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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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## Conflict of interest statement

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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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**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 = randomised 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

ABSTRACT

To inform the Clinical Practice Guidelines recommendations developed by the European Academy of Allergy and Clinical Immunology systematic reviews (SR) assessed using GRADE the impact of environmental tobacco smoke (ETS) and active smoking on the risk of new-onset asthma/recurrent wheeze (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 asthma and of RW (moderate certainty evidence) and may impact LF (low certainty evidence). Combined in utero and post-natal 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).

## 1 | INTRODUCTION

Asthma is a prevalent chronic disease, which poses a significant global public health challenge, impacting worldwide more then 300 million individuals across all age groups (1, 2). 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 under-diagnosis and under-treatment. These countries also have a high prevalence of active or passive exposure to tobacco smoke (3,4,5).

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 (3,4,5).

Tobacco smoke comprises a complex mixture of over 6000 chemical compounds, including, potent respiratory irritants and immune modulators like acrolein, acrylamide, formaldehyde, sulphur dioxide, and ammonia, besides nicotine (6,7,8,9). The World Health Organization (WHO) has nominated nine key toxic substances: N-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanon, acetaldehyde, acrolein, benzene, benzo[a]pyrene, 1,3-butadiene, carbon monoxide and formaldehyde (10).

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 wheeze, 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 (11,12,13,14,15,16,17,18,19,20,21). 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 (22,23). 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 over-production of epithelial derived cytokines, impaired response to infections, mucus hypersecretion, oxidative stress, amplification of the type 2 (T2) and non-T2 chronic airway inflammation (7,8, 24,25,26,27,28,29,30,31,32,33,34,35,36,37,38). 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 (17). There is now increasing evidence that alpha7 nicotinic acetylcholine receptors are critical players in nicotine effects on airways (7).

The specific aims of these systematic reviews (SR) and meta-analyses are to synthesise 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 post-natal or combined pre- and post-natal 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; 1–3 of limited importance), (39). 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], 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 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, air pollution, etc.) 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 (40). 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-randomised studies, the ROB was assessed by applying the Risk Of Bias In Non-randomised Studies of Exposures (ROBINS-E) tool (41). 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 & 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.(42) A $p$-value of the Q-Cochran test <0.10 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 or 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 (43) 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 (44). 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 (45).

## 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(26, 46-111) (Table S3), 24 publications met the eligibility criteria for Q2 (91, 112-134) (Table S4), and 25 studies for Q3 (122, 130, 135-157) (Table S5).

### 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 844003 participants. The mean (range) proportion of female participants was 47.9% (25.6% to 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, seven (29%) in Europe, two in Asia (8%) and one in Australia (4%). Most studies had an observational design (14 prospective cohort studies, two 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% to 100%). Nine studies presented a high ROB, 14 a moderate ROB, and one 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 one quasi-experimental study. The number of included participants included ranged from 10 to 17480 participants. The mean (range) proportion of females was 62% (15% to 100%). 21 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 – S1L. 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 (pre-natal exposure)

Thirty-one studies reported on the impact of pre-natal exposure to combustion smoking on new-onset asthma (table S3A). The pooled analysis from 23 studies (Figure S1A) showed that pre-natal; 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<0.001) (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<0.001).

#### 3.3.2| Recurrent wheezing (pre-natal exposure)

Twenty-three studies examined the impact of pre-natal exposure to combustion smoking on the risk of recurrent wheezing (table 3A). Pooled adjusted results from 21 studies (Figure S1C) showed that pre-natal 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<0.001) (moderate certainty evidence). The 2 studies not included in the meta-analysis (due to unavailable data), also suggested that pre-natal exposure to combustion smoking could increase the risk of recurring wheezing (47, 70). 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=0.283) (Figure S1D).

#### 3.3.3| Low lung function (pre-natal exposure)

Three studies reported the impact of pre-natal exposure to smoking on incident low lung function (59, 64, 91). These studies presented results using different effect size measures (mean differences, OR, and percent changes) and lung function measures (FEV1 and FEV/FVC), which precluded from pooling their results. One study (59) 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 (64) 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 (91) suggested that pre-natal tobacco exposure was associated with decreased FEV1 (adjusted mean difference= -0.07 L, 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 (post-natal exposure)

The SR identified 16 studies examining the impact of post-natal ETS (combustion smoke) on the risk of new-onset asthma (Table S3B). The metanalysis of 13 studies (Figure S1E) reporting adjusted estimates shows that post-natal 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=0.007) (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=0.956) 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=0.006) or the father smoking (OR=1.05; 95%CI=0.96-1.14; $I^2$=0%; Q-Cochran test *p*-value=0.775) (Figure S1F).

3.3.5| Recurrent wheezing (post-natal exposure)

Seventeen studies examined the impact of post-natal 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=0.155) (moderate certainty evidence). The pooled estimate was consistent with the findings from the other 2 studies not included in the meta-analysis (57, 70). 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=0.820) or when only the mother smoked (OR=1.36; 95%CI=1.06-1.74; $I^2$=56.8%; Q-Cochran test *p*-value=0.031) (Figure S1H).

3.3.6| Low lung function (post-natal 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; FEV/FVC), which precluded from pooling their results. One prospective cohort study (57) observed that, for each person smoking indoors, ETS was associated with an average decrease in FEV1 of 0.30% (6.8 mL). Another study (59) reported no significant detrimental effects on lung function from ETS (effect estimates not reported). A third study (87) 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 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 (98). Overall, the certainty of evidence was considered low.

3.3.7| New-onset asthma (combined pre- and post-natal exposure)

Ten studies examined the impact of pre- and postnatal ETS (combustion smoke) on the risk of new-onset asthma (Table 3 C). 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<0.001) (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=0.026) but not for paternal smoking (OR=1.52; 95%CI=0.73-3.16; $I^2$=98%; Q-Cochran test *p*-value<0.001) (Figure S1J).

3.3.8| Recurrent wheezing (combine pre- and post-natal 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) suggests 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=0.007) (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=0.232) (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 – S1I. 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 (116, 117, 121), while one study examined hospital admissions during pregnancy (130). 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=0.158) (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 (118, 121). 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 (91, 115, 116, 126, 134) 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, heart and respiratory rate), in another as a combined composite index (the need for oral prednisolone or high dose ICS, or need for hospitalisation), while the other 3 studies provided no definition for asthma exacerbations. Pooled data from the three 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=0.728) (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=0.800) (moderate certainty of evidence). The pooled estimate was supported by the findings from the other 5 studies (82, 83, 87, 95, 98) not included in the metanalysis. 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 assesed the impact of ETS on asthma-related QoL (117, 118, 126). Pooled data from these 3 studies (Figure S2G, Table 3) suggests 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=0.153) (very low certainty evidence).

#### 3.4.5 | Lung function (acute exposure)

Six experimental studies (120, 124, 125, 128, 131, 132) 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 hours. Pooled data from 3 studies (Figure S2H) suggests 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=0.861) (very low certainty evidence). The other 3 studies not included in the metanalysis reported inconsistent results (Table 3).

3.4.6 | Lung function (long-term exposure)

Eight studies (112, 115, 122, 126, 127, 129, 130, 133) 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=0.427) (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 (127) 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 (112, 116, 117) 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 Tables 4A and 4B and detailed in Figures S3 A – F.

3.5.1 | Severe asthma exacerbations (combustion cigarette smoking)

The SR identified 4 studies (99, 137, 149, 156) 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=0.734) (moderate certainty evidence).

One study (150) reported severe asthma exacerbations defined as a worsening of respiratory symptoms for more than 24h and requiring treatment with systemic corticosteroids for at least three 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 non-smokers. 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 non-smokers (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<0.001) (moderate certainty evidence). The observed increased risk is supported by the findings of 5 studies not included in the meta-analysis (122, 142, 146, 148, 152).

3.5.3 | Quality of Life (combustion cigarette smoking)

Four studies examined the impact of smoking asthma-related QoL (139, 144, 145, 152). Pooled data from 2 of these studies (Figures S3C and S3D) 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<0.001) (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 (157) provided adjusted estimates (Figure S3E) and suggested that active smoking may decrease mean FEV1% (pooled MD = (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 one-hour 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 (135). The experiment found no significant impact of the one-hour 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 non-smokers 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 (156). After 12 months follow-up there were no significant differences between non-smokers 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 >0.05) 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 post-natal ETS (combustion cigarette) increased the risk of new-onset asthma, of recurrent wheezing and of low-lung function. Pre-natal 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 post-natal 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 post-natal ETS is controversial. Combined in utero and post-natal 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-cigarretes our systematic review found no studies that assesed 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 one-hour 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 (10). Thus, our SR reveals an important knowledge gap and calls for more high-quality research on the impact of e-cigarretes 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(158-161), on the risk of new-onset asthma (159, 162-164), and the effect of active smoking (combustion or e-cigarette) on asthma related outcomes in adolescents or adults with asthma (159, 165).

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, air pollution, etc.) were not included, while other SR report

on the combined exposure to allergen, ETS, poor air quality and unfuelled heaters (158) or on psycho-social factors (161).

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 (165) 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 to 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 (165).

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) (166). 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 hand-searching 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 (158). We also exclude other contributing factors to asthma severity like psycho-social factors, evaluated by Shahunja et al in their SR (160). In addition, different from other SRs like SmokeHaz (159), we do not report on other smoke-related co-morbidities, such as lung cancer, sleep apnoea or of tuberculosis and other lower respiratory infections which might impact asthma severity as co-morbidities. 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 (163). In addition, other combustible tobacco products (cigars, hookah/water pipes, pipe) were excluded from this SR, although it was recently reported that they might increase the risk of new-onset asthma (167). 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 post-natal 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, etc.

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 (24,25,26,168). 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 programmes, 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 socio-economic 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 (169). 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,

752 comprehensive studies with a sufficiently large sample size should employ validated
753 scoring systems to assess symptoms and utilize objective data through pulmonary
754 function testing.

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

758 **References**

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761 1. Asher MI, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide
762 asthma prevalence. European Respiratory Journal. 2020;56(6).

763 2. Agache I, Annesi-Maesano I, Bonertz A, Branca F, Cant A, Fras Z, et al.
764 Prioritizing research challenges and funding for allergy and asthma and the need
765 for translational research-The European Strategic Forum on Allergic Diseases.
766 Allergy. 2019;74(11):2064-2076

767 3. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global
768 burden of 369 diseases and injuries in 204 countries and territories, 1990–2019:
769 a systematic analysis for the Global Burden of Disease Study 2019. The Lancet.
770 2020;396(10258):1204-22.

771 4. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204
772 countries and territories, 1990-2019: a systematic analysis for the Global Burden
773 of Disease Study 2019. Lancet. 2020;396(10258):1223-1249

774 5. GBD 2019 Tobacco Collaborators. Spatial, temporal, and demographic patterns
775 in prevalence of smoking tobacco use and attributable disease burden in 204
776 countries and territories, 1990-2019: a systematic analysis from the Global
777 Burden of Disease Study 2019. Lancet. 2021 ;397(10292):2337-2360

778 6. Pappas RS. Toxic elements in tobacco and in cigarette smoke: inflammation and
779 sensitization. Metallomics. 2011;3(11):1181-98

780 7. Borkar NA, Thompson MA, Bartman CM, Khalfaoui L, Sine SM, Sathish V, et al.
781 Nicotinic Receptors in Airway Disease. Am J Physiol Lung Cell Mol Physiol. 2024;
782 326(2):L149-L163

783 8. Hikisz P, Jacenik D. The Tobacco Smoke Component, Acrolein, as a Major
784 Culprit in Lung Diseases and Respiratory Cancers: Molecular Mechanisms of
785 Acrolein Cytotoxic Activity. Cells. 2023;12(6):879

786 9. Su HH, Cheng CM, Yang YN, Chang YW, Li CY, Wu ST, Lin CC, Wu HE, Suen
787 JL. Acrylamide, an air pollutant, enhances allergen-induced eosinophilic lung
788 inflammation via group 2 innate lymphoid cells. Mucosal Immunol. 2023:S1933-
789 0219(23)00073-9

790 10. https://www.who.int/news-room/fact-sheets/detail/tobacco; accessed 20 Dec
791 2023

11. Kilanowski A, Thiering E, Wang G, Kumar A, Kress S, Flexeder C, et al. Allergic disease trajectories up to adolescence: Characteristics, early-life, and genetic determinants. Allergy. 2023;78(3):836-850

12. Chung SJ, Kim BK, Oh JH, Shim JS, Chang YS, Cho SH, et al. Novel tobacco products including electronic cigarette and heated tobacco products increase risk of allergic rhinitis and asthma in adolescents: Analysis of Korean youth survey. Allergy. 2020;75(7):1640-1648

13. Forster F, Ege MJ, Gerlich J, Weinmann T, Kreißl S, Weinmayr G, Genuneit J, Nowak D, von Mutius E, Vogelberg C, Radon K. Trajectories of asthma and allergy symptoms from childhood to adulthood. Allergy. 2022;77(4):1192-1203

14. Xepapadaki P, Manios Y, Liarigkovinos T, Grammatikaki E, Douladiris N, Kortsalioudaki C, et al. Association of passive exposure of pregnant women to environmental tobacco smoke with asthma symptoms in children. Pediatr Allergy Immunol. 2009;20(5):423-9

15. Anderson J, Do LAH, Wurzel D, Licciardi PV. Understanding the increased susceptibility to asthma development in preterm infants. Allergy. 2023;78(4):928-939

16. Chen T, Shi S, Li X, Zhou L, Yu Y, Cai Y, et al. Improved ambient air quality is associated with decreased prevalence of childhood asthma and infancy shortly after weaning is a sensitive exposure window. Allergy. 2023 Jul 17. doi: 10.1111/all.15815. Epub ahead of print

17. McEvoy CT, Spindel ER. Pulmonary Effects of Maternal Smoking on the Fetus and Child: Effects on Lung Development, Respiratory Morbidities, and Life Long Lung Health. Paediatr Respir Rev. 2017;21:27-33.

18. Greiner B, Elenwo C, Hartwell M. Increased serum cotinine and obesity negatively impact asthma exacerbations and hospitalizations: A cross-sectional analysis of NHANES. J Clin Transl Sci. 2022;7(1):e10

19. Comhair SA, Gaston BM, Ricci KS, Hammel J, Dweik RA, Teague WG, et al; National Heart Lung Blood Institute Severe Asthma Research Program. Detrimental effects of environmental tobacco smoke in relation to asthma severity. PLoS One. 2011;6(5):e18574

20. Lin T, Pham J, Denton E, Lee J, Hore-Lacy F, Sverrild A, et al. Trait profiles in difficult-to-treat asthma: Clinical impact and response to systematic assessment. Allergy. 2023;78(9):2418-2427

21. Neophytou AM, Oh SS, White MJ, Mak ACY, Hu D, Huntsman S, et al. Secondhand smoke exposure and asthma outcomes among African-American and Latino children with asthma. Thorax. 2018;73(11):1041-1048

22. Delmas MC, Pasquereau A, Renuy A, Bénézet L, Ribet C, Zins M, et al. Electronic cigarette use and respiratory symptoms in the French population-based Constances cohort. Respir Med. 2023:107496

23. Tackett AP, Urman R, Barrington-Trimis J, Liu F, Hong H, Pentz MA, et al. Prospective study of e-cigarette use and respiratory symptoms in adolescents and young adults. Thorax. 2024;79(2):163-168.

24. Reddy KD, Lan A, Boudewijn IM, Rathnayake SNH, Koppelman GH, Aliee H, et al. Current Smoking Alters Gene Expression and DNA Methylation in the Nasal Epithelium of Patients with Asthma. Am J Respir Cell Mol Biol. 2021;65(4):366-377

25. Thürmann L, Klös M, Mackowiak SD, Bieg M, Bauer T, Ishaque N, et al. Global hypomethylation in childhood asthma identified by genome-wide DNA-methylation sequencing preferentially affects enhancer regions. Allergy. 2023;78(6):1489-1506

26. Accordini S, Calciano L, Johannessen A, Portas L, Benediktsdóttir B, Bertelsen RJ, et al; Ageing Lungs in European Cohorts (ALEC) Study. A three-generation study on the association of tobacco smoking with asthma. Int J Epidemiol. 2018;47(4):1106-1117

27. McAlees JW, Baker T, Kaur D, McKnight C, Lindsley A, Strait RT, Zhang X, Biagini Myers JM, Butsch Kovacic M, Lewkowich IP. Age and early maternal smoking contribute to epithelial cell IL-13 responsiveness in a pediatric asthma population. Allergy. 2019;74(12):2485-248

28. Klingbeil EC, Hew KM, Nygaard UC, Nadeau KC. Polycyclic aromatic hydrocarbons, tobacco smoke, and epigenetic remodeling in asthma. Immunol Res. 2014;58(2-3):369-73

29. Heijink IH, Kuchibhotla VNS, Roffel MP, Maes T, Knight DA, Sayers I, Nawijn MC. Epithelial cell dysfunction, a major driver of asthma development. Allergy. 2020;75(8):1902-1917

30. Celebi Sozener Z, Ozdel Ozturk B, Cerci P, Turk M, Gorgulu Akin B, et al. Epithelial barrier hypothesis: Effect of the external exposome on the microbiome and epithelial barriers in allergic disease. Allergy. 2022;77(5):1418-1449

31. Agache I, Miller R, Gern JE, Hellings PW, Jutel M, Muraro A, et al. Emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma: a Practall document. Allergy. 2019;74(3):449-463

32. Jutel M, Mosnaim GS, Bernstein JA, Del Giacco S, Khan DA, Nadeau KC, et al. The One Health approach for allergic diseases and asthma. Allergy. 2023;78(7):1777-1793.

33. Mertens TCJ, van der Does AM, Kistemaker LE, Ninaber DK, Taube C, Hiemstra PS. Cigarette smoke differentially affects IL-13-induced gene expression in human airway epithelial cells. Physiol Rep. 2017;5(13):e13347

34. Emma R, Bansal AT, Kolmert J, Wheelock CE, Dahlen SE, Loza MJ, et al; U-BIOPRED Study Group. Enhanced oxidative stress in smoking and ex-smoking severe asthma in the U-BIOPRED cohort. PLoS One. 2018;13(9):e0203874

35. Uchida M, Anderson EL, Squillace DL, Patil N, Maniak PJ, Iijima K, et al. Oxidative stress serves as a key checkpoint for IL-33 release by airway epithelium. Allergy. 2017;72(10):1521-1531

36. Bucchieri F, Marino Gammazza A, Pitruzzella A, Fucarino A, Farina F, Howarth P, et al. Cigarette smoke causes caspase-independent apoptosis of bronchial epithelial cells from asthmatic donors. PLoS One. 2015;10(3):e0120510

37. Törmänen S, Lauhkonen E, Riikonen R, Koponen P, Huhtala H, Helminen M, Korppi M, Nuolivirta K. Risk factors for asthma after infant bronchiolitis. Allergy. 2018;73(4):916-922

38. Thomson NC, Chaudhuri R, Spears M, Messow CM, Jelinsky S, Miele G, Nocka K, Takahashi E, Hilmi OJ, Shepherd MC, Miller DK, McSharry C. Arachidonic acid metabolites and enzyme transcripts in asthma are altered by cigarette smoking. Allergy. 2014;69(4):527-36

39. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiology. 2011;64(4):395-400

40. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928

41. Wang WW, Zhou QX, Ma L, Feng SH, Yang ZR, Sun F, et al. [Introduction of a tool to assess Risk of Bias in Non-randomized Studies-of Environmental Exposure (ROBINS-E)]. Zhonghua Liu Xing Bing Xue Za Zhi. 2022;43(1):98-104

42. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I2 in assessing heterogeneity may mislead. BMC Medical Research Methodology. 2008;8(1):79

43. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ 2020;192(32):E90

44. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2

45. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020;119:126-35

46. Alati R, Al Mamun A, O'Callaghan M, Najman J, Williams G. In utero and postnatal maternal smoking and asthma in adolescence. Epidemiology 2006;17(2):138-44.

47. Bentouhami H, Casas L, Weyler J. The Association between the Occurrence of Asthma and Antecedents of Exposure to Environmental Tobacco Smoke in the Previous Year in Children: An Incidence-Density Study. Int J Environ Res Public Health. 2022;19(5).

48. Bjerg A, Hedman L, Perzanowski M, Lundbäck B, Rönmark E. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. Pediatrics. 2011;127(4):e905-12.

