardized mean difference.

<sup>a</sup>Serious risk of bias: all three studies had some concerns in relation to the risk of bias derived from potential selection bias (Murphy 2010, Çolak 2015), missing data (Çolak 2015), and self-reported outcomes (To 2012).

<sup>b</sup>Serious risk of bias: concerns of risk of bias due to self-reported smoking status, an unclear method for selecting the study participants (potential selection bias), and unclear information about missing data.

<sup>c</sup>Serious imprecision: small sample size, leading to imprecise estimates.

<sup>d</sup>Three of the four studies presented some concerns due to potential selection bias (Tiotiu 2021), and self-reported outcomes (To 2012 and Westerhof 2014). One study (Polosa 2011) presented a high risk of bias due to the measurement of the outcome and smoking status (self-reported), as well as concerns about selection bias, and missing data.

<sup>e</sup>Very serious risk of bias: Jang 2010 rated as "some concerns" due to potential selection bias, (the study randomized participants to smokers and quitters without further description) and confounding bias. Tønnesen 2004 rated as "high risk of bias" due to missing data (>50% withdrawal rate in the intervention group) and confounding bias.

<sup>f</sup>Serious risk of bias: Vignoud 2011 presented some concerns due to loss to follow-up and reporting the exposure.

<sup>g</sup>Serious imprecision: wide confidence intervals.

<sup>h</sup>Very serious risk of bias: risk of confounding bias (unadjusted estimates), and selection bias (unclear method of selecting participants).

<sup>i</sup>Very serious risk of bias: due to bias arising from self-reported exposure and outcome measurement.

<sup>j</sup>Serious indirectness: only acute effect is measured (1h exposition).

<sup>k</sup>Serious imprecision: very small sample size (10 participants).

\*Basal risk computed based on the mean proportion of events in the not exposed group.

impact of the 1-h vaping on lung function parameters (FEV1, FVC, and FEV1/FVC) (low certainty evidence) (Table 4B).

### 3.5.6 | Asthma well-controlled days (combustion cigarette smoking)

The impact of active cigarette smoking on the frequency of asthma well-controlled days was assessed in 2210 pregnant women with asthma (130). Significant differences between nonsmokers and smokers were observed on the mean number of symptomatic days (69.3 vs. 78.8), total night sleep disturbance (39.2 vs. 48.4), and total days of restricted activity (23.4 vs. 26.8) (low evidence certainty) (Table 4).

### 3.5.7 | Asthma medication (combustion cigarette smoking)

A prospective cohort study enrolled 519 patients with asthma and examined the impact of active cigarette smoking on asthma medication use.<sup>156</sup> After 12 months follow-up, there were no significant differences between nonsmokers and smokers on the percentage of patients using asthma controllers (73.5% vs. 79.5%) or reliever medication (83.3% vs. 85.3%) (low certainty evidence) (Table 4).

## 3.6 | Subgroup analyses

The results of the subgroup analysis have low credibility for all the outcomes assessed (i.e., likely no impact modification) because chance is a very likely explanation of the apparent effect (meta-regressions  $p$  value > .05) and the meta-analysis included a small number of studies.

## 4 | DISCUSSION

### 4.1 | Main findings

Three SRs assessed the impact of smoking on the risk of new-onset asthma and on asthma-related outcomes. Almost all studies provided data on combustion cigarettes smoking, with only one study assessing the impact of electronic cigarettes on lung function.

Overall, combined pre- and postnatal ETS (combustion cigarette) increased the risk of new-onset asthma, of recurrent wheezing and of low-lung function. Prenatal ETS may increase the risk of new-onset asthma and of low lung function (low certainty evidence) and increases the risk of recurrent wheezing (moderate certainty evidence). The postnatal ETS increases the risk of new-onset asthma, especially when both parents smoked (moderate certainty evidence). The risk of recurrent wheezing is also increased when both parents or the mother are smoking (moderate certainty evidence). The risk of low lung function following postnatal ETS is controversial. Combined in utero and postnatal ETS may increase the risk of new-onset asthma (low certainty

evidence) and increases the risk of recurrent wheezing (moderate certainty evidence). Consistent findings were found when considering maternal smoking but not paternal smoking.

The second SR showed increased risk of severe asthma exacerbations (hospital admissions and emergency department visits), impaired asthma control, and decreased lung function following ETS (combustion cigarette) (moderate certainty evidence). There might be an impact on asthma-related quality of life (very low certainty evidence).

In the third SR, active smoking (combustion cigarette) was associated with increased risk of severe asthma exacerbations and of suboptimal asthma control (moderate certainty evidence) and may impact asthma-related quality of life and lung function (low certainty evidence).

Although the search protocol aimed to examine the burden of both active and passive exposure to e-cigarettes our systematic review found no studies that assessed the impact of ETS to e-cigarettes on the risk of developing asthma or on asthma-related outcomes. The only study that met the entry criteria was a crossover placebo-controlled RCT that examined the impact of a 1-h acute vaping session in 10 patients with asthma that provided low certainty evidence on the impact of this exposure on the pulmonary function. E-cigarette emissions typically contain nicotine and other toxic substances that are harmful to for active users or for those exposed passively, as they can increase the risk of heart disease and lung disorders. Some products claiming to be nicotine-free have been found to contain nicotine.<sup>10</sup> Thus, our SR reveals an important knowledge gap and calls for more high-quality research on the impact of e-cigarettes on lung health.

### 4.2 | Results in the context of previous research

Previous SRs had examined the impact of ETS (combustion or e-cigarette) on asthma-related outcomes,<sup>158-161</sup> on the risk of new-onset asthma,<sup>159,162-164</sup> and the effect of active smoking (combustion or e-cigarette) on asthma-related outcomes in adolescents or adults with asthma.<sup>159,165</sup>

Most of these previous SRs included cross-sectional studies, while our SR focused only on longitudinal evaluations. In addition, studies in which smoking was not considered as the primary exposure variable (i.e., studies including “smoking” as part of a wider group of exposures, e.g., alcohol and air pollution) were not included, while other SR report on the combined exposure to allergen, ETS, poor air quality, and unfueled heaters<sup>158</sup> or on psychosocial factors.<sup>161</sup>

It is also worth noting that our SR included only studies in which “hand exposure to smoking was the primary exposure variable.” This was an important criterion based on which we excluded references that had been included in previous SRs.

In terms of effect estimates, all the results from the previous SRs are consistent with our reports. The only relevant exception is the SR by Robijn et al.<sup>165</sup> reporting a significant impact of active smoking on the risk of asthma exacerbations (relative risk 1.35, 95% CI 1.04-1.75), whereas in our review we observed a minor effect (RR=1.03, 95%CI=0.79-1.35). We consider the focus on a specific

subpopulation of pregnant women a good explanation for the different result. In addition, the magnitude of ETS impact on asthma exacerbations in Robjin's SR should be judged in the context of possible interaction with other significant risk factors identified by the SR such as maternal age, multiparity, Black ethnicity, depression/anxiety, obesity, and asthma severity.<sup>165</sup>

The risk of bias was generally aligned with the previous systematic reviews. Importantly, it is not possible to directly compare our results of certainty of evidence assessment with previous systematic reviews, because none of them formally assessed the certainty of evidence using GRADE or any other equivalent method. In that aspect, our systematic review offers novel information not previously reported.

One SR evaluated the impact of e-cigarettes on asthma-related outcomes and reported a significant association between current e-cigarette use and asthma (pOR=1.36, 95% CI 1.21-1.52) and ever e-cigarette use and asthma (pOR=1.24 95% CI 1.13-1.36).<sup>166</sup> However, it included only cross-sectional studies and the heterogeneity and inconsistencies between covariates limits the interpretation of the results.