49. Braback L, Lodge CJ, Lowe AJ, Dharmage SC, Olsson D, Forsberg B. Childhood asthma and smoking exposures before conception-A three-generational cohort study. Pediatr Allergy Immunol. 2018;29(4):361-8.

50. Carlsten C, Dimich-Ward H, DyBuncio A, Becker AB, Chan-Yeung M. Cotinine versus questionnaire: early-life environmental tobacco smoke exposure and incident asthma. BMC Pediatr. 2012;12:187.

51. Ciaccio CE, DiDonna A, Kennedy K, Barnes CS, Portnoy JM, Rosenwasser LJ. Secondhand tobacco smoke exposure in low-income children and its association with asthma. Allergy Asthma Proc. 2014;35(6):462-6.

52. Dai X, Dharmage SC, Lowe AJ, Allen KJ, Thomas PS, Perret J, et al. Early smoke exposure is associated with asthma and lung function deficits in adolescents. J Asthma. 2017;54(6):662-9.

53. den Dekker HT, Voort A, de Jongste JC, Reiss IK, Hofman A, Jaddoe VWV, et al. Tobacco Smoke Exposure, Airway Resistance, and Asthma in School-age Children: The Generation R Study. Chest. 2015;148(3):607-17.

54. Dezateux C, Stocks J, Dundas I, ME F. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. Am J Respir Crit Care Med. 1999;159(2):403-10.

55. Duijts L, Jaddoe V, van der Valk R, Henderson J, Hofman A, Raat H, et al. Fetal exposure to maternal and paternal smoking and the risks of wheezing in preschool children: the Generation R Study. Chest. 2012;141(4):876-85.

56. Fergusson D, Horwood L. Parental smoking and respiratory illness during early childhood: a six-year longitudinal study. Pediatr Pulmonol. 1985;1(2):99-106.

57. Fernández-Plata R, Rojas-Martínez R, Martínez-Briseño D, García-Sancho C, Pérez-Padilla R. Effect of Passive Smoking on the Growth of Pulmonary Function and Respiratory Symptoms in Schoolchildren. Rev Invest Clin; 2016;68(3):119-27.

58. Fuentes-Leonarte V, Estarlich M, Ballester F, Murcia M, Esplugues A, Aurrekoetxea J, et al. Pre- and postnatal exposure to tobacco smoke and respiratory outcomes during the first year. Indoor air. 2015;25(1):4-12.

59. Gilliland F, Berhane K, Li Y, Rappaport E, Peters J. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. Am J Resp Crit Care Med. 2003;167(6):917-24.

60. Gilliland F, Islam T, Berhane K, Gauderman W, McConnell R, Avol E, et al. Regular smoking and asthma incidence in adolescents. Am J Resp Crit Care Med. 2006;174(10):1094-100.

61. Grazuleviciene R, Andrusaityte S, Uzdanaviciute I, Kudzyte J, Kevalas R, Nieuwenhuijsen M. The impact of tobacco smoke exposure on wheezing and overweight in 4-6-year-old children. Biomed Res Int. 2014;2014:240757.

62. Håberg S, Stigum H, Nystad W, Nafstad P. Effects of pre- and postnatal exposure to parental smoking on early childhood respiratory health. Am J Epidemiol. 2007;166(6):679-86.

63. Harju M, Keski-Nisula L, Georgiadis L, Heinonen S. Parental smoking and cessation during pregnancy and the risk of childhood asthma. BMC public health. 2016;16:428.

64. Henderson A, Newson R, Rose-Zerilli M, Ring S, Holloway J, Shaheen S. Maternal Nrf2 and gluthathione-S-transferase polymorphisms do modinot fy associations of prenatal tobacco smoke exposure with asthma and lung function in school-aged children. Thorax. 2010;65(10):897-902.

65. Hunt A, Crawford J, Rosenbaum P, Abraham J. Levels of household particulate matter and environmental tobacco smoke exposure in the first year of life for a cohort at risk for asthma in urban Syracuse, NY. Environ Int. 2011;37(7):1196-205.

66. Jaakkola J, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health. 2004;94(1):136-40.

67. Jaakkola J, Gissler M. Are girls more susceptible to the effects of prenatal exposure to tobacco smoke on asthma? Epidemiology. 2007;18(5):573-6.

68. Jaakkola J, Nafstad P, Magnus P. Environmental tobacco smoke, parental atopy, and childhood asthma. Environ Health Perspect. 2001;109(6):579-82.

69. Johansson E, Martin L, He H, Chen X, Weirauch M, Kroner J, et al. Second-hand smoke and NFE2L2 genotype interaction increases paediatric asthma risk and severity. Clin Exp Allergy 2021;51(6):801-10.

70. Karmaus W, Dobai AL, Ogbuanu I, Arshard SH, Matthews S, Ewart S. Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. J Asthma. 2008;45(8):688-95.

71. Keil T, Lau S, Roll S, Grüber C, Nickel R, Niggemann B, et al. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. Allergy. 2009;64(3):445-51.

72. Lannerö E, Wickman M, Pershagen G, Nordvall SL. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). Respir Res. 2006;7.

73. Lin M, Caffrey J, Lin Y, Chen P, Lin C, Ho W, et al. Low birth weight and environmental tobacco smoke increases the risk of wheezing in adolescents: a retrospective cohort study. BMC Public Health. 2014;14:688.

74. Lundholm C, Gunnerbeck A, D'Onofrio B, Larsson H, Pershagen G, Almqvist C. Smoking and snuff use in pregnancy and the risk of asthma and wheeze in pre-schoolchildren-A population-based register study. Clin Exp Allergy 2020;50(5):597-608.

75. Magnus M, Håberg S, Karlstad Ø, Nafstad P, London S, Nystad W. Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian Mother and Child Cohort Study. Thorax. 2015;70(3):237-43.

76. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy. 2005;35(12):1550-6.

77. McConnochie K, Roghmann K. Breast feeding and maternal smoking as predictors of wheezing in children age 6 to 10 years. Pediatr Pulmonol. 1986;2(5):260-8.

78. Menezes A, Hallal P, Muiño A, Chatkin M, Araújo C, Barros F. Risk factors for wheezing in early adolescence: a prospective birth cohort study in Brazil. Ann Allergy Asthma Immunol. 2007;98(5):427-31

79. Moradzadeh R, Mansournia M, Baghfalaki T, Nadrian H, Gustafson P, McCandless L. The impact of maternal smoking during pregnancy on childhood asthma: adjusted for exposure misclassification; results from the National Health and Nutrition Examination Survey, 2011-2012. Ann Epidemiol. 2018;28(10):697-703.

80. Neuman Å, Hohmann C, Orsini N, Pershagen G, Eller E, Kjaer H, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. Am J Respir Crit Care Med.2012;186(10):1037-43.

81. Neuspiel D, Rush D, Butler N, Golding J, Bijur P, Kurzon M. Parental smoking and post-infancy wheezing in children: a prospective cohort study. Am J Public Health. 1989;79(2):168-71

82. Pattemore P, Silvers K, Frampton C, Wickens K, Ingham T, Fishwick D, et al. Hair nicotine at 15 months old, tobacco exposure and wheeze or asthma from 15 months to 6 years old. Pediatr pulmonol. 2018;53(4):443-51.

83. Ramadas RA, Sadeghnejad A, Karmaus W, Arshad SH, Matthews S, Huebner M, et al. Interleukin-1R antagonist gene and pre-natal smoke exposure are associated with childhood asthma. Eur Respir J. 2007;29(3):502-8.

84. Rivas-Juesas C, Monge L, Vicente A, García A, Crespo M, Sinisterra A. Maternal smoking during pregnancy and asthma during the first year of life: a comparative study between smokers and nonsmoker mothers. Allergol Immunopathol. 2021;49(5):32-41.

85. Robison R, Kumar R, Arguelles L, Hong X, Wang G, Apollon S, et al. Maternal smoking during pregnancy, prematurity and recurrent wheezing in early childhood. Pediatr pulmonol. 2012;47(7):666-73.

86. Scherman A, Spindel E, Park B, Tepper R, Erikson D, Morris C, et al. Maternal Prenatal Hair Cortisol Is Associated with Child Wheeze among Mothers and Infants with Tobacco Smoke Exposure and Who Face High Socioeconomic Adversity. Int J Environ Res Public Health. 2021;18(5).

87. Sherrill DL, Martinez FD, Lebowitz MD, Holdaway MD, Flannery EM, Herbison GP, et al. Longitudinal effects of passive smoking on pulmonary function in New Zealand children. Am Rev Respir Dis. 1992;145(5):1136-41.

88. Snodgrass A, Tan P, Soh S, Goh A, Shek L, van Bever H, et al. Tobacco smoke exposure and respiratory morbidity in young children. Tob Control. 2016;25:e75-e82.

89. Spanier A, Kahn R, Xu Y, Hornung R, Lanphear B. Comparison of biomarkers and parent report of tobacco exposure to predict wheeze. J Pediatr. 2011;159(5):776-82.

90. Stein RT, Holberg CJ, Sherrill D, Wright AL, Morgan WJ, Taussig L, et al. Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. Am J Epidemiol. 1999;149(11):1030-7.

91. Sunde R, Thorsen J, Pedersen C, Stokholm J, Bønnelykke K, Chawes B, et al. Prenatal tobacco exposure and risk of asthma and allergy outcomes in childhood. The Eur Resp J. 2022;59(2).

92. Svanes C, Koplin J, Skulstad SM, Johannessen A, Bertelsen RJ, Benediktsdottir B, et al. Father's environment before conception and asthma risk in his children: a multi-generation analysis of the Respiratory Health In Northern Europe study. Int J Epidemiol. 2017;46(1):235-45.

93. Tabuchi T, Fujiwara T, Nakayama T, Miyashiro I, Tsukuma H, Ozaki K, et al. Maternal and paternal indoor or outdoor smoking and the risk of asthma in their children: a nationwide prospective birth cohort study. Drug Alcohol Depend. 2015;147:103-8.

94. Tanaka K, Arakawa M, Miyake Y. Perinatal smoking exposure and risk of asthma in the first three years of life: A prospective prebirth cohort study. Allergol Immunopathol. 2020;48(6):530-6.

95. Tanaka K, Miyake Y, Furukawa S, Arakawa M. Secondhand smoke exposure and risk of wheeze in early childhood: a prospective pregnancy birth cohort study. Tob Induc Dis. 2017;15:30.

96. Tanaka K, Miyake Y, Sasaki S, Ohya Y, Hirota Y. Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka Maternal and Child Health Study. J Asthma 2008;45(9):833-8.

97. Tariq S, Hakim E, Matthews S, Arshad S. Influence of smoking on asthmatic symptoms and allergen sensitisation in early childhood. Postgrad Med J. 2000;76(901):694-9.

98. Tashkin D, Clark V, Simmons M, Reems C, Coulson A, Bourque L, et al. The UCLA population studies of chronic obstructive respiratory disease. VII. Relationship between parental smoking and children's lung function. Am Rev Respir Dis. 1984;129(6):891-7.

99. Thacher J, Gruzieva O, Pershagen G, Neuman Å, Wickman M, Kull I, et al. Pre- and postnatal exposure to parental smoking and allergic disease through adolescence. Pediatrics. 2014;134(3):428-34.

100. Thacher JD, Gehring U, Gruzieva O, Standl M, Pershagen G, Bauer CP, et al. Maternal Smoking during Pregnancy and Early Childhood and Development of Asthma and Rhinoconjunctivitis - a MeDALL Project. Environ Health Perspect. 2018;126(4):047005.

101. Vanker A, Barnett W, Workman L, Nduru P, Sly P, Gie R, et al. Early-life exposure to indoor air pollution or tobacco smoke and lower respiratory tract illness and wheezing in African infants: a longitudinal birth cohort study. Lancet Planet Health. 2017;1(8):e328-e36.

102. Vardavas C, Hohmann C, Patelarou E, Martinez D, Henderson A, Granell R, et al. The independent role of prenatal and postnatal exposure to active and passive smoking on the development of early wheeze in children. Eur Respir J 2016;48(1):115-24.

103. Wada T, Adachi Y, Murakami S, Ito Y, Itazawa T, Tsuchida A, et al. Maternal exposure to smoking and infant's wheeze and asthma: Japan Environment and Children's Study. Allergol Int. 2021;70(4):445-51.

104. Wang C, Salam M, Islam T, Wenten M, Gauderman W, Gilliland F. Effects of in utero and childhood tobacco smoke exposure and beta2-adrenergic receptor genotype on childhood asthma and wheezing. Pediatrics. 2008;122(1):e107-14.

105. Werhmeister F, Nunes B, Loret de Mola C, Gómez-Cofré N, de Oliveira P, Marco P, et al. Intrauterine exposure to smoking and wheezing in adolescence: the 1993 Pelotas Birth Cohort. J Dev Orig Health Dis. 2015;6(3):217-24.

106. Wright A, Holberg C, Martinez F, Taussig L. Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illnesses in infancy. Group Health Medical Associates. J Pediatr. 1991;118(2):207-14.

107. Wu C, Hsu T, Chang J, Ou C, Kuo H, Liu C, et al. Paternal Tobacco Smoke Correlated to Offspring Asthma and Prenatal Epigenetic Programming. Front Genet. 2019;10:471.

108. Wu CC, Ou CY, Chang JC, Hsu TY, Kuo HC, Liu CA, et al. Gender-dependent effect of GSTM1 genotype on childhood asthma associated with prenatal tobacco smoke exposure. Biomed Res Int. 2014;2014:769452.

109. Wu J, Hankinson J, Kopec-Harding K, Custovic A, Simpson A. Interaction between glutathione S-transferase variants, maternal smoking and childhood wheezing changes with age. Pediatr Allergy Immunol. 2013;24(5):501-8.

110. Young S, Sherrill D, Arnott J, Diepeveen D, LeSouëf P, Landau L. Parental factors affecting respiratory function during the first year of life. Pediatr Pulmonol. 2000;29(5):331-40.

111. Zhang X, Johnson N, Carrillo G, Xu X. Decreasing trend in passive tobacco smoke exposure and association with asthma in U.S. children. Environ Res. 2018;166:35-41.

112. Boskabady M, Hajizadeh A, Ahanchian H, Memarzia A, Jafarnezhad M, Golafshani A, et al. The effect of 3-year parental smoking on asthma status of their children. Clin Resp J. 2022;16(5):394-401.

113. Butz A, Breysse P, Rand C, Curtin-Brosnan J, Eggleston P, Diette G, et al. Household smoking behavior: effects on indoor air quality and health of urban children with asthma. Matern Child Health J. 2011;15(4):460-8.

114. Butz A, Tsoukleris M, Elizabeth Bollinger M, Jassal M, Bellin M, Kub J, et al. Association between second hand smoke (SHS) exposure and caregiver stress in children with poorly controlled asthma. J Asthma 2019;56(9):915-26.

115. Chilmonczyk BA, Salmun LM, Megathlin KN, Neveux LM, Palomaki GE, Knight GJ, et al. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. N Engl J Med. 1993;328(23):1665-9.

116. Eisner M, Blanc P. Environmental tobacco smoke exposure during travel among adults with asthma. Chest. 2002;122(3):826-8.

117. Eisner M, Katz P, Yelin E, Hammond S, Blanc P. Measurement of environmental tobacco smoke exposure among adults with asthma. Envir Health Perspect. 2001;109(8):809-14.

118. Eisner M, Klein J, Hammond S, Koren G, Lactao G, Iribarren C. Directly measured second hand smoke exposure and asthma health outcomes. Thorax. 2005;60(10):814-21.

119. Eisner M, Yelin E, Katz P, Earnest G, Blanc P. Exposure to indoor combustion and adult asthma outcomes: environmental tobacco smoke, gas stoves, and woodsmoke. Thorax. 2002;57(11):973-8.

120. Gaisberger M, Wass RE, Dobias H, Grabcanovic-Musija F, Weiss G, Lamprecht B, et al. Acute Exposure to Environmental Tobacco Smoke: A Controlled Study in Adults with Asthma. Respiration. 2020;99(10):1-8.

121. Gerald L, Gerald J, Gibson L, Patel K, Zhang S, McClure L. Changes in environmental tobacco smoke exposure and asthma morbidity among urban school children. Chest. 2009;135(4):911-6.

122. Grarup P, Janner J, Ulrik C. Passive smoking is associated with poor asthma control during pregnancy: a prospective study of 500 pregnancies. PloS One 2014;9(11):e112435.

123. Jassal M, Lewis-Land C, Thompson R, Butz A. Linkage of Maternal Caregiver Smoking Behaviors on Environmental and Clinical Outcomes of Children with Asthma: A Post-Hoc Analysis of a Financial Incentive Trial Targeting Reduction in Pediatric Tobacco Smoke Exposures. Int J Environ Res Public Health. 2020;17(22).

124. Keogan S, Alonso T, Sunday S, Tigova O, Fernández E, López M, et al. Lung function changes in patients with chronic obstructive pulmonary disease (COPD) and asthma exposed to secondhand smoke in outdoor areas. J Asthma. 2021;58(9):1169-75.

125. Knight A, Breslin A. Passive cigarette smoking and patients with asthma. Med J Aust. 1985;142(3):194-5.

126. Lang JE, Dozor AJ, Holbrook JT, Mougey E, Krishnan S, Sweeten S, et al. Biologic mechanisms of environmental tobacco smoke in children with poorly controlled asthma: results from a multicenter clinical trial. J Allergy Clin Immunol Pract. 2013;1(2):172-80.

127. Li Y, Gilliland F, Berhane K, McConnell R, Gauderman W, Rappaport E, et al. Effects of in utero and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. Am J Respir Crit Care Med. 2000;162(6):2097-104.

128. Magnussen H, Lehnigk B, Oldigs M, Jörres R. Effects of acute passive smoking on exercise-induced bronchoconstriction in asthmatic children. J Appl Physiol. 1993;75(2):553-8.

129. Murray A, Morrison B. The decrease in severity of asthma in children of parents who smoke since the parents have been exposing them to less cigarette smoke. J Allergy Clin Immunol. 1993;91(1):102-10.

130. Newman R, Momirova V, Dombrowski M, Schatz M, Wise R, Landon M, et al. The effect of active and passive household cigarette smoke exposure on pregnant women with asthma. Chest. 2010;137(3):601-8.

131. Nowak D, Jörres R, Martinez-Müller L, Grimminger F, Seeger W, Koops F, et al. Effect of 3 hours of passive smoke exposure in the evening on inflammatory markers in bronchoalveolar and nasal lavage fluid in subjects with mild asthma. Int Arch Occup Environ Health. 1997;70(2):85-93.

132. Shephard R, Collins R, Silverman F. "Passive" exposure of asthmatic subjects to cigarette smoke. Environ Res. 1979;20(2):392-402.

133. Soussan D, Liard R, Zureik M, Touron D, Rogeaux Y, Neukirch F. Treatment compliance, passive smoking, and asthma control: a three year cohort study. Arch Dis Child. 2003;88(3):229-33.

134. Sutaryono S, Hartono H, Probandari ARI, Setyono P. Impact of Environmental Tobacco Smoke Exposure on Adults with Asthma Exacerbation. Asian J Pharm Clin Res 2019;12(3):125-9.

135. Boulay ME, Henry C, Bosse Y, Boulet LP, Morissette MC. Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals. Respir Res. 2017;18(1):33.

136. Arshad S, Hodgekiss C, Holloway J, Kurukulaaratchy R, Karmaus W, Zhang H, et al. Association of asthma and smoking with lung function impairment in adolescence and early adulthood: the Isle of Wight Birth Cohort Study. Eur Respir J. 2020;55(3).

137. Colak Y, Afzal S, Nordestgaard BG, Lange P. Characteristics and Prognosis of Never-Smokers and Smokers with Asthma in the Copenhagen General Population Study. A Prospective Cohort Study. Am J Respir Crit Care Med. 2015;192(2):172-81.

138. James A, Palmer L, Kicic E, Maxwell P, Lagan S, Ryan G, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. Am J Respir Crit Care Med. 2005;171(2):109-14.

139. Gallefoss F, Bakke P. Does smoking affect the outcome of patient education and self-management in asthmatics? Patient Educ Couns 2003;49(1):91-7.

140. Murphy VE, Clifton VL, Gibson PG. The effect of cigarette smoking on asthma control during exacerbations in pregnant women. Thorax. 2010;65(8):739-44.

141. Hancox R, Gray A, Poulton R, Sears M. The Effect of Cigarette Smoking on Lung Function in Young Adults with Asthma. Am J Respir Crit Care Med. 2016;194(3):276-84.

142. Westergaard CG, Porsbjerg C, Backer V. The effect of smoking cessation on airway inflammation in young asthma patients. Clin Exp Allergy. 2014;44(3):353-61.

143. Tommola M, Ilmarinen P, Tuomisto LE, Haanpaa J, Kankaanranta T, Niemela O, et al. The effect of smoking on lung function: a clinical study of adult-onset asthma. Eur Respir J. 2016;48(5):1298-306.

144. Tønnesen P, Pisinger C, Hvidberg S, Wennike P, Bremann L, Westin A, et al. Effects of smoking cessation and reduction in asthmatics. Nicotine Tob Res. 2005;7(1):139-48.

145. Jang AS, Park SW, Kim DJ, Uh S, Kim YH, Whang HG, et al. Effects of smoking cessation on airflow obstruction and quality of life in asthmatic smokers. Allergy Asthma Immunol Res. 2010;2(4):254-9.

146. Chaudhuri R, Livingston E, McMahon A, Lafferty J, Fraser I, Spears M, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. Am J Respir Crit Care Med. 2006;174(2):127-33.

147. Polosa R, Russo C, Caponnetto P, Bertino G, Sarvà M, Antic T, et al. Greater severity of new onset asthma in allergic subjects who smoke: a 10-year longitudinal study. Respir Res. 2011;12(1):16.

148. Cerveri I, Cazzoletti L, Corsico A, Marcon A, Niniano R, Grosso A, et al. The impact of cigarette smoking on asthma: a population-based international cohort study. Int Arch Allergy Immunol. 2012;158(2):175-83.

149. Jang A, Park J, Lee J, Park S, Kim D, Uh S, et al. The impact of smoking on clinical and therapeutic effects in asthmatics. J Korean Med Sci. 2009;24(2):209-14.

150. Tiotiu A, Ioan I, Wirth N, Romero-Fernandez R, González-Barcala F. The Impact of Tobacco Smoking on Adult Asthma Outcomes. Int J Environ Res Public Health. 2021;18(3).

151. Telenga E, Kerstjens H, Ten Hacken N, Postma D, van den Berge M. Inflammation and corticosteroid responsiveness in ex-, current- and never-smoking asthmatics. BMC Pulm Med. 2013;13:58.

152. Eisner M, Iribarren C. The influence of cigarette smoking on adult asthma outcomes. Nicotine Tob Res 2007;9(1):53-6.

153. Shimoda T, Obase Y, Kishikawa R, Iwanaga T. Influence of cigarette smoking on airway inflammation and inhaled corticosteroid treatment in patients with asthma. Allergy Asthma Proc. 2016;37(4):50-8.

154. Chalmers G, Macleod K, Little S, Thomson L, McSharry C, Thomson N. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax. 2002;57(3):226-30.

155. Westerhof G, Vollema E, Weersink E, Reinartz S, de Nijs S, Bel E. Predictors for the development of progressive severity in new-onset adult asthma. J Allergy Clin Immunol. 2014;134(5):1051-6.e2.

156. To T, Daly C, Feldman R, McLimont S. Results from a community-based program evaluating the effect of changing smoking status on asthma symptom control. BMC Public Health. 2012;12:293.

157. Vignoud L, Pin I, Boudier A, Pison C, Nadif R, Le Moual N, et al. Smoking and asthma: disentangling their mutual influences using a longitudinal approach. Respir Med. 2011;105(12):1805-14.

158. Dick S, Doust E, Cowie H, Ayres JG, Turner S. Associations between environmental exposures and asthma control and exacerbations in young children: a systematic review. BMJ Open. 2014;4(2):e003827

159. Jayes L, Haslam PL, Gratziou CG, Powell P, Britton J, Vardavas C, et al. SmokeHaz: Systematic Reviews and Meta-analyses of the Effects of Smoking on Respiratory Health. Chest. 2016;150(1):164-79.

160. Wang Z, May SM, Charoenlap S, Pyle R, Ott NL, Mohammed K, et al. Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2015;115(5):396-401.e2.

161. Shahunja KM, Sly PD, Begum T, Biswas T, Mamun A. Family, neighborhood and psychosocial environmental factors and their associations with asthma in Australia: a systematic review and Meta-analysis. J Asthma 2022;59(12):2539-52

162. He Z, Wu H, Zhang S, Lin Y, Li R, Xie L, et al. The association between secondhand smoke and childhood asthma: A systematic review and meta-analysis. Pediatr Pulmonol. 2020;55(10):2518-31.

163. Bao Y, Chen Z, Liu E, Xiang L, Zhao D, Hong J. Risk Factors in Preschool Children for Predicting Asthma During the Preschool Age and the Early School Age: a Systematic Review and Meta-Analysis. Curr Allergy Asthma Rep. 2017;17(12):85.

164. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129(4):735-44.

165. Robijn AL, Bokern MP, Jensen ME, Barker D, Baines KJ, Murphy VE. Risk factors for asthma exacerbations during pregnancy: a systematic review and meta-analysis. Eur Respir Rev 2022;31(164).

166. Chand BR, Hosseinzadeh H. Association between e-cigarette use and asthma: a systematic review and meta-analysis. J Asthma 2022;59(9):1722-31.

167. Mattingly DT, Cook S, Hirschtick JL, Patel A, Arenberg DA, Barnes GD, et al. Longitudinal associations between exclusive, dual, and polytobacco use and asthma among US youth. Prev Med. 2023;171:107512.

168. Zacharasiewicz A. Maternal smoking in pregnancy and its influence on childhood asthma. ERJ Open Res. 2016;2(3):00042-2016

169. Patel M.S., Patel S.B., Steinberg M.B. Smoking Cessation. Ann. Intern. Med. 2021 174:

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

| Research Question | Population | Exposure | Comparator | Outcomes |
|---|---|---|---|---|
| Q1: Does pre- or post-natal or combined pre- and post-natal ETS (combustion or e-cigarette) increase the risk of new-onset asthma? | Healthy children | Environmental exposure to:<br>- Cigarette/pipe/other combustion smoking<br>- E-cigarettes | No exposure | Critical<br>- New-onset asthma<br>- Recurrent wheezing<br>- Low lung function (FEV1) |
| Q2: Does ETS (combustion or e-cigarette) impact asthma-related outcomes? | Children or adults with asthma | Environmental exposure to:<br>- Cigarette/pipe/other combustion smoking<br>- E-cigarettes | No exposure | Critical<br>- Severe asthma exacerbations (ED visits/hospitalizations or systemic steroid for at least 3 days)<br>- Asthma control (ACT, ACQ)<br>- Asthma-related QoL<br>- Lung function (FEV1, FEV1/FVC, PEF)<br>Important<br>- Asthma well controlled days<br>- Asthma rescue and/or controller medication |
| Q3: Does active smoking (cigarette/pipe/other combustion/e-cigarette) impact asthma-related outcomes? | Children, adolescents or adults with asthma | Active smoking of:<br>- Cigarette/pipe/other combustion smoking<br>- E-cigarettes | No exposure | Critical<br>-Severe asthma exacerbations (ED visits/hospitalizations or systemic steroid for at least 3 days)<br>- Asthma control (ACT, ACQ)<br>- Asthma-related QoL<br>- Lung function (FEV1, FEV1/FVC, PEF)<br>Important<br>- Asthma well controlled days<br>- Asthma medication |

ACQ = asthma control questionnaire; ACT = asthma control test; ED = emergency department; ETS = environmental tobacco smoke; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; PEF: Peak expiratory flow

Table 2. Summary of findings for the impact of ETS (combustion smoke) pre- or post-natal 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 to 22)] | ⊕⊕◯◯[a,b] 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 to 24)] | ⊕⊕⊕◯[c] 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 to 24)] [median: 7; range:7 to 8] | ⊕⊕◯◯[d] Low | - 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.<br>- 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.<br>- 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). | | |
| New-onset asthma (post-natal exposure) | 13 [median: 8; range:2 to 18] | ⊕⊕⊕◯[e] Moderate | aOR 1.12 (1.01 to 1.24) | 8.3% | +9 per 1000 (+1 to +18) |
| Recurrent wheezing (post-natal exposure) | 10 [median: 2; range:1 to 8] | ⊕⊕⊕◯[f] Moderate | aOR 1.15 (1.04 to 1.27) | 21.0% | +24 per 1000 (+7 to +42) |
| Low lung function (post-natal exposure) | 4 [median: 8; range:6 to 15] | ⊕⊕◯◯[g] Low | - Fernández-Plata et 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.<br>- Gilliland et al. assessed 5,933 children and found no evidence for impact of ETS on lung function (effect estimates not reported).<br>- Sherrill et al. examined in a 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.<br>- Tashkin et al. analysed 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. | | |
| New-onset asthma (*in utero* and post-natal exposure) | 6 [median: 4.2; range:1.8 to 8] | ⊕⊕◯◯[h,i] Low | aOR 1.49 (1.12 to 1.99) | 6.0% | +27 per 1000 (+7 to +53) |

| | | | | | |
|---|---|---|---|---|---|
| Recurrent wheezing (*in utero* and post-natal exposure) | 8 [median: 6; range:1.5 to 11] | ⊕⊕⊕◯[j] Moderate | aOR 1.46 (1.28 to 1.66) | 23.5% | +75 per 1000 (+47 to +103) |

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

**CI:** confidence interval; **FEF:** Forced expiratory flow; **FEV1:** Forced expiratory volume in 1 second; **FVC:** Forced vital capacity; **OR:** odds ratio; **aOR:** adjusted odds ratio

*Basal risk computed based on the mean proportion of events in the non-exposed group

a. 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.
b. Serious inconsistency: large, unexplained heterogeneity ($I^2$=67.5%)
c. 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).
d. 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 commons 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)
e. 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).
f. 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.
g. 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.
h. 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.
i. Serious inconsistency: large unexplained heterogeneity ($I^2$=95%)
j. 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.

Table 3. Summary of findings for the impact of post-natal 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) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk compared with no exposure* | Risk difference in the exposed group |
| Severe asthma exacerbations (hospital admissions) | 2 [12 months] | ⊕⊕◯◯[a,b] 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] | ⊕⊕⊕◯[c] 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)] | ⊕⊕⊕◯[d] 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] | ⊕⊕⊕◯[e] Moderate | aOR 2.24 (1.56 to 3.23) | Not reported | - |
| Quality of life | 3 [median: 12 months; 24 weeks to 4 years] | ⊕◯◯◯[f,g,h] Very low | - | - | MD -0.9 (- 4.32 to +2.52) |
| Lung function (acute exposure) | 3 [median: 2 hours; 54 minutes to 3 hours] | ⊕◯◯◯[h,i] 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] | ⊕⊕⊕◯[j] 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] | ⊕◯◯◯[k,l] Very low | - 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.<br>- Eisner 2001: Significant extra bronchodilator use among those exposed to ETS (OR= 8.1; 95%CI = 1.3 to 50.0)<br>- 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 | | |

* Basal risk computed based on the mean proportion of events in the not exposed group
**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
a. 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).
b. Serious imprecision: wide confidence intervals
c. 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)
d. 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).
e. 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)
f. Very serious risk of bias: nonresponse bias is concerning in Eisner 2005. Bias arising from self-reported exposure status is high in Eisner 2002.
g. Serious inconsistency: inconsistent results observed across studies
h. Wide confidence intervals due to inconsistent results

i. 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.
j. 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 Grarup 2014 were at risk of selection bias.
k. 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.
l. 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.

Table 4A. Summary of findings for impact of active smoking (combustion) on asthma-related outcomes in adolescents or 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 |
| Severe asthma exacerbation (hospitalisation or ED visit for asthma) | 3 [median: 4 years; 1 to 15 years] | ⊕⊕⊕◯[a] 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 three days) | 1 [not reported] | ⊕⊕◯◯[b,c] 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] | ⊕⊕⊕◯[d] 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] | ⊕⊕⊕◯[e] Moderate | - | - | SMD -2.53 (-6.19 to +1.13) |
| Lung function | 4 [median: 6 months; 3 months to 12 years] | ⊕⊕◯◯[f,g] Low | - | - | MD -6.23 (-11.28 to -1.19) |
| Asthma well controlled days | 1 [not reported] | ⊕⊕◯◯[h] Low | In 2010 pregnant women with asthma, Newman et al observed significant differences between smokers and non-smokers in:<br>- Mean total number of symptomatic days (78.8 vs 69.3)<br>- Mean total number of nights with sleep disturbance (48.4 vs 39.2)<br>- Mean total number of days with restricted activity (23.4 vs 26.8,). | | |
| Asthma medication (rescue and controller) | 1 [12 months] | ⊕⊕◯◯[i] 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%). | | |

Table 4B. Summary of findings for impact of active smoking (e-cigarette) on asthma-related outcomes in adults with asthma

| | | | |
|---|---|---|---|
| Lung function (electronic cigarette smoking) | 1 [1 hour] | ⊕⊕◯◯[j,k] Low | A placebo-controlled crossover trial investigating the impact of a 1-hour acute vaping session of nicotine-free and flavour-free e-liquid on the pulmonary function of 10 asthmatic individuals found no significant differences in any of the lung function outcomes examined:<br>- FEV1: pre-post difference of 0.014 (0.013 to 0.015) in the intervention group vs -0.01 (−0.01 to − 0.01) in the placebo group;<br>- FVC: pre-post difference of -0.069 (-0.070 to -0.068) in the intervention group vs -0.05 (-0.05 to -0.05) in the placebo group<br>- FEV1/FVC: pre-post difference of 1.550 (1.516 to 1.584) in the intervention group vs -1.10 (-1.13 to -1.11) in the placebo group. |

aOR: adjusted odds ratio; CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio; SMD: standardised mean difference;

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

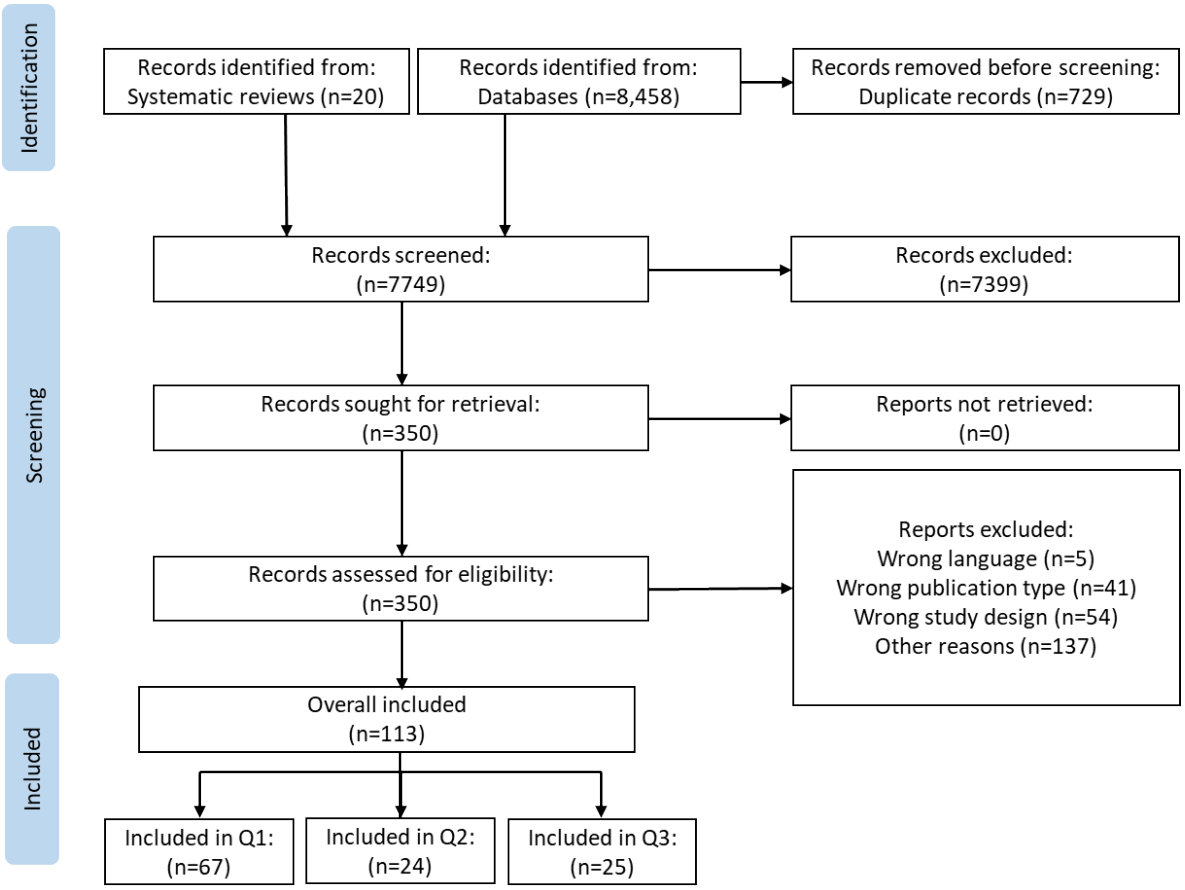
a. Serious risk of bias: all three studies had some concerns in relation to the risk of bias derived from potential selection bias (Murphy 2010, Çolak 2015), missing data (Çolak 2015), and self-reported outcomes (To 2012).

b. 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.

c. Serious imprecision: small sample size, leading to imprecise estimates

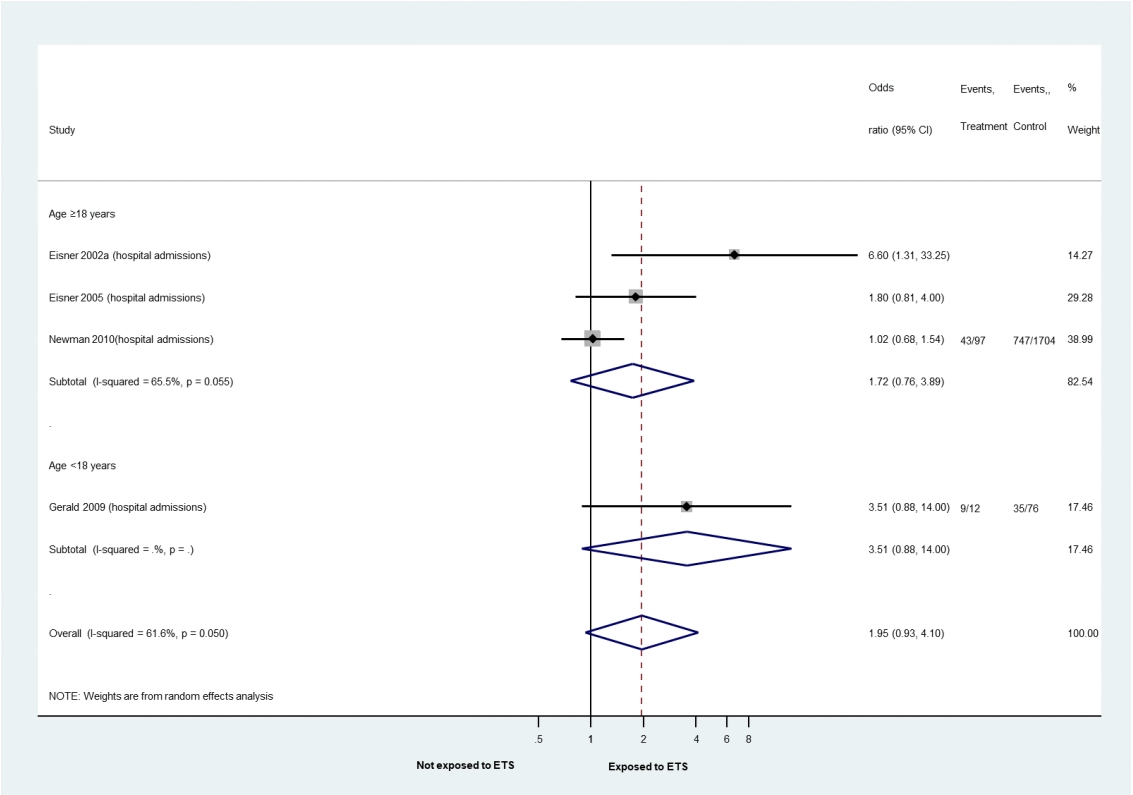
d. Three of the four studies presented some concerns due to potential selection bias (Tiotiu 2021), and self-reported outcomes (To 2012 and Westerhof 2014). One study (Polosa 2011) presented a high risk of bias due to the measurement of the outcome and smoking status (self-reported), as well as concerns about selection bias, and missing data.
e. 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.
f. Serious risk of bias: Vignoud 2011 presented some concerns due to loss to follow-up and reporting the exposure.
g. Serious imprecision: wide confidence intervals
h. Very serious risk of bias: risk of confounding bias (unadjusted estimates), and selection bias (unclear method of selecting participants).
i. Very serious risk of bias: due to bias arising from self-reported exposure and outcome measurement.
j. Serious indirectness: only acute effect is measured (1 hour exposition)
k. Serious imprecision: very small sample size (10 participants).