#### 4.3 | Limitations and strengths

Several strengths can be found in the current systematic review, including the application of rigorous methods, such as the use of the GRADE approach to assess the certainty of evidence. Furthermore, the questions and outcomes being assessed had been prioritized by the GDG. The results are presented in the format of summary of findings tables to optimally facilitate transparent communication between healthcare professionals, patients, regulatory bodies, and other interested parties.

There are limitations to this systematic review as well. Although the absolute effects were calculated versus the basal exacerbation rate, no subgroup or sensitivity analysis were conducted based on the basal exacerbation rate. Only studies published in English were included, although attempts were made to mitigate the potential for missing studies by handsearching through previously conducted systematic reviews and by incorporating additional studies suggested by the GDG. One major limitation is that we included only studies where smoking was the primary exposure and excluded studies where smoking was a part of a wider group of exposures. Thus, we cannot provide data on the combined impact of multiple exposures, like for example the interaction between aeroallergens and ETS as described by Dick et al in their systematic review.<sup>158</sup> We also exclude other contributing factors to asthma severity like psychosocial factors, evaluated by Shahunja et al. in their SR.<sup>160</sup> In addition, different from other SRs like SmokeHaz,<sup>159</sup> we do not report on other smoke-related comorbidities, such as lung cancer, sleep apnea or of tuberculosis, and other lower respiratory infections which might impact asthma severity as comorbidities. Similarly, for the risk of new-onset asthma our SR did not focus on the impact of ETS in the context of other risk factors such as atopic dermatitis, family history

of asthma and/or wheezing, or allergen sensitization as reported in the SR by Baol et al.<sup>163</sup> In addition, other combustible tobacco products (cigars, hookah/water pipes, and pipe) were excluded from this SR, although it was recently reported that they might increase the risk of new-onset asthma.<sup>167</sup> Another important limitation is that although asthma controller medication was evaluated as an important asthma-related outcome we do not report separate on the use and/or the dose or oral corticosteroids.

#### 4.4 | Implications for policy, practice, and research

This SR confirms that pre- and postnatal or combined exposure to tobacco smoke in various forms significantly increases the likelihood of children developing asthma, recurrent wheeze, or start their life with a low lung function. Our SR also supports the profound impact of ETS or of active smoking on asthma-related outcomes with increased risk of exacerbations, impaired asthma control, and lung function.

Consequently, parents and families should prioritize the prevention of any tobacco exposure, including among others good pregnancy habits, smoking cessation, and improving air quality within homes and playgrounds.

At the societal level it has become evident that a considerable part of the increase in asthma prevalence worldwide is due to maternal smoking in pregnancy or due to early-life exposure of children to environmental tobacco smoke acting through epigenetic transgenerational effects.<sup>24-26,168</sup> Thus, the decision-makers should implement regulations to ensure a clean and healthy environment through prenatal education, environmental preservation, smoking policy bans and comprehensive smoking cessation programs, advertising bans and information hazards on packaging, all specifically aimed at safeguarding the well-being of healthy children and of patients with asthma. For example, Article 8 of the WHO Framework Convention on Tobacco Control and the Guidelines for its implementation also call on all parties to prohibit smoking in outdoor or quasi-outdoor places, appropriately based on evidence as to the possible health hazards. Sadly, the implementation of this regulation in low- and middle-income countries is very much hampered by socioeconomic and political reasons and thus we observe an acceleration in asthma prevalence and severity in these countries.

It is well-established that tobacco cessation is a cost-effective measure and it has been shown that smoking cessation impacts asthma patients' overall health and physical status, as well as their asthma prognosis.<sup>169</sup> Thus, its impact on mitigating the adverse effects of tobacco exposure on asthma-related outcomes should be further thoroughly investigated.

Our SR shows that the direct evidence on the impact of tobacco smoke on asthma is low to moderate certainty and a causal association cannot be claimed. In addition, there is lack of progress in better understanding the smoker asthma phenotype due to the exclusion of smokers and former smokers from most investigative studies and large clinical trials.