**Figure 1. PRISMA flowchart illustrating study selection**



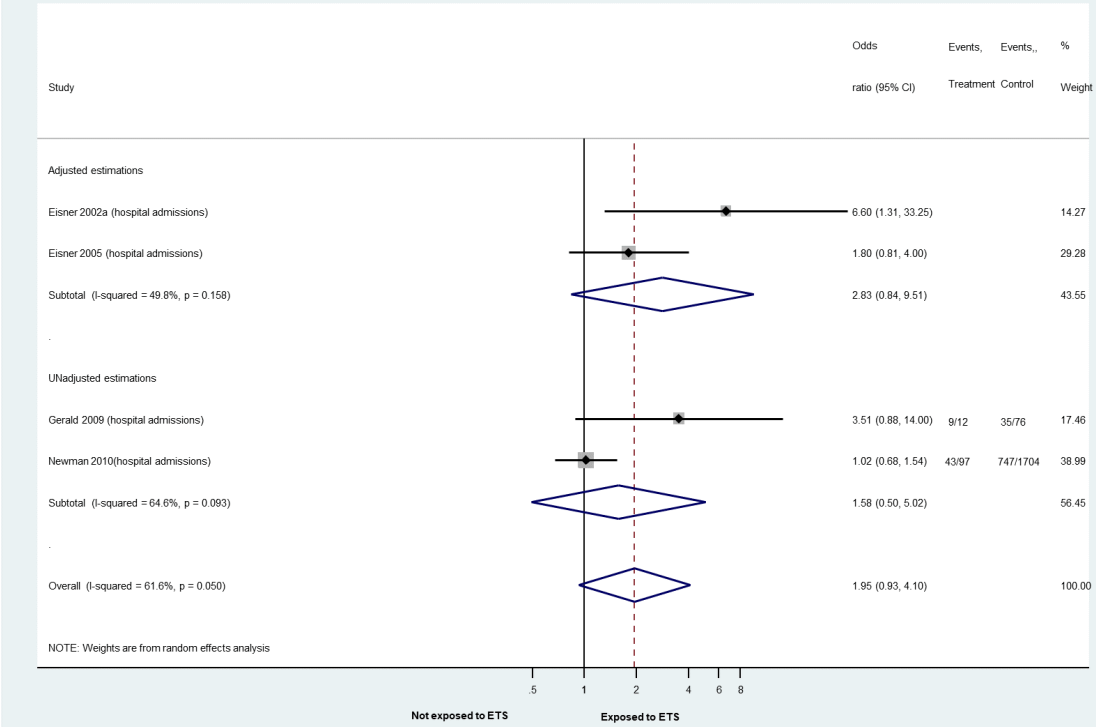
## Supporting information

Figure S2A. The impact of ETS (combustion smoke) on the risk of severe asthma exacerbations (defined as hospital admissions) - overall * and stratified by age



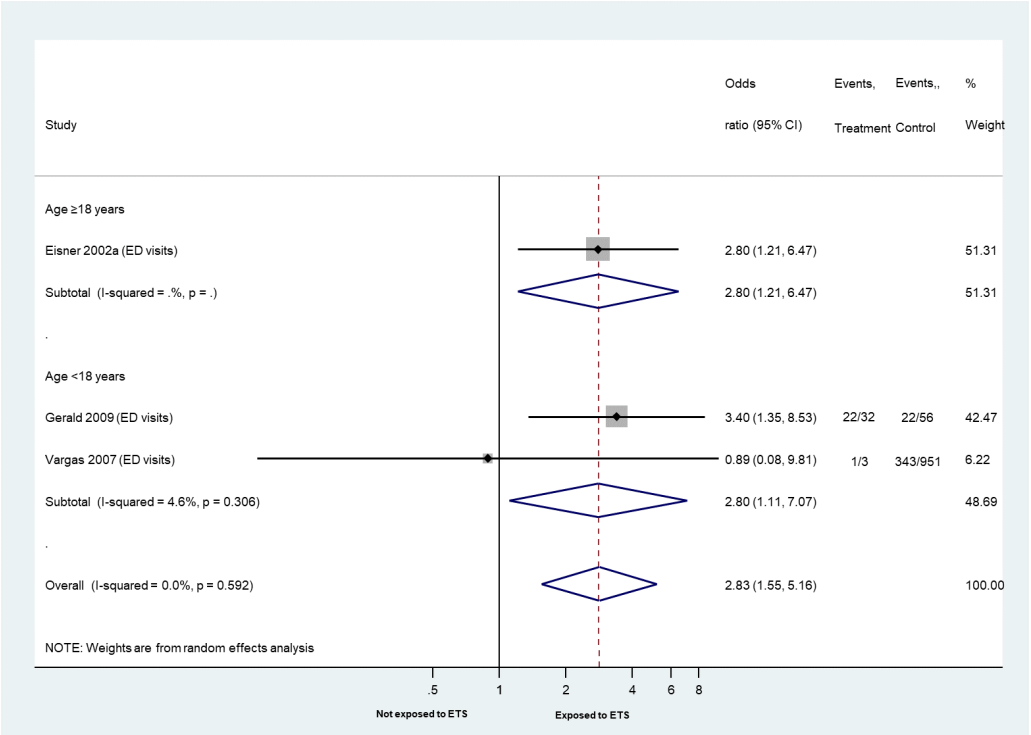

* Number of events by group not originally reported in two of the studies included (Eisner 2002a; Eisner 2005), and therefore not included in the Forest Plot.

**Figure S2B. The impact of ETS (combustion smoke) on the risk of severe asthma exacerbations (defined as hospital admissions) - overall and adjusted for confounding variables***



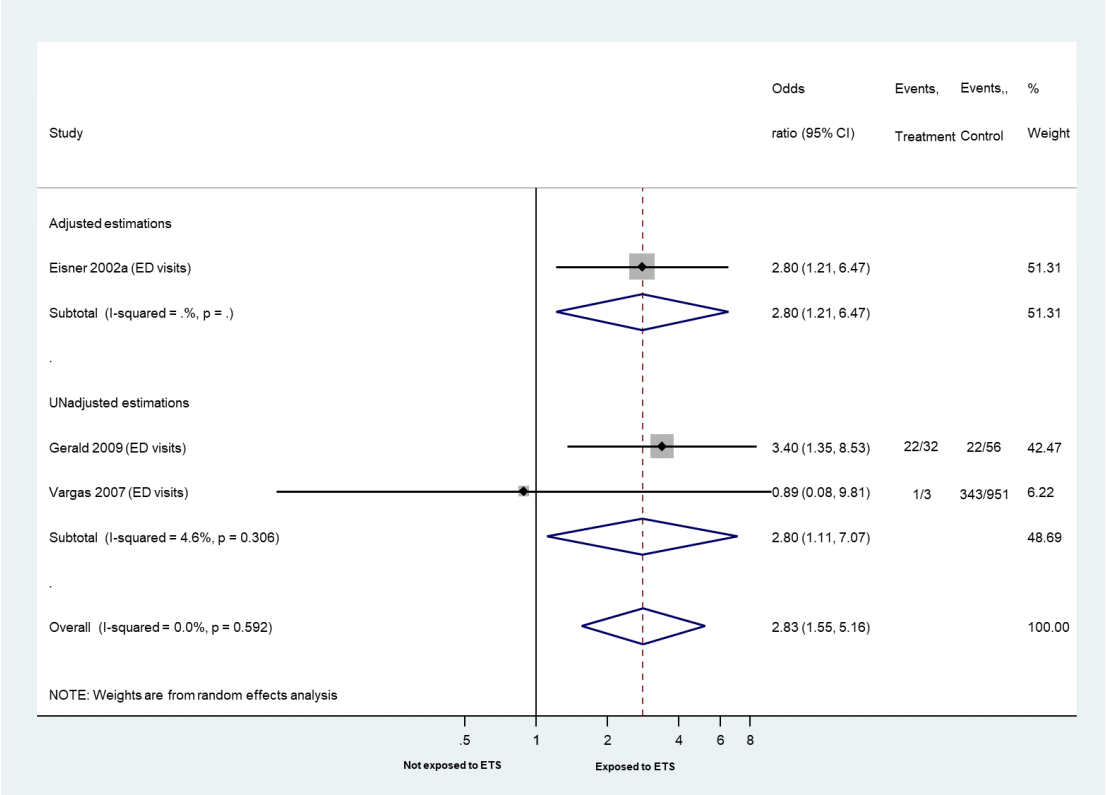

* Number of events by group not reported in two of the included studies (Eisner 2002a; Eisner 2005), and therefore not included in the forest plot.

**Figure S2C. The impact of ETS (combustion smoke) on the risk of severe asthma exacerbations (defined as ED visits) - overall and stratified by age***



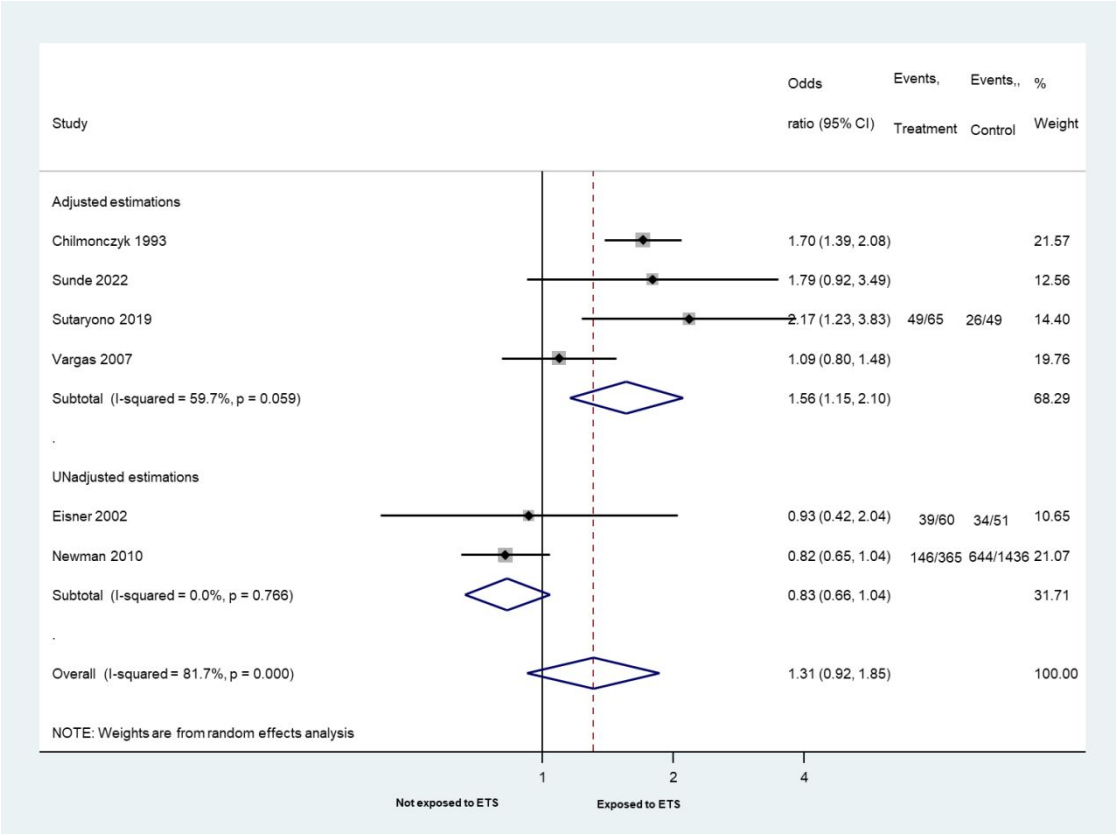
* Number of events by group not originally reported Eisner 2002a, and therefore not included in the forest plot. Right direction conveys increased risk of asthma exacerbations (therefore, this forest plot indicates that exposure to environmental tobacco smoking is associated with increased risk of asthma exacerbations).

**Figure S2D. The impact of ETS (combustion smoke) on the risk of severe asthma exacerbations (defined as ED visits) - overall and adjusted for confounding variables***



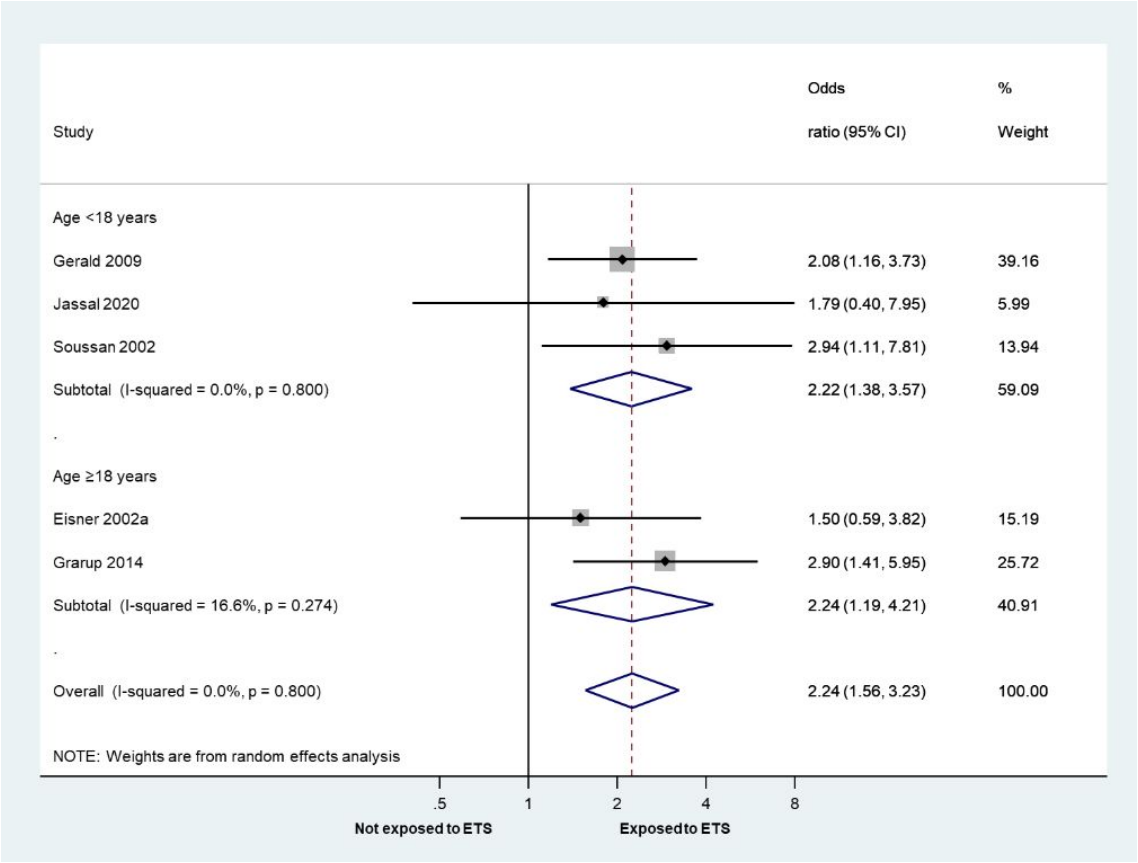

* Number of events by group not originally reported Eisner 2002a, and therefore not included in the forest plot. Right direction conveys increased risk of asthma exacerbations (therefore, this forest plot indicates that exposure to environmental tobacco smoking is associated with increased risk of asthma exacerbations).

**Figure S2E. The impact of ETS (combustion smoke) on the risk of asthma exacerbations (no clear definition) - overall and adjustmented by confounders ***




* Number of events by group not originally reported in three of the included studies (Sunde 2022; Vargas 2007; Chilmonczyk 1993), and therefore not included in the forest plot.

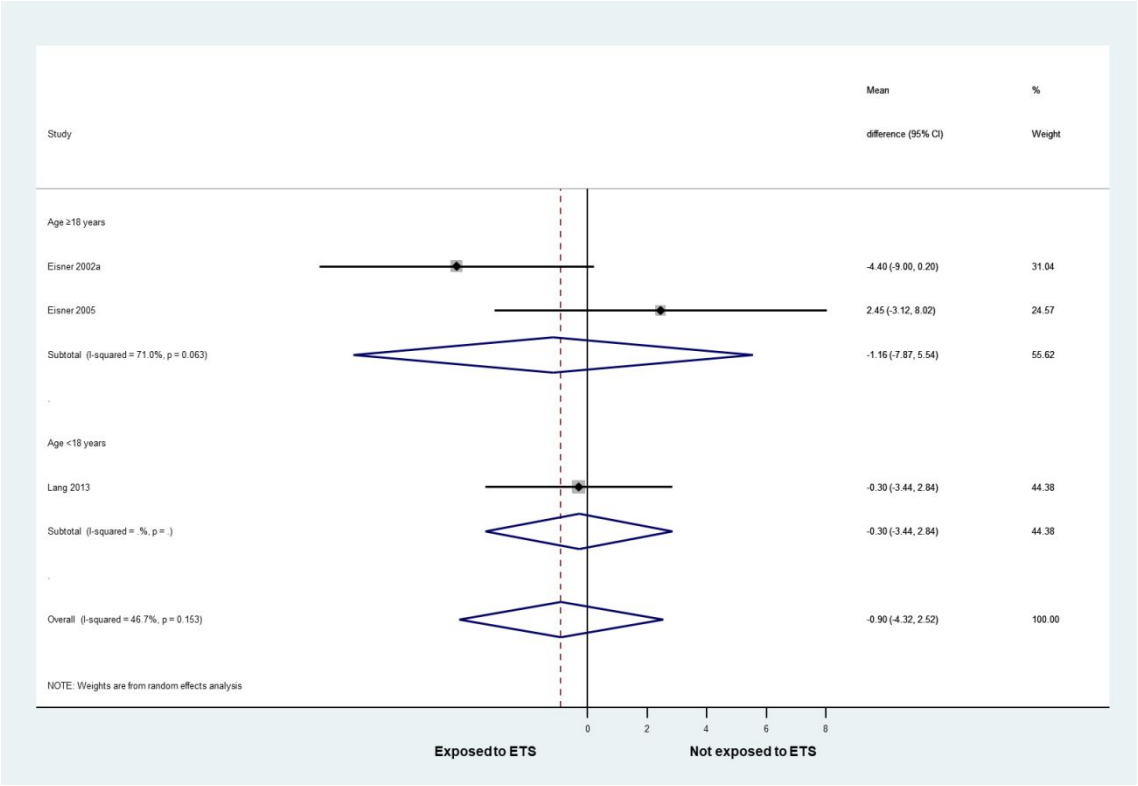
**Figure S2F. The impact of ETS (combustion smoke) on asthma control - overall and stratified by age***




ǂ Asthma control measured with Patient-Reported Outcome Measures.

* Number of events by group not reported in the included studies, and therefore not included in the forest plot. Right direction conveys worse asthma control (therefore, this forest plot indicates that exposure to environmental tobacco smoking is associated with worse asthma control).

**Figure S2G. The impact of ETS (combustion smoke) on asthma-related quality of life - overall and stratified by age***




ǂ Quality of life measured with Patient-Reported Outcome Measures.

* Mean quality of life scores by group not reported in the included studies, and therefore not included in the forest plot. Right direction conveys better quality of life.

**Figure S2H. The impact of acute ETS (combustion smoke) on lung function (FEV1) - overall and stratified by age**

FEV1: Forced expiratory volume (liters) in 1 second

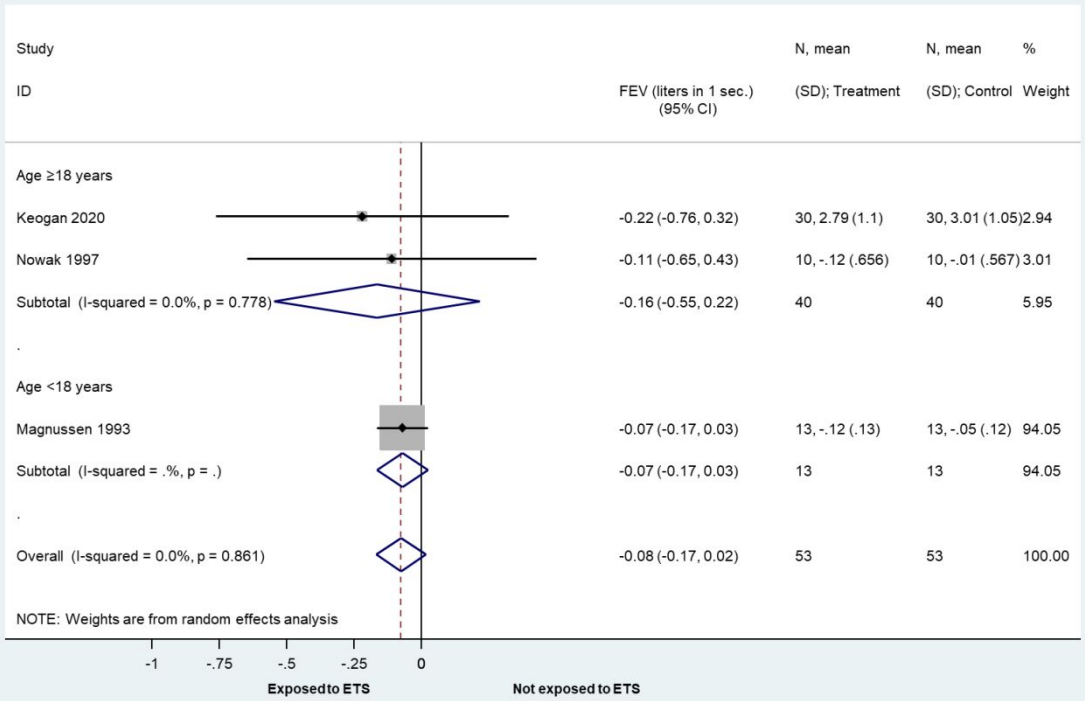

Study
ID
FEV (liters in 1 sec.) (95% CI)
N, mean (SD); Treatment
N, mean (SD); Control
% Weight
Age ≥18 years
Keogan 2020
-0.22 (-0.76, 0.32)
30, 2.79 (1.1)
30, 3.01 (1.05)
2.94
Nowak 1997
-0.11 (-0.65, 0.43)
10, -.12 (.656)
10, -.01 (.567)
3.01
Subtotal (I-squared = 0.0%, p = 0.778)
-0.16 (-0.55, 0.22)
40
40
5.95
.
Age <18 years
Magnussen 1993
-0.07 (-0.17, 0.03)
13, -.12 (.13)
13, -.05 (.12)
94.05
Subtotal (I-squared = .%, p = .)
-0.07 (-0.17, 0.03)
13
13
94.05
.
Overall (I-squared = 0.0%, p = 0.861)
-0.08 (-0.17, 0.02)
53
53
100.00
NOTE: Weights are from random effects analysis
-1
-.75
-.5
-.25
0
Exposed to ETS
Not exposed to ETS

**Figure S2l. The impact of long-term ETS (combustion smoke) on lung function (FEV1% predicted) (FEV1) – overall and adjusted by confounding factors**

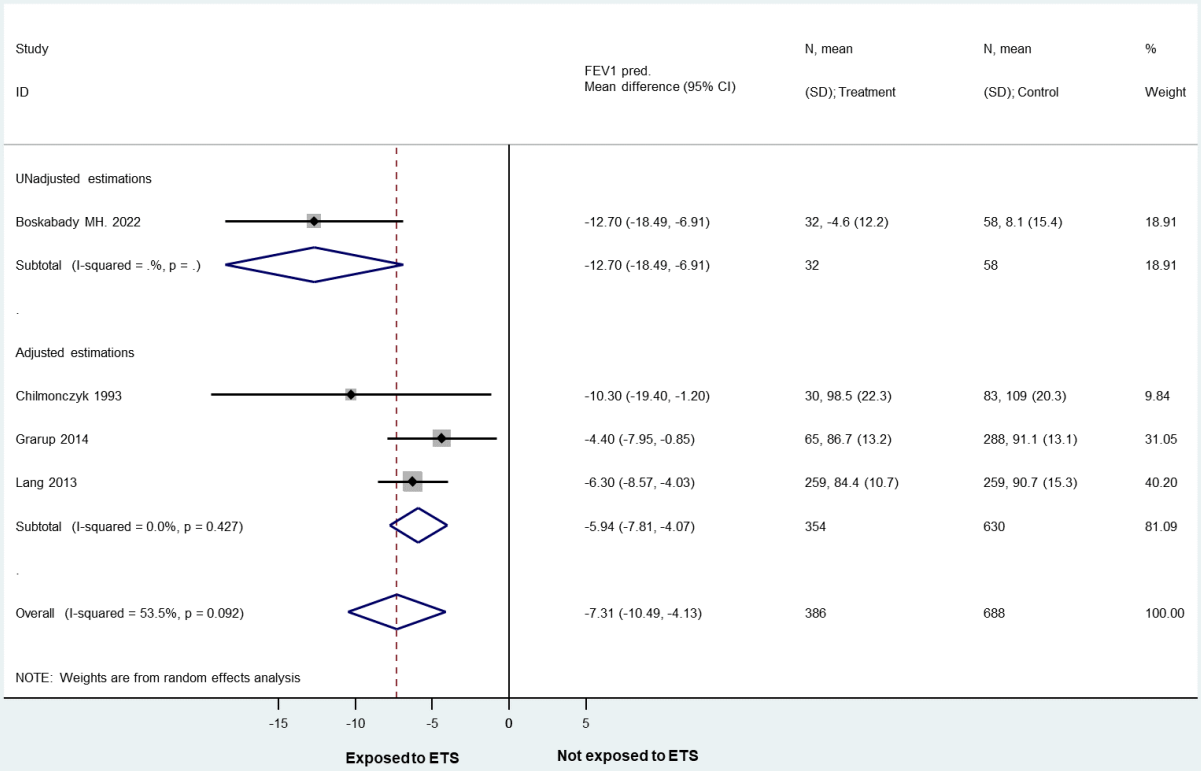


**Figure S1A. Impact of in utero exposure to combustion smoking on the risk of new-onset asthma (overall)**

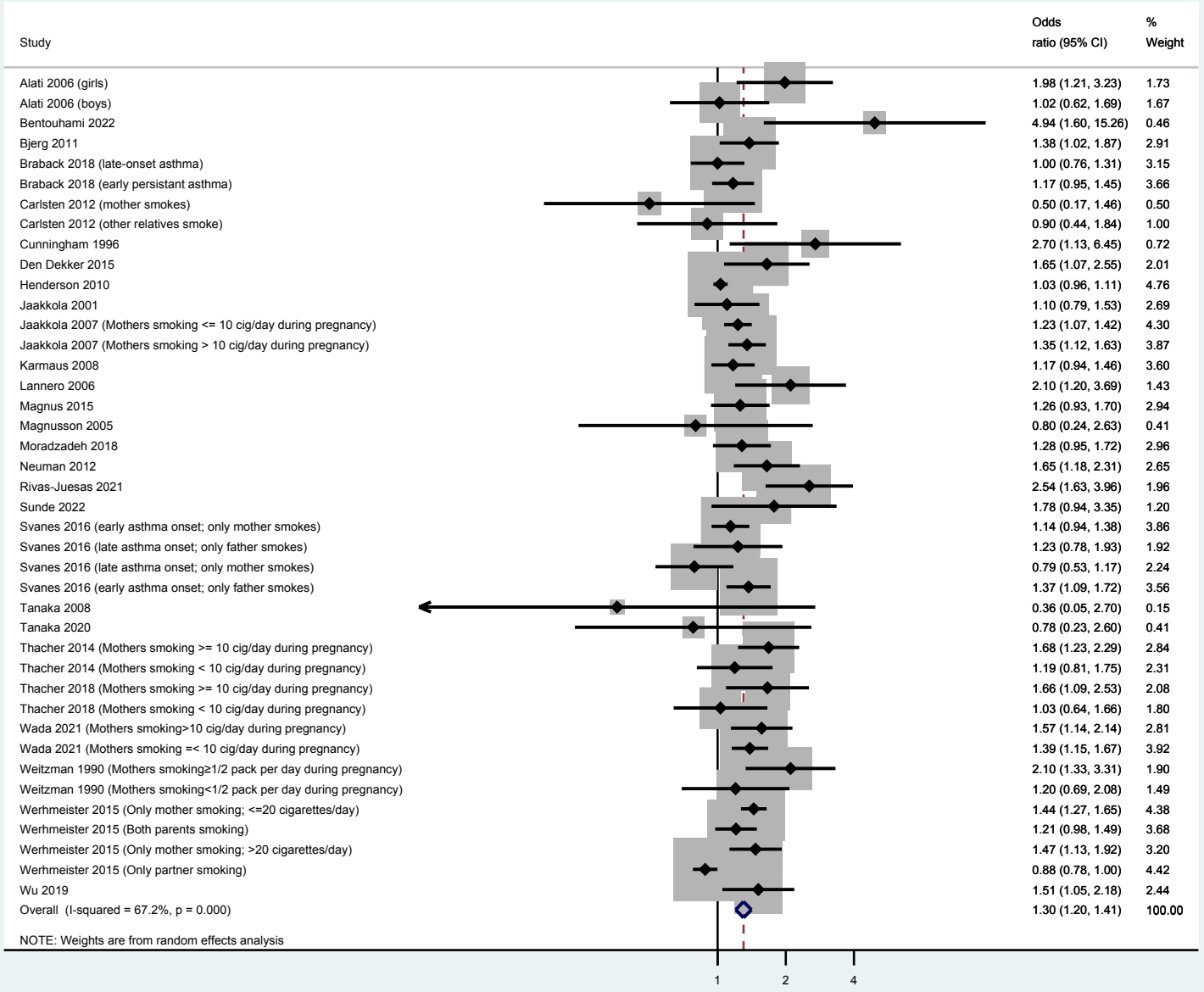


**Figure S1 B. Impact of in utero exposure to combustion smoking on the risk of new-onset asthma stratified by person smoking (mother/father/both/other relatives)**

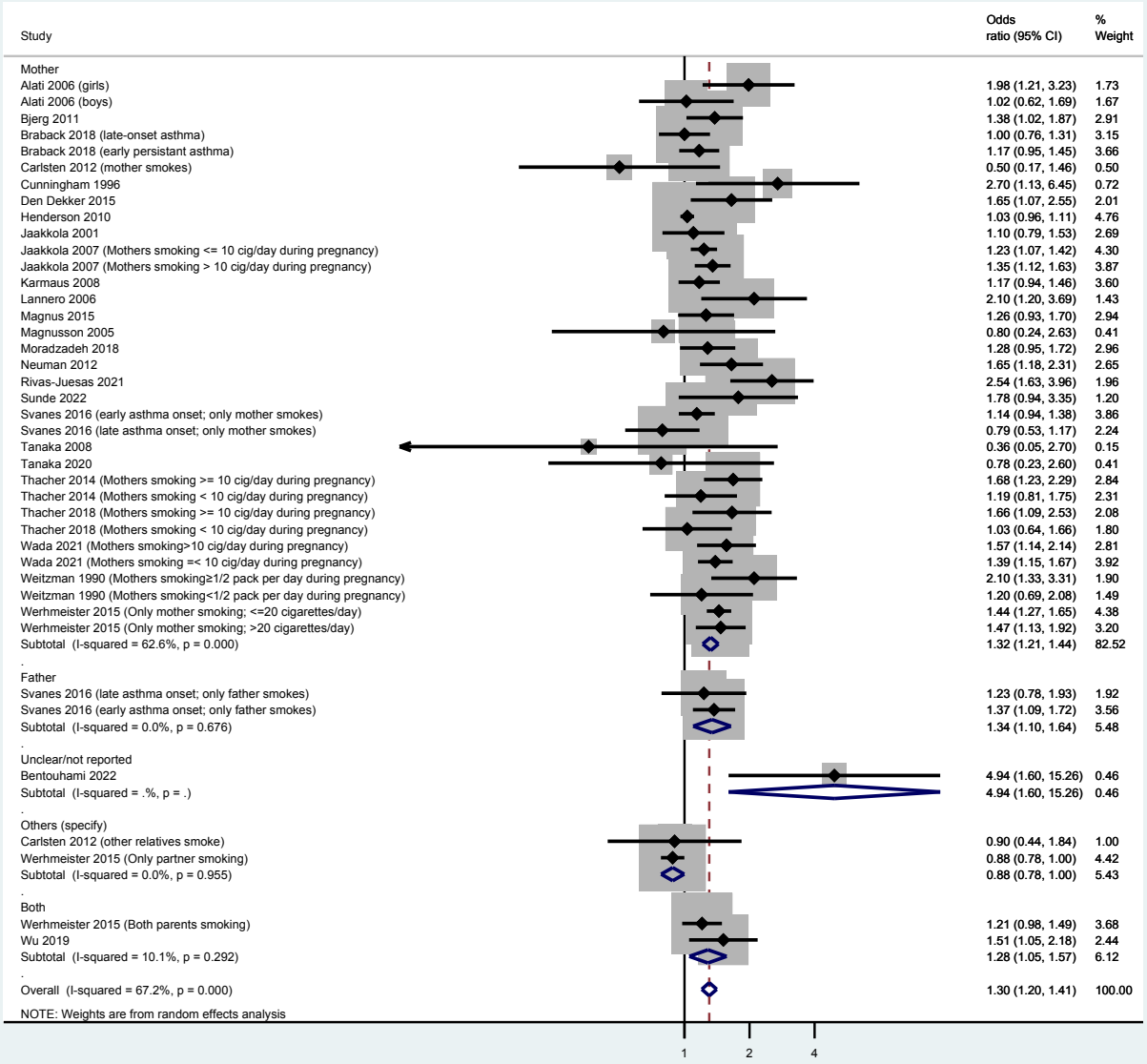


**Figure S1C. Impact of in utero exposure to combustion smoke on the risk of recurrent wheezing (overall)**

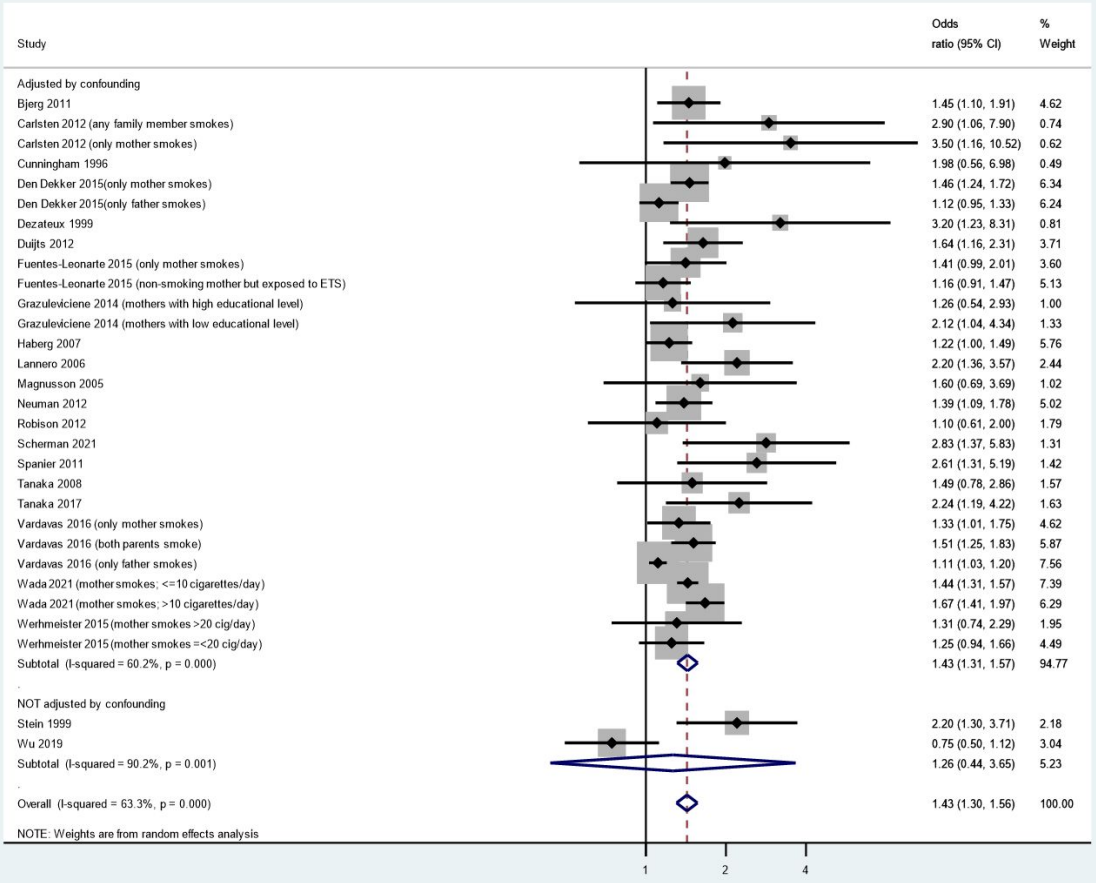


**Figure S1D. Impact of in utero exposure to combustion smoking on the risk of recurrent wheezing (stratified by person smoking)**

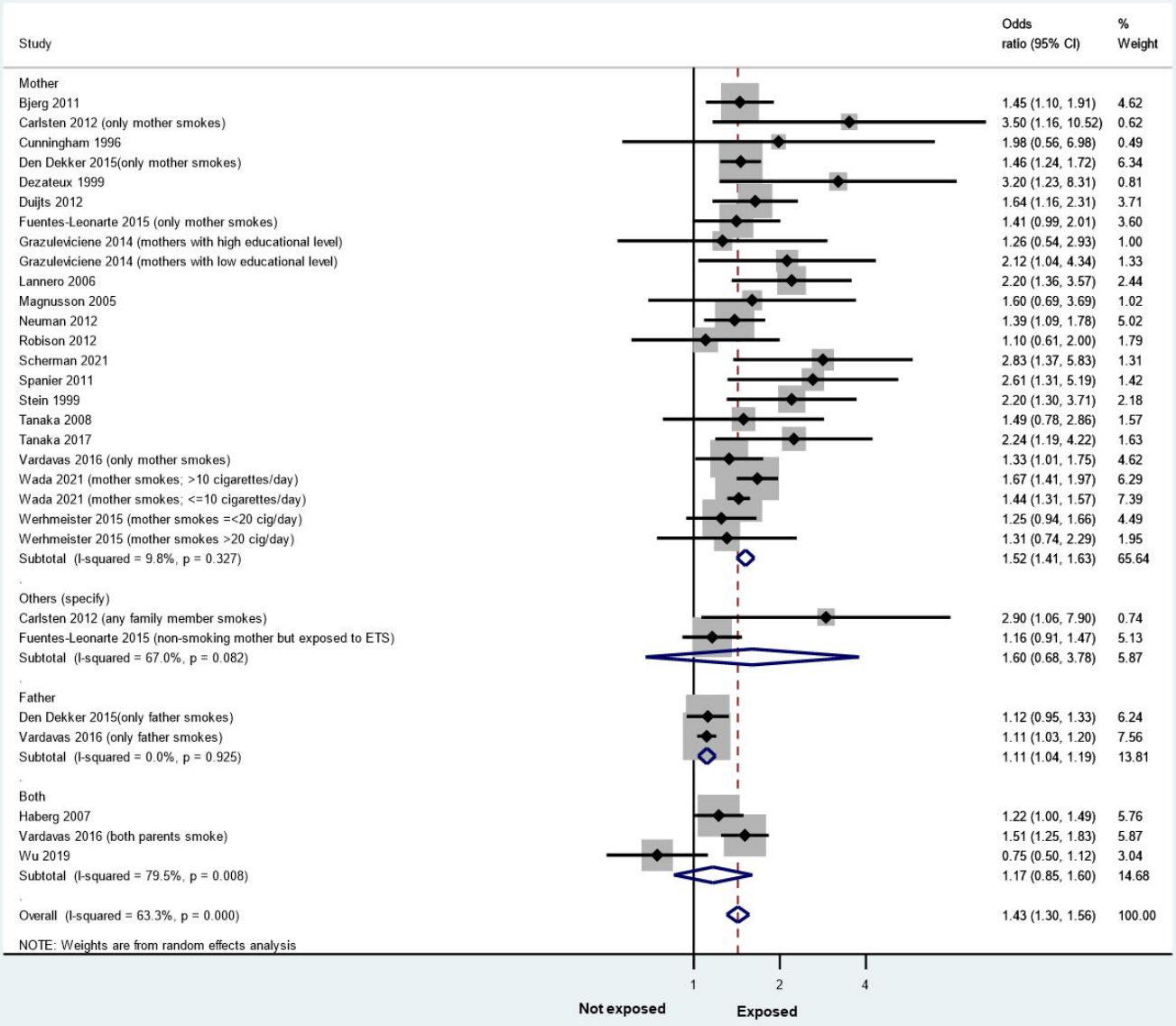


**Figure S1E. Impact of postnatal exposure to ETS (combustion smoke) on the risk of incident asthma (overall and adjusted by confounding factors)**