Thus, better quality research is warranted to explore the causal association between ETS and asthma-related outcomes. Increasing the quality of the evidence should involve the implementation of standardized methods for assessing and documenting smoke exposure, while distinguishing between parental and other household, occupational or environmental sources of smoke. Objective measures of tobacco exposure, such as urine and/or salivary cotinine measurements, should also be employed. Moreover, comprehensive studies with a sufficiently large sample size should employ validated scoring systems to assess symptoms and utilize objective data through pulmonary function testing.

As most of the studies focused on exposure to combustion cigarettes, while e-cigarettes are frequently marketed as “a safer alternative.” Future studies investigating the causal association between e-cigarette use and asthma are urgently needed.

#### AUTHOR CONTRIBUTIONS

Ioana Agache, Ignacio Ricci Cabello, Pablo Alonso-Coello, Marek Jutel and Cezmi Akdis drafted the detailed protocols for the systematic reviews, supervised the overall research process and wrote the manuscript. Carlos Canelo-Aybar, Josephina Salazar, Miquel Colom, Maria Antònia Fiol, Lucía Gorreto, Narges Malih, Laura Moro, Marina García Pardo, Patricia García Pazo, Rocío Zamanillo Campos, conducted the searches and the analysis under the supervision of Ignacio Ricci Cabello and Pablo Alonso-Coello. All the other authors revised and approved the search protocols, revised the data from the systematic reviews and the final manuscript.

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#### CONFLICT OF INTEREST STATEMENT

Ioana Agache reports Deputy Editor of Allergy journal. Marek Jutel reports personal fees outside of submitted work from Allergopharma, ALK-Abello, Stallergenes, Anergis, Allergy Therapeutics, Leti, HAL, GSK, Novartis, Teva, Takeda, Chiesi, Pfizer, Regeneron, Astra-Zeneca, Lallemand, Shire, Celltrion Inc., Genentech, Roche, Verona, Lek Pharmaceuticals, Arcutis Biotherapeutics, and FAES FARMA. Kari Nadeau reports grants from National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Environmental Health Sciences (NIEHS), and Food Allergy Research & Education (FARE); Stock options from IgGenix, Seed Health, ClostraBio, Cour, Alladapt; Advisor at Cour Pharma; Consultant for Excellergy, Red tree ventures, Before Brands, Alladapt, Cour, Latitude, Regeneron, and IgGenix; Co-founder of Before Brands, Alladapt, Latitude, and IgGenix; National Scientific Committee member at Immune Tolerance Network (ITN), and National Institutes of Health (NIH) clinical research centers; patents include, “Mixed allergen composition and methods for using the same,” “Granulocyte-based methods for detecting and monitoring immune system disorders,” and “Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders.” Fan Chung has received honoraria for participating in Advisory Board meetings of GSK, AZ, Roche, Merck, Shionogi, and Rickett-Beckinson, for speaking

engagements for Novartis, GSK, and AZ, and for participating on the Scientific Advisory Board of the Clean Breathing Institute supported by Haleon. He has received research funding through his institution, Imperial College London, from UK Research and Innovation and the US National Institute for Environmental Health Sciences on air pollution and respiratory health, and on precision medicine for asthma, from GSK on eosinophils and asthma, and from Merck on ATP and chronic cough. Santiago Quirce has been on advisory boards for and has received speaker's honoraria from Allergy Therapeutics, AstraZeneca, GlaxoSmithKline, Novartis, Chiesi, Mundipharma, and Sanofi. Stephen Holgate reports being member of Dyson SAB on clean air, cofounder and NEB member of Synairgen (spin-out respiratory company developing inhaled anti-viral Interferon beta), advisor to Healthy Air Technology (Air purifiers), special Advisor to the Royal College of Physicians on Air Quality, UKRI Clean Air Champion, and Chair of MRC Joint Steering Committee EMINENT (Experimental Medicine Initiative to Explore New Therapies). IRC, PAC, CCA, JS, MC, MAF, LG, NM, LM, MGP, PGP, and RZC work for Centro Cochrane Iberoamericano; the center received funding for conducting the systematic reviews of the evidence. All the other authors report no COIs in relation to the manuscript.

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## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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