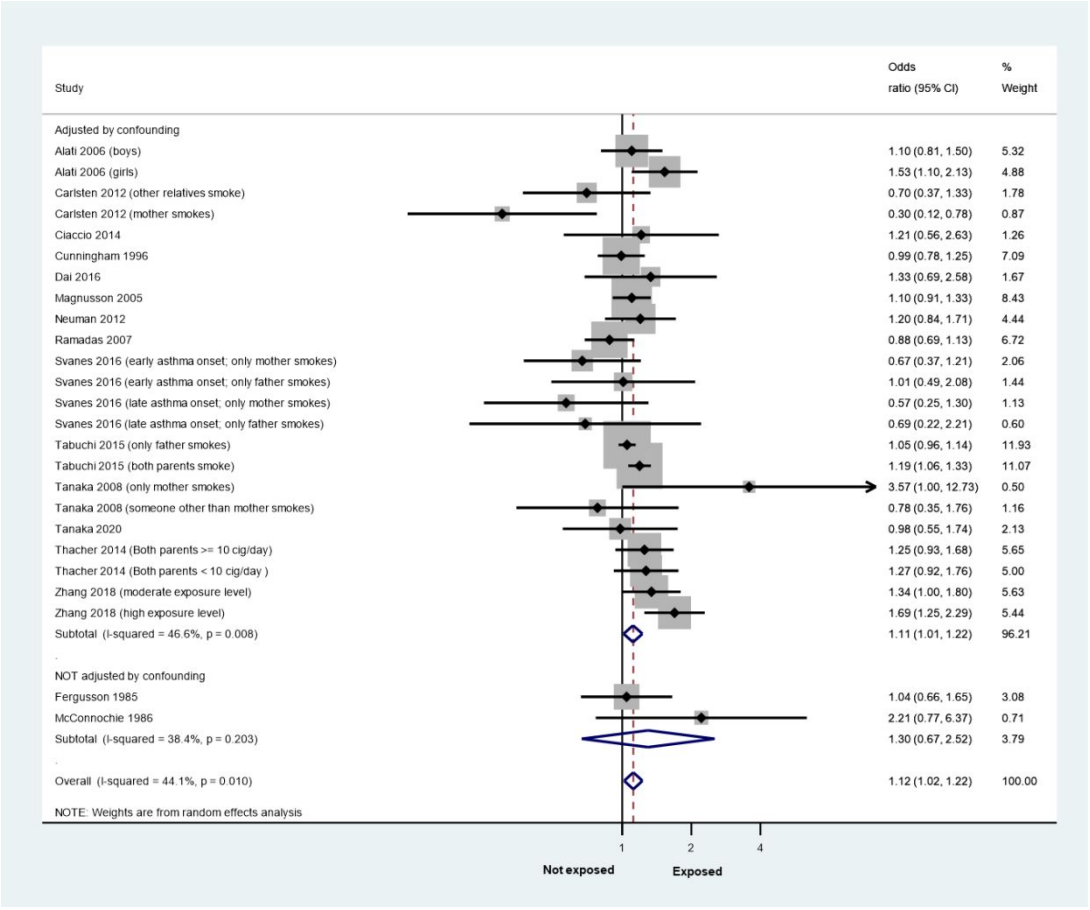


**Figure S1F. Impact of postnatal ETS (combustion smoke) on the risk of new-onset asthma (stratified by person smoking – mother, father, both, relatives, other)**

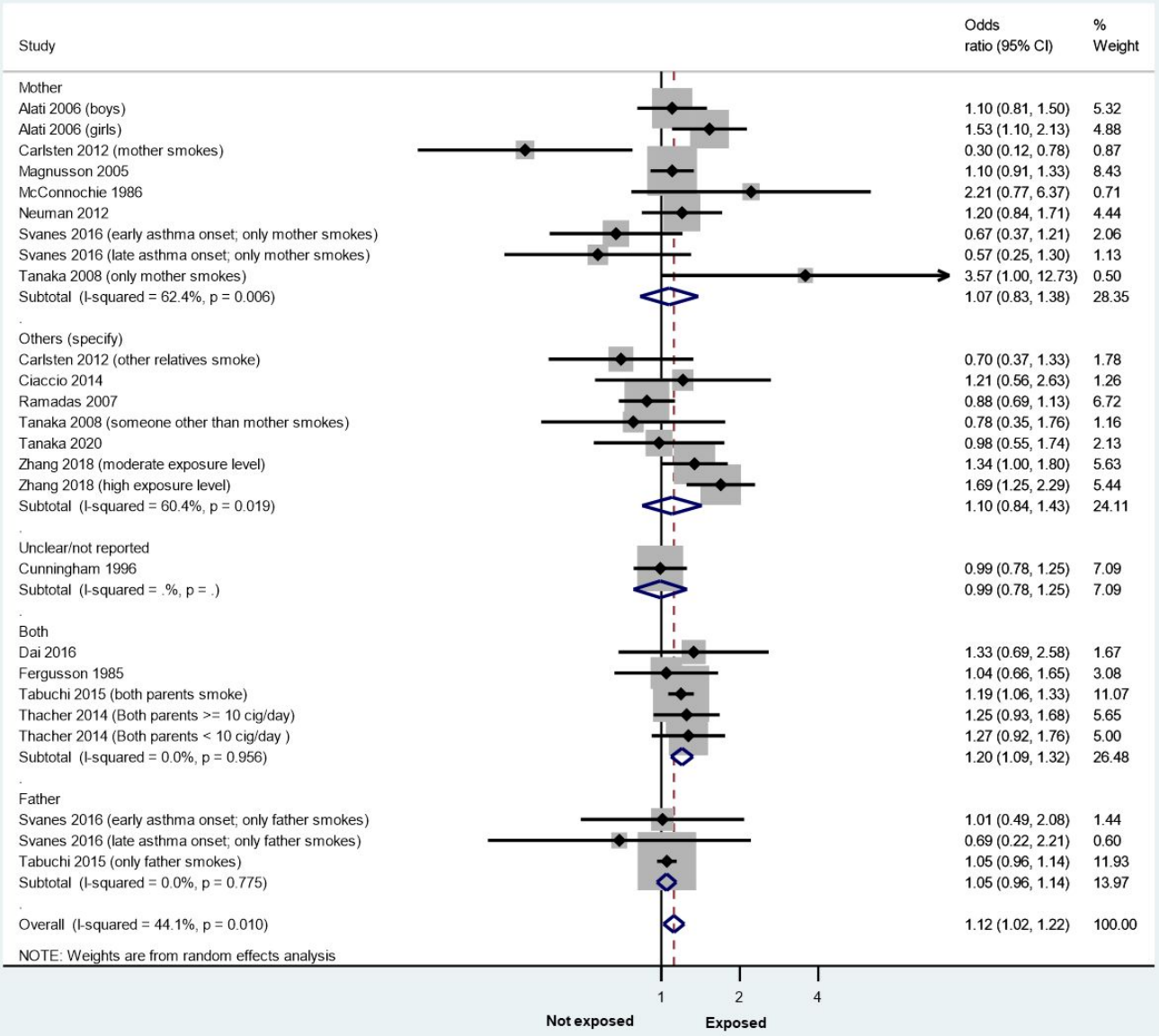


**Figure S1G. Impact of postnatal ETS (combustion smoke) on the risk of recurrent wheezing (overall and adjusted by confounding factors)**

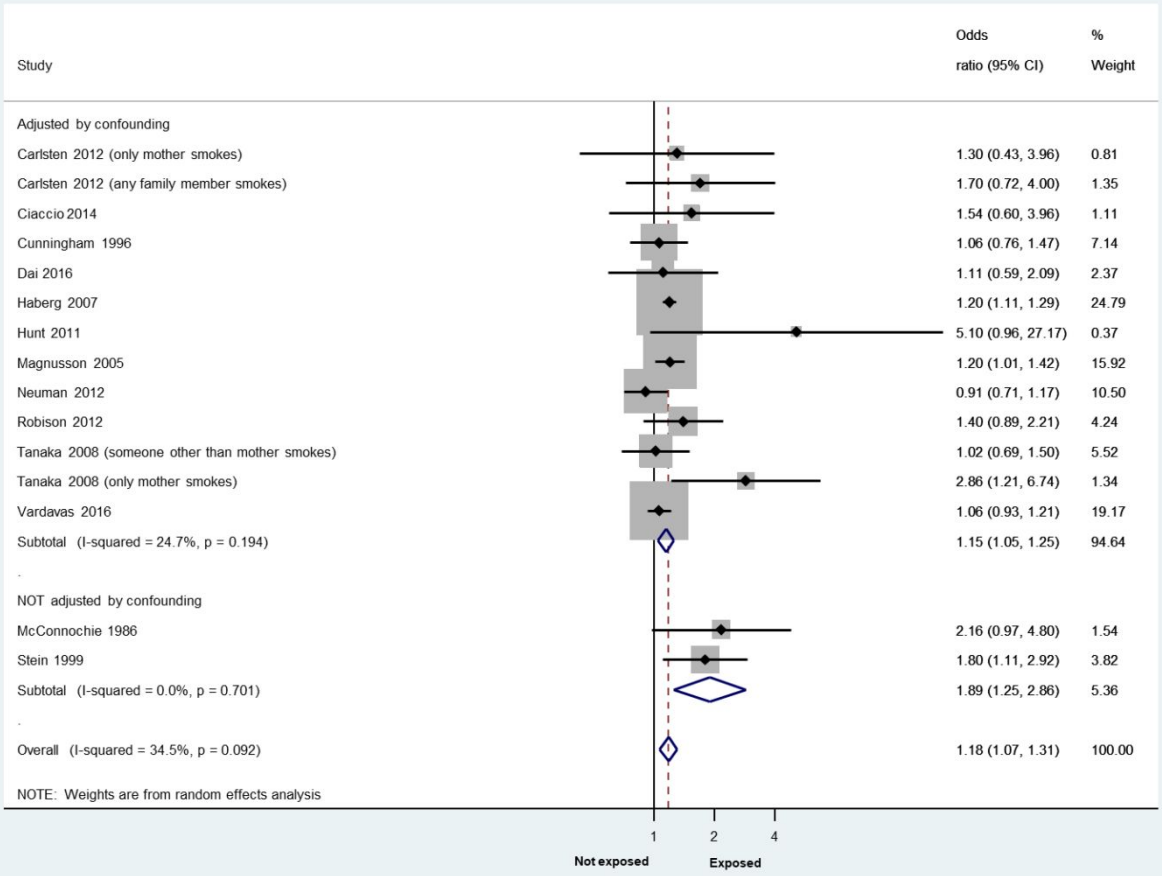


**Figure S1H. Impact of postnatal ETS (combustion smoke) on the risk of recurrent wheezing (stratified by person smoking – mother/father/both/relatives/others)**

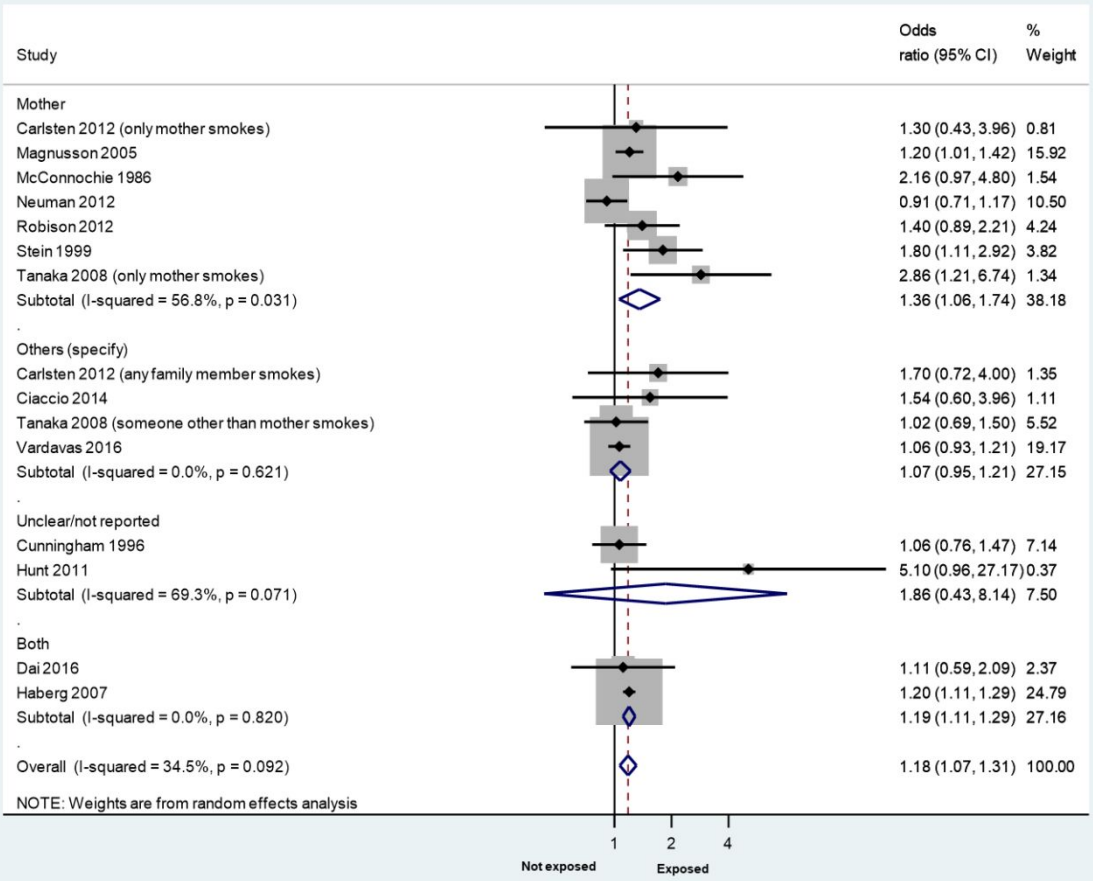


**Figure S1l. Impact of combined pre and postnatal ETS (combustion smoke) on the risk of new-onset asthma (overall and by adjustmented by confounders)**

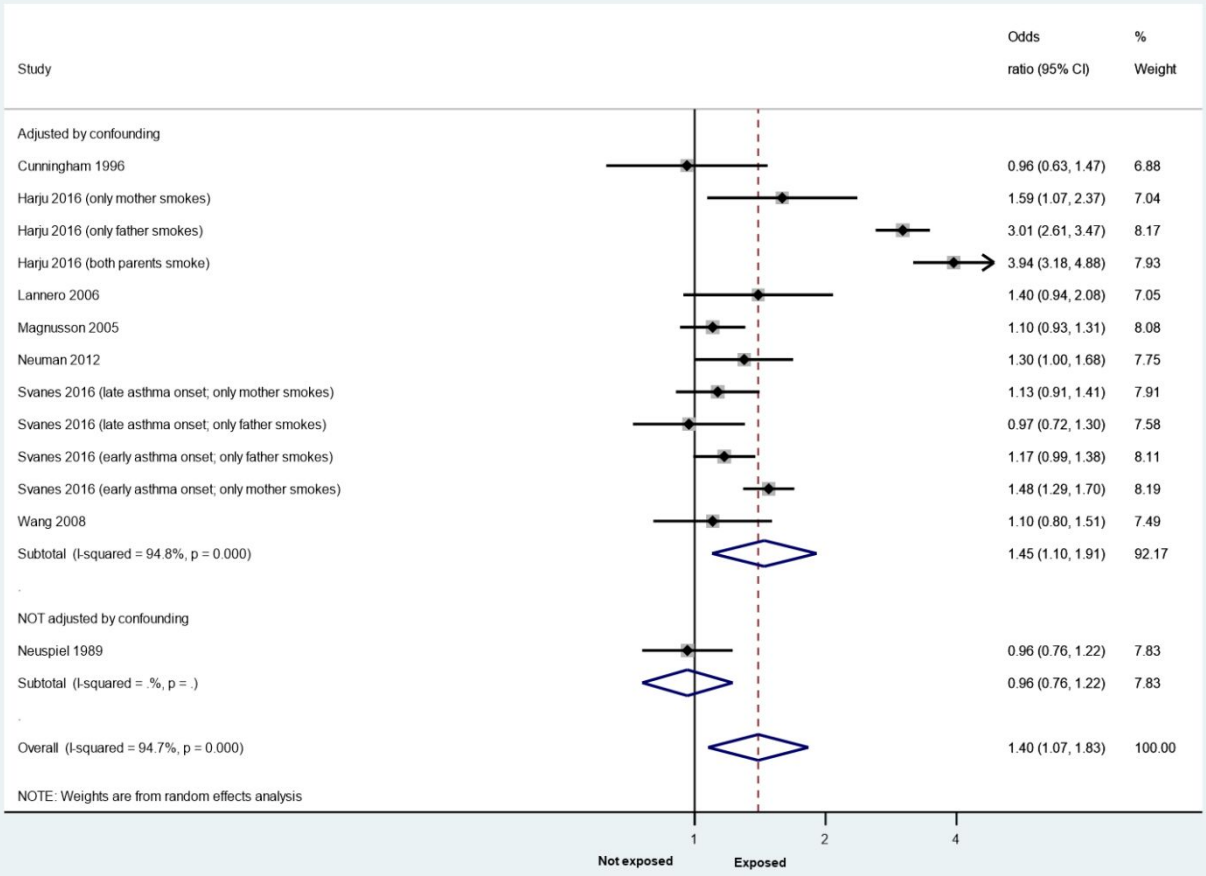


**Figure S1J. Impact of combined pre and postnatal ETS (combustion smoke) on the risk of new-onset asthma (stratified by person smoking – mother/father/both/relative/other)**

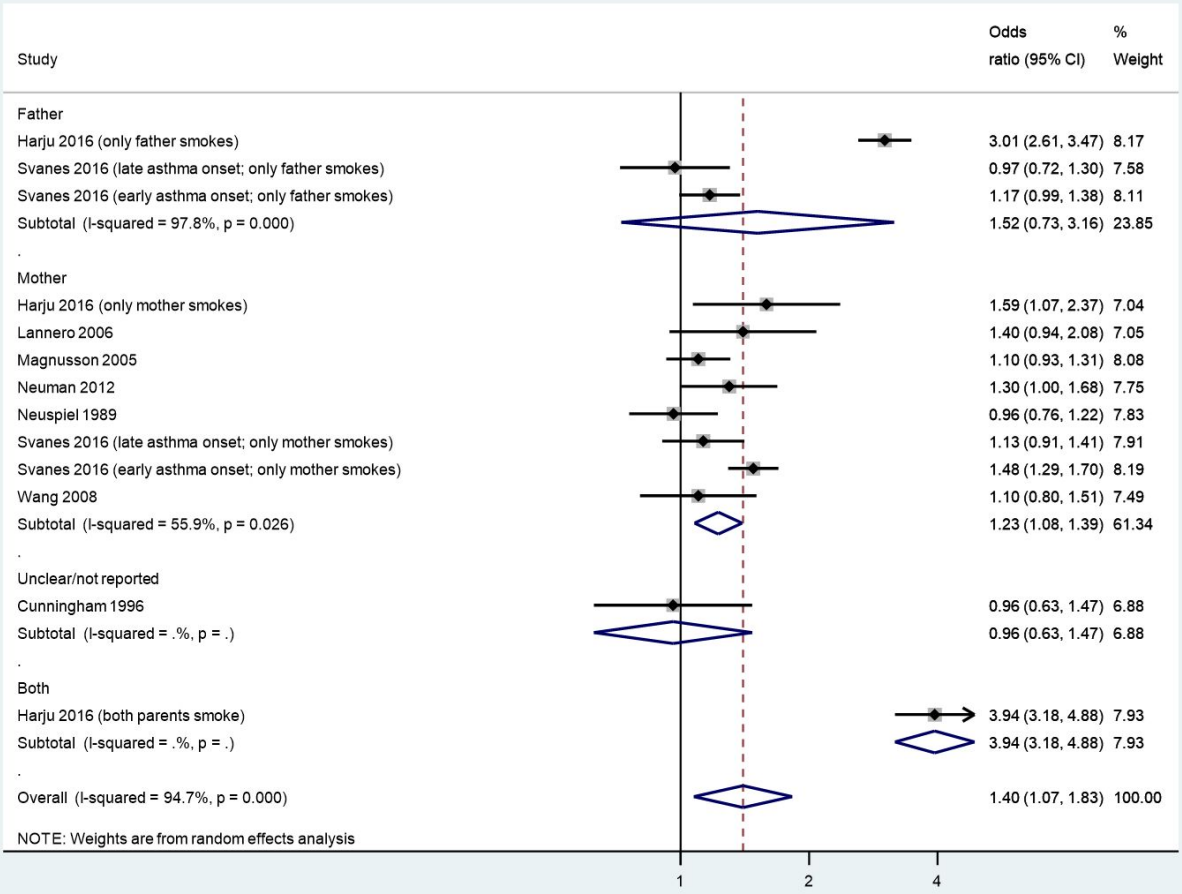


**Figure S1K. Impact of combined pre and postnatal ETS (combustion smoke) on the risk of recurrent wheezing (overall)**

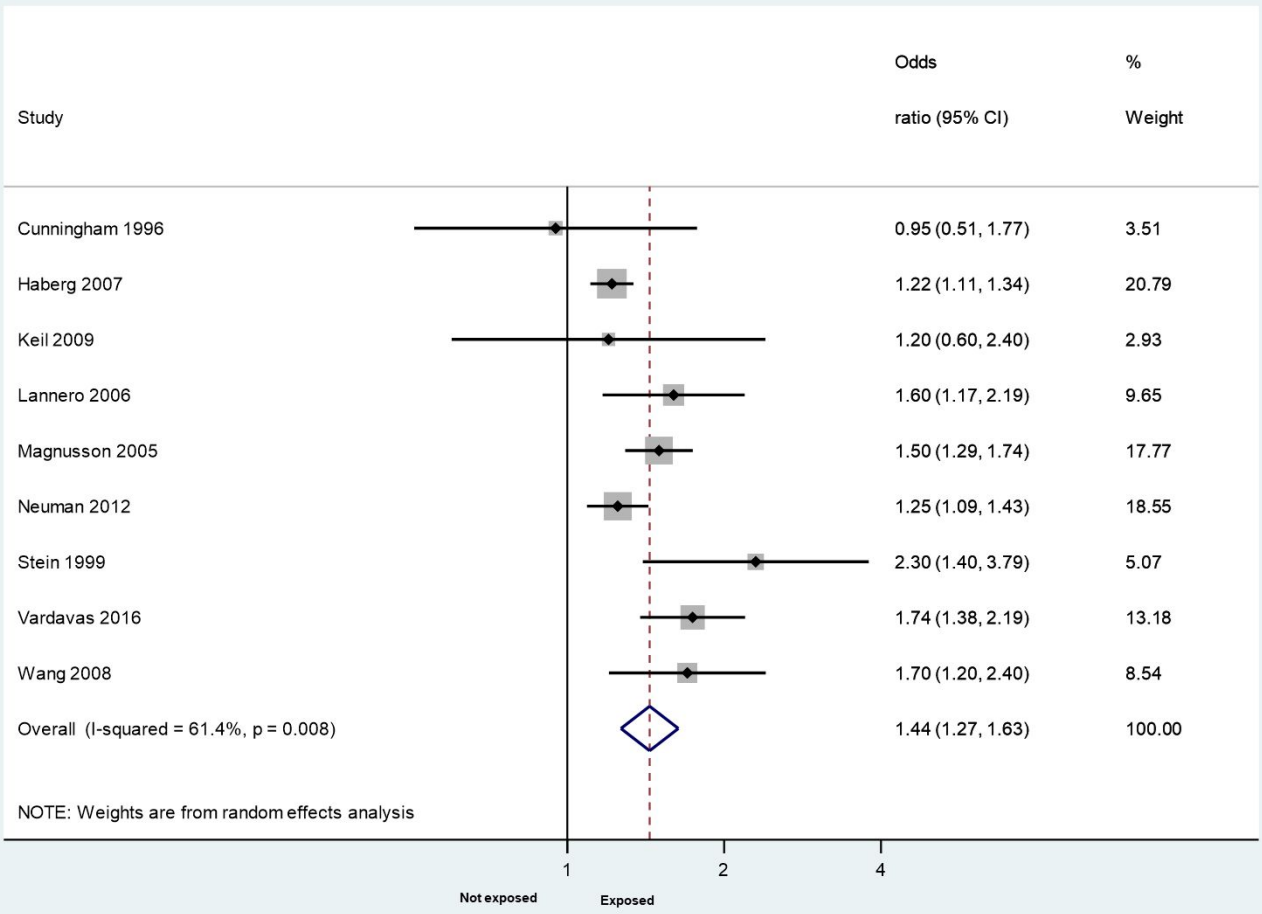


**Figure S1L. Impact of combined pre and postnatal ETS (combustion smoke) on the risk of recurrent wheezing (stratified by person smoking – mother/father/both/relative/other)**

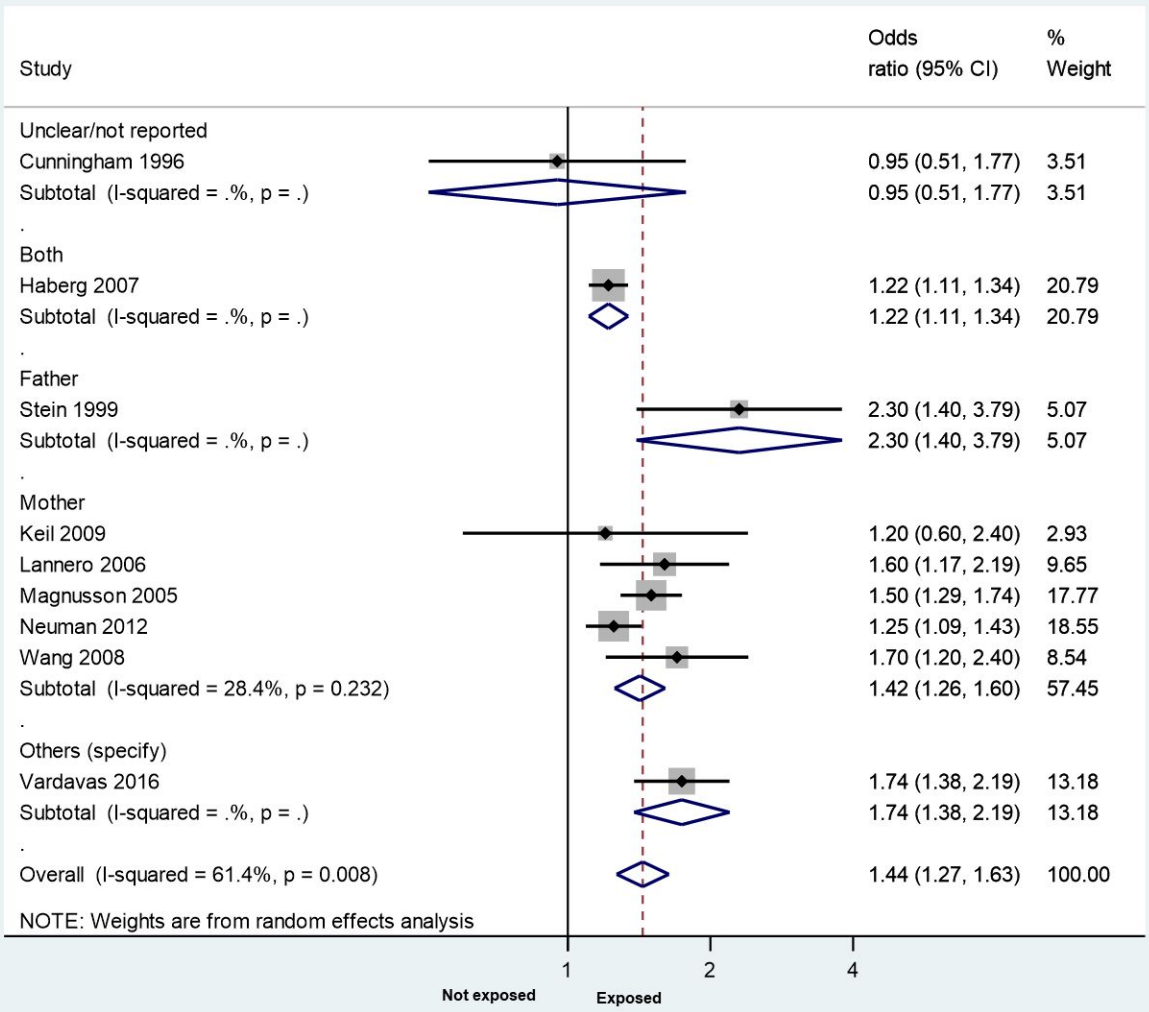


**Figure S3A. Impact of active smoking on the risk of severe asthma exacerbations - overall and adjusted for confounders**

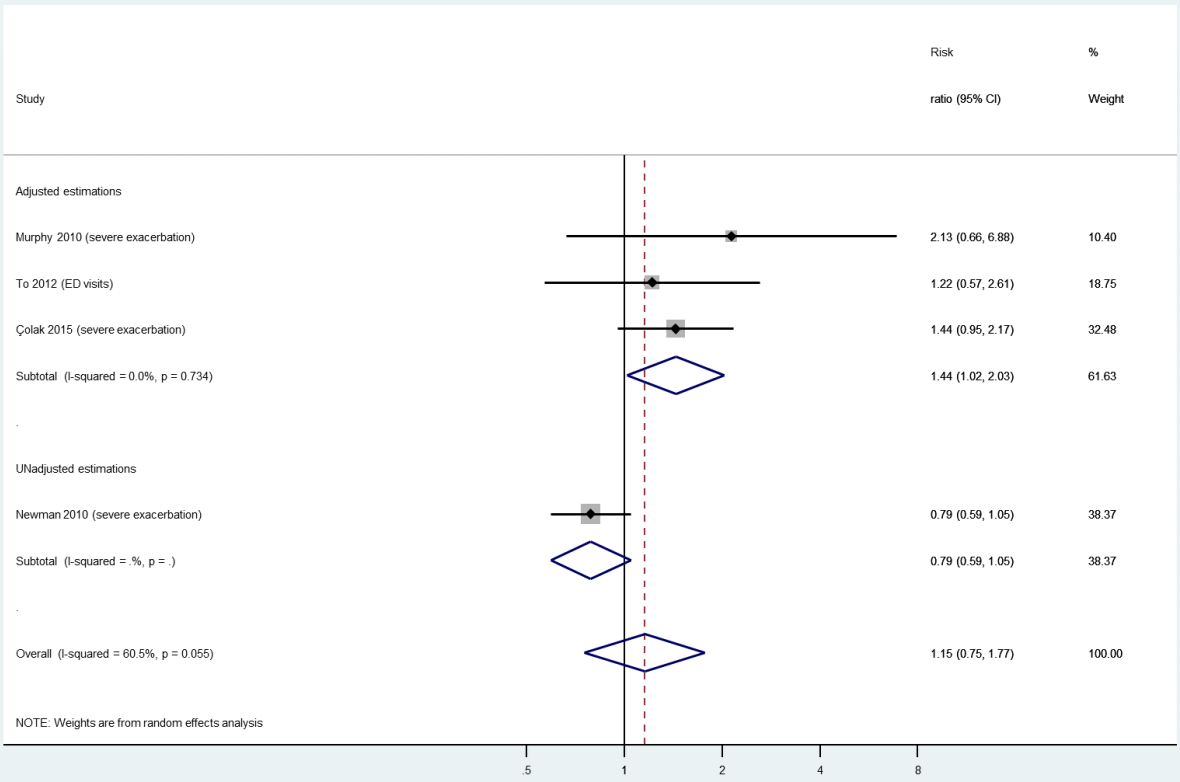
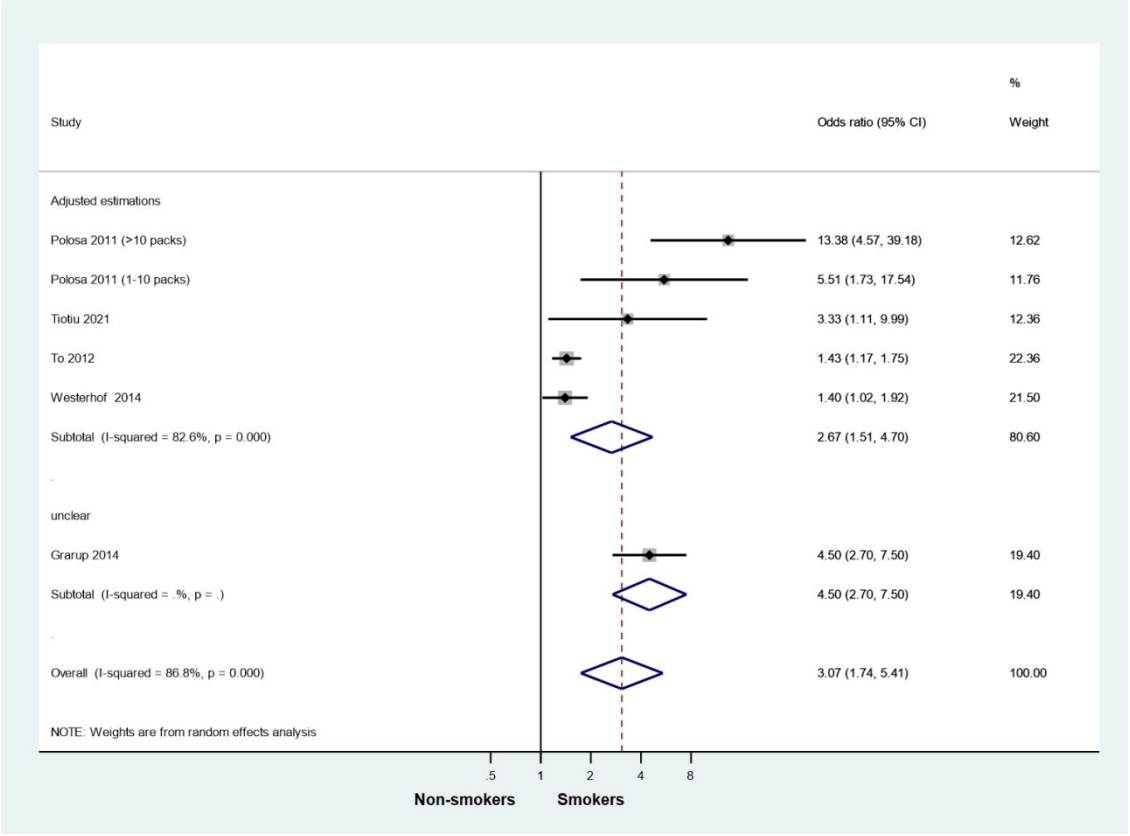


**Figure S3B. Impact of active smoking on asthma control ***




* Number of events by group not reported in the studies included, and therefore not included in the Forest Plot.

**Figure S3C. Impact of active smoking on asthma-related quality of life**

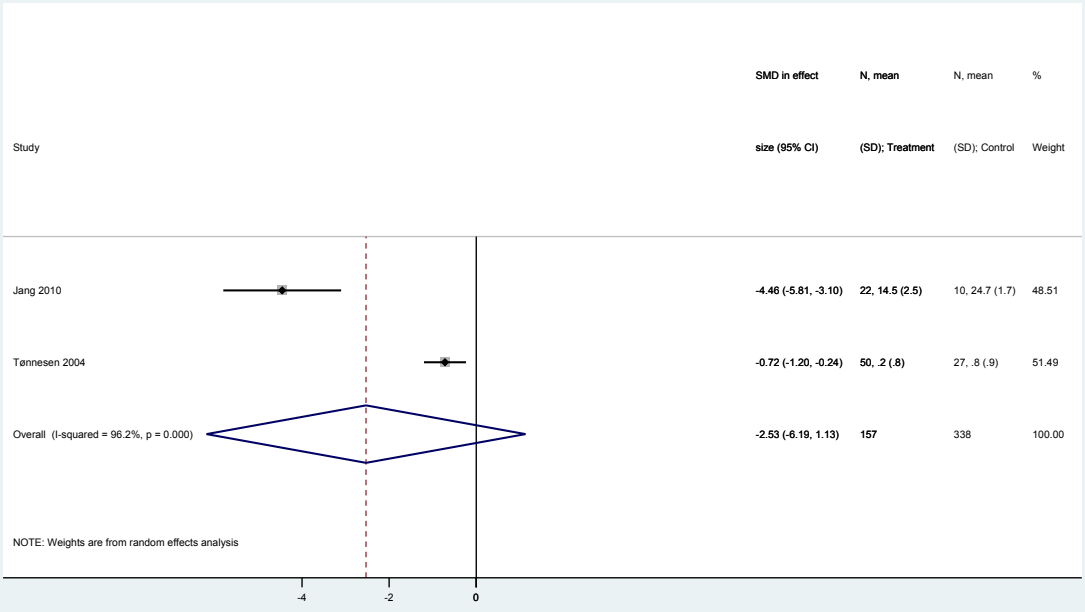


**Figure S3D. Impact of active smoking on asthma-related quality of life in adults with asthma - overall and adjusted for confounding variables**

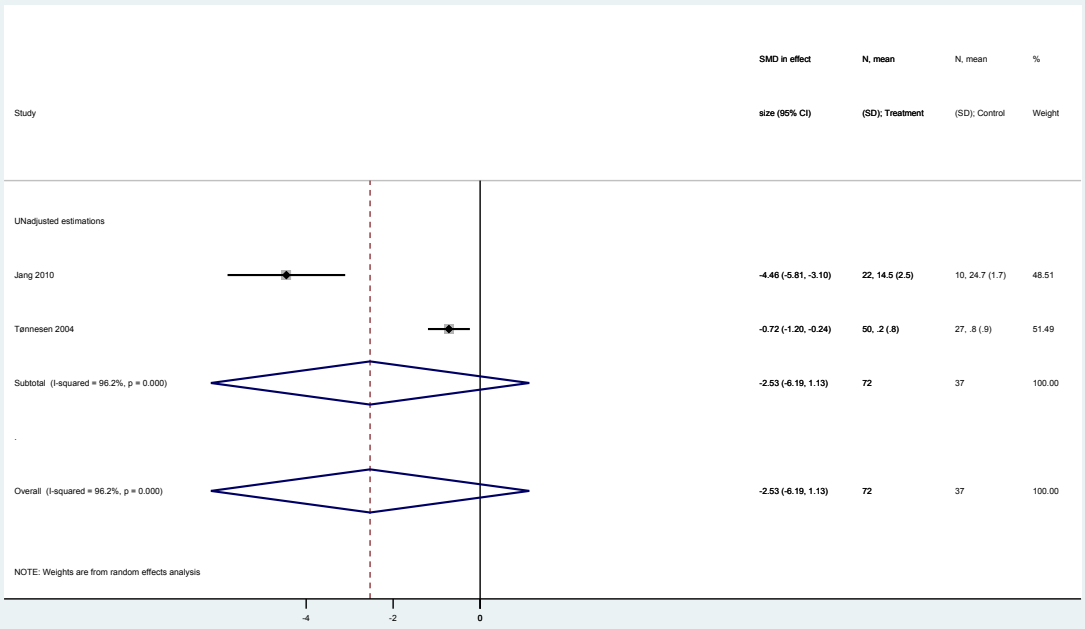



**Figure S3E. Impact of active smoking on lung function (FEV1 % predicted) in patients with asthma - overall and by stratified by age group**

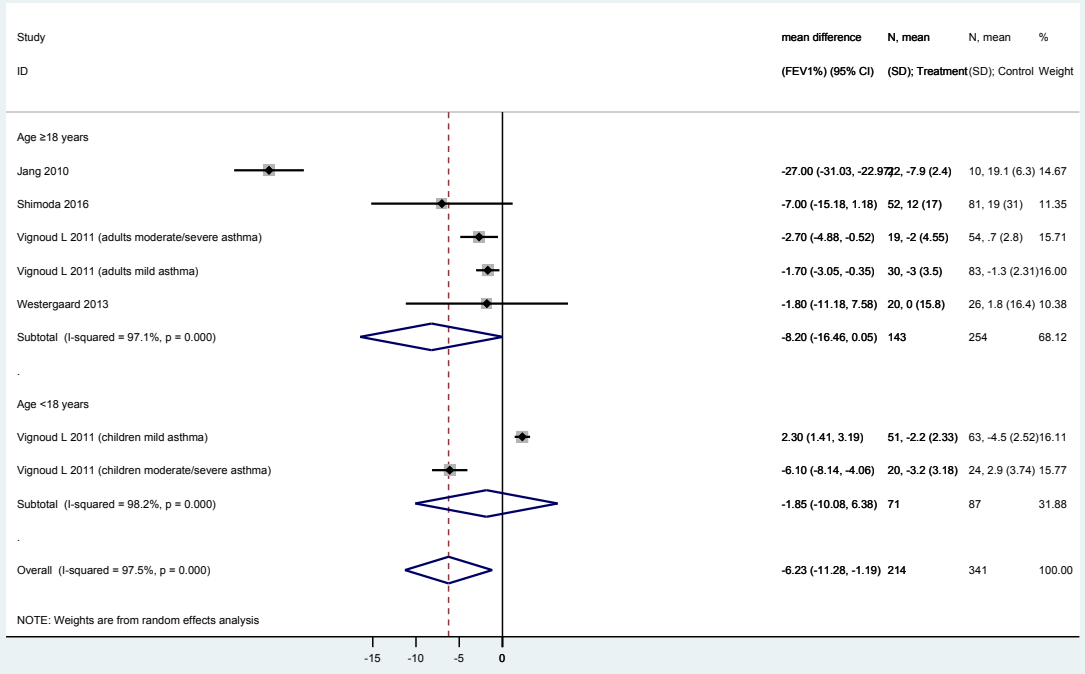


**Figure S3F. Impact of active smoking on lung function (FEV1% predicted) in patients with asthma - overall and adjusted by confounding factors**

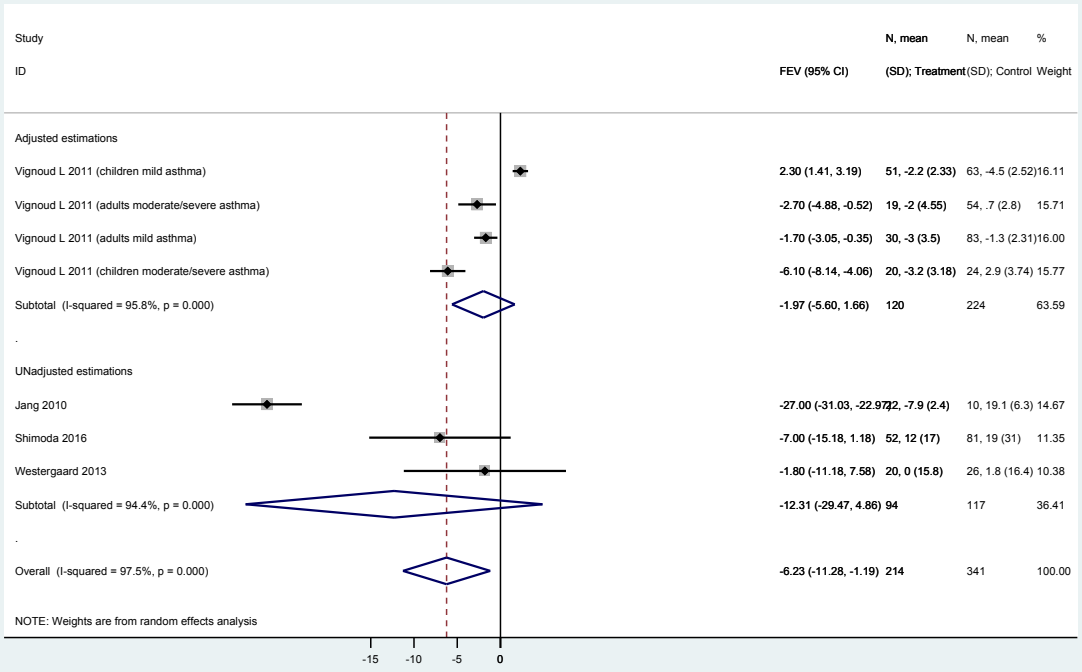


**Table S1. Search strategy in Medline (PubMed, 29/07/2022)**

| | | |
|---|---|---|
| 1 | "Asthma"[Mesh] | 138,399 |
| 2 | asthma*[tiab] | 174,688 |
| 3 | wheez*[tiab] | 15,156 |
| 4 | cough*[ti] | 12,206 |
| 5 | #1 OR #2 OR #3 OR #4 | 210,602 |
| 6 | "Smoking"[Mesh] | 158,173 |
| 7 | "Tobacco Smoke Pollution"[Mesh] | 14,271 |
| 8 | "Tobacco Smoking"[Mesh] | 5,548 |
| 9 | "Smoking Devices"[Mesh] | 15,668 |
| 10 | cigarette*[ti] | 28,085 |
| 11 | e-cigarette[ti] | 2,18 |
| 12 | tobacco[ti] | 44,834 |
| 13 | smoking[ti] | 65,714 |
| 14 | (environment*[ti] OR secondhand[ti] OR "second hand"[ti]) AND (smok*[ti]) | 4,084 |
| 15 | (maternal[ti] OR pregnan*[ti] OR prenatal[ti] OR postnatal[ti] OR bedshare*[ti] OR parent*[ti] OR early[ti] OR "Maternal Behavior"[Mesh]) AND (smok*[ti]) | 6,881 |
| 16 | "in utero smoke"[ti] OR "in utero smoking"[ti] | 7 |
| 17 | "intrauterine smoke"[ti] OR "intrauterine smoking"[ti] | 7 |
| 18 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 | 215,692 |
| 19 | #5 AND #18 | 6,721 |
| 20 | (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh]) | 4,789,828 |
| 21 | #19 AND #20 | 1,714 |
| 22 | #19 NOT #21 | 5,007 |
| 23 | "Cohort Studies"[Mesh:NoExp] | 316,217 |
| 24 | "Follow-Up Studies"[Mesh] | 686,391 |
| 25 | "Prospective Studies"[Mesh] | 633,873 |
| 26 | "Comparative Study"[pt] | 1,911,324 |
| 27 | "Case-Control Studies"[Mesh] | 1,339,313 |
| 28 | "Observational Study"[pt] | 130,162 |
| 29 | "Cross-Sectional Studies"[Mesh] | 433,883 |
| 30 | cohort[tiab] | 705,107 |
| 31 | compare*[tiab] | 4,532,523 |
| 32 | prospective*[tiab] | 817,202 |
| 33 | propensity[tiab] | 80,626 |
| 34 | "case control"[tiab] | 146,378 |
| 35 | case[tiab] AND control[ti] AND match*[ti] | 2,011 |
| 36 | "cross sectional"[ti] | 76,536 |
| 37 | #23 OR #24 OR #25 OR #26 OR #28 OR #30 OR #31 OR #32 OR #33 | 7,116,531 |
| 38 | #22 AND #37 | 2,051 |
| 39 | #19 NOT (#21 OR #38) | 2,956 |
| 40 | #27 OR #34 OR #35 | 1,385,552 |
| 41 | #39 AND #40 | 190 |
| 42 | #19 NOT (#21 OR #38 OR #41) | 2,766 |
| 43 | #29 OR #36 | 454,944 |
| 44 | #42 AND #43 | 332 |
| 45 | #21 OR #38 OR #41 OR #44 | 4,287 |

**Table S2. Search strategy in EMBASE (embase.com, 29/07/2022)**

#1 'asthma'/exp AND [embase]/lim 258820
#2 asthma*:ti AND [embase]/lim 117951
#3 #1 OR #2 261143
#4 'smoking and smoking related phenomena'/exp AND [embase]/lim 433997
#5 'smoking'/exp AND [embase]/lim 390182
#6 'tobacco smoke'/exp AND [embase]/lim 13506
#7 'smoking device'/exp AND [embase]/lim 11022
#8 cigarette*:ti AND [embase]/lim 26056
#9 'e-cigarette*':ti AND [embase]/lim 2959
#10 tobacco:ti AND [embase]/lim 29807
#11 smoking:ti AND [embase]/lim 59403
#12 (environment*:ti OR secondhand:ti OR 'second hand':ti) AND smok*:ti AND [embase]/lim 3784
#13 (maternal:ti OR pregnan*:ti OR prenatal:ti OR postnatal:ti OR bedshare*:ti OR parent*:ti OR early:ti) AND smok*:ti AND [embase]/lim 6367
#14 'maternal behavior'/exp AND smok*:ti AND [embase]/lim 377
#15 ('in utero smoke':ti OR 'in utero smoking':ti) AND [embase]/lim 20
#16 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 448723
#17 #3 AND #16 20073
#18 (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt) AND [embase]/lim 478785
#19 ((controlled NEAR/8 (study OR design OR trial)):ti,ab,tt) AND [embase]/lim 365277
#20 'cohort analysis'/exp AND [embase]/lim 812933
#21 'prospective study'/exp AND [embase]/lim 674175
#22 'comparative study'/mj AND [embase]/lim 15401
#23 cohort*:ti,ab AND [embase]/lim 1180726
#24 propensity:ti,ab AND [embase]/lim 97725
#25 prospective*:ti,ab AND [embase]/lim 1137620
#26 'controlled study'/mj AND [embase]/lim 7038
#27 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 3023103
#28 #17 AND #27 4693
#29 #17 NOT #28 15380
#30 'case control study'/exp AND [embase]/lim 152475
#31 'case control*':ti,ab,tt AND [embase]/lim 174195
#32 #30 OR #31 212623
#33 #29 AND #32 475
#34 #17 NOT (#28 OR #33) 14905
#35 'cross-sectional study'/exp AND [embase]/lim 355931
#36 'cross sectional':ti,ab AND [embase]/lim 481037
#37 #35 OR #36 553646
#38 #34 AND #37 1745
#39 #28 OR #33 OR #38 6913

**Table S3. Characteristics of individual studies included in the SR on the effect of ETS (combustion or e-cigarette) on the risk of new-onset asthma**

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **A. Pre-natal environmental exposure to smoking** | | | | | | | | | |
| **Accordini 2018** | Cohort study (prospective) | Australia; Belgium; Denmark; Estonia; France; Germany; Iceland; Italy; Norway; Spain; Sweden; United Kingdom | 1991-2013 | Not reported | To examine the pattern of associations between tobacco smoking and asthma across three generations (grandparents, parents, offspring), during different developmental stages within those generations | Subjects who had participated in ECRHS I and III, and who had reported at least one offspring at the ECRHS III clinical interview | 8858 | Offspring in maternal line: 26 years; Offspring in paternal line: 24 years | 50 |
| **Alati 2006** | Cohort study (prospective) | Australia | 1981-1984 | 14 years | To evaluate the link between maternal smoking during pregnancy and parental smoking soon after birth and the development of asthma symptoms in adolescence | Birth cohort study of mothers and children enrolled at the first antenatal visit at a single hospital. | 3915 | 14 | 48 |
| **Bentouhami 2022** | Cohort study (prospective) | Belgium | 1997-not reported- | 7 years | To assess whether the relationship between current asthma occurrence in children and recent ETS exposure is modified by perinatal exposure to ETS | Children of a cohort study in the province of Antwerp (Belgium) | 156 | 48 months (30 months) | 25.6 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Bjerg 2011** | Cohort study (prospective) | Sweden | 1996 -2001 | 4 years | To study the independent and joint effects of prenatal smoking and low birth weight on childhood asthma. | School children in first and second grade (aged 7–8 years) in 3 municipal areas (Kiruna, Luleå, and Piteå) in northern Sweden. | 3389 | NR | 49 |
| **Braback 2018** | Cohort study (prospective) | Swedish | 1982-2005 | 6 years | To investigate whether the sex of the exposed parent and/or grandchild modifies the association between grand maternal smoking and grandchild asthma | Women who gave birth to a child between 1982 and 1986 and their children were identified from the Medical Birth Register, and for whom there was full information on smoking habits in early pregnancy for mothers, maternal and paternal grandmothers | 10329 | NR | 48,5 |
| **Carlsten 2012** | Cohort study (prospective) | Canada | NR | 7 years | To compare questionnaire-based ETS estimates with bio-markers of ETS on associated risk for recurrent wheeze, physician-diagnosed asthma, and measures of bronchial hyperresponsiveness. | Having, according to parental report, at least one first-degree relative with asthma or two first-degree relatives with other IgE-mediated allergic disease (atopic dermatitis, seasonal or | 545 | NR | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | perennial allergic rhinitis, or food allergy). | | | |
| **Cunningham 1996** | Cross-sectional | USA and Canada | 1988-1990 | N/A | To examine the relationship between current and past exposure to maternal, paternal, and nonparental ETS in the home and several measures of asthma and wheeze in school-aged children from 24 communities across the United States and Canada | School-aged children aged 8-11 years | 11534 | NR | 51 |
| **Den Dekker 2015** | Cohort study (prospective) | The Netherlands | 2002-2012 | 6 years | To examine the associations of maternal and paternal smoking in different periods of pregnancy and childhood with airway resistance, airway inflammation, wheezing patterns, and physician-diagnosed asthma in school-aged children | Pregnant women and their children. Eligible mothers were those who were resident in the study area at their delivery date and had a delivery date from April 2002 until January 2006. | 6007 | 6 years | 49.3 |
| **Dezateux 1999** | Cohort study (prospective) | England | NR | 1 year | To examine the association between premorbid airway function and subsequent wheezing in the first year of life and to | Healthy Caucasian term (> 35 weeks) infants without major congenital abnormalities or neonatal | 101 | 7.7 weeks | 52 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | explore the influence on this association of a family history of asthma and maternal smoking during pregnancy. | respiratory illness. Families were excluded if social or medical reasons precluded contact, or if planning to leave the area during the next year | | | |
| **Duijts 2012** | Cohort study (prospective) | The Netherlands | 2002-2006 | 4 years | To examine the associations of parental smoking during pregnancy with wheezing in preschool children and whether these associations are explained by postnatal smoke exposure or small for gestational age at birth | Mothers at their first routine ultra-sound measurement in pregnancy. | 4574 | NR | 51 |
| **Fuentes-Leonarte 2015** | Cohort study (prospective) | Spain | 2003-2008 | 1 year | To assess the effects of prenatal and postnatal exposure on the risk of respiratory outcomes during the first year of life of infants from a Spanish multicentre cohort study | Women with at least 16 years of age, singleton pregnancy, and enrolment at 10–13 weeks of gestation, no assisted conception, and delivery scheduled at the reference hospital, and no communication | 2039 | NR | 49 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | handicap. Exclusion of women who had a spontaneous abortion or foetal loss. | | | |
| **Gilliland 2003** | Cohort study (prospective) | USA | 1993-not reported | 8 years | To investigate effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function | Volunteer schoolchildren except those in special classes for gifted or learning-disabled students. | 5933 | NR | 51.6 |
| **Gilliland 2006** | Cohort study (prospective) | USA | 1993-1996 | 8 years | To determine whether regular smoking is associated with the new onset of asthma during adolescence. | Children with no lifetime history of asthma or wheezing who were recruited from fourth- and seventh-grade classrooms and followedannually in schools in 12 southern California communities | 2609 | NR | 50 |
| **Grazuleviciene 2014** | Cohort study (prospective) | Lithuania | 2007-2013 | 4-6 years (age of children) | To investigate the association between maternal smoking during pregnancy, second-hand tobacco smoke exposure, education level, and preschool children's wheezing and overweight. | Children who had reached 18 months of age and for whom there was information on all (prenatal and postnatal) applied questionnaires. | 22390 | NR | 48.7 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Haberg 2007** | Cohort study (prospective) | Norway | 2000-2004 | 18 months | To assess the effects of prenatal and postnatal smoking on early childhood respiratory health. | Clinical birth cohort of a University Hospital, with exclusion of stillbirths | 39306 | NR | NR |
| **Henderson 2010** | Cohort study (prospective) | UK | 1991-1999 | 7.5 years | To examine whether functional polymorphisms of GST and Nrf2 genes modified the effects of prenatal tobacco smoke exposure on lung function and asthma in childhood. | Documented history of maternal asthma, and an expectation of the mother remaining in the same home for at least 1 year in urban Syracuse or an adjacent urban location. Each baby also had to have a gestational age of 37 weeks or more, a birth weight of≥2500 g, the absence of any major congenital abnormality, and singleton birth. | 103 | NR | NR |
| **Jaakkola 2001** | Cohort study (prospective) | Norway | 1992-1993 | 4 years | To investigate whether the joint effect of genetic propensity to asthma and exposure to ETS on the risk of childhood asthma is greater than expected on the | Population-based cohort study, where all singleton births were followed using nationwide registries | 58841 | 7 years | 48.8 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | basis of their independent effects. | | | | |
| **Jaakkola 2004** | Cohort study (prospective) | Finland | 1987-1994 | 7 years | To examine the relationships among maternal smoking in pregnancy, foetal development, and the risk of asthma in childhood. | Children born in Finland in 1987 and followed using national administrative health registries | 56629 | NR | 48.5 |
| **Jaakkola 2007** | Cohort study (prospective) | Finland | 1987-NR | 7 years | To explore potential differences in the susceptibility of boys and girls to the effects of maternal smoking on asthma, using data from a cohort of Finnish children born in 1987 | Finnish singleton babies born in1987 through 5 nationwide registries for 7 years and identified allcases of doctor-diagnosed asthma (ICD-9 code 493) | 58841 | 6.8 (median) | 41.6 |
| **Karmaus 2008** | Cohort study (prospective) | UK | 1989–1990 | 10 years | To characterize the joint effects of a risk-triad consisting of maternal smoking during pregnancy, breastfeeding for less than 3 months, and recurrent lower respiratory tract infections on physician-diagnosed childhood asthma. | Children born on the Isle of Wight between January 1, 1989 and February 28, 1990. | 1336 | N/A | 49 |
| **Lannero 2006** | Cohort study (prospective) | Sweden | February 1994-November 1996 | 22 months | To assess the possible effects of exposure to cigarette smoking in utero on lower respiratory | Newborn infants born in Stockholm at their first visit to the Child Health Centre. Infants | 3790 | NR | 49.4 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | disease in children up to two years of age. | were excluded if they had a serious disease or if the families planned to move within a year, had insufficient knowledge of Swedish or had an already enrolled older sibling. | | | |
| **Lundholm 2019** | Cohort study (prospective) | Sweden | 2005-2015 | 6 years | To estimate the association between tobacco use in pregnancy (both smoking and Swedish oral moist snuff) and asthma/wheeze in the offspring, how it varies by the child's age and explore the influence of measured and unmeasured familial confounding | All children born in Sweden between 2005 and 2012. Exclusion criteria: children who were stillborn, children missing information on mother's identity or migrated to/from Sweden during pregnancy, and children themselves not registered as residents in Sweden. | 788508 | NR | |
| **Magnus 2015** | Cohort study (prospective) | Norway | 1999-2008 | 7 years | To examine the association between grandmother's smoking during pregnancy and asthma development in the grandchild. | Pregnant women at approximately 18 weeks gestation. Exclusion criteria: Children not linked to the | 53169 | NR | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | national birth registry and children and from multiple births | | | |
| **Magnusson 2005** | Cohort study (prospective) | Denmark | 1984-1987 | 8 years | To investigate the effects of maternal smoking in pregnancy on asthma, hay fever, atopic eczema, and wheezing in the offspring up to the age of 14–18. | All pregnant women in the two Danish cities, Odense and Aalborg. | 7844 | Follow-up up to the ages of 14–18 years old | 48.4 |
| **Menezes 2007** | Cohort study (prospective) | Brazil | 1993-2005 | 4 years | To evaluate risk factors for wheezing in early adolescence, with emphasis on sex differences. | All mothers giving birth in hospitals of Pelotas, Brazil (1993). | 5249 | NR | NR |
| **Moradzadeh 2018** | Cohort study (retrospective) | USA | 2011-2012 | NR | To examine the effect of self-reported maternal smoking during pregnancy on childhood asthma | Noninstitutionalized civilian resident population of the United States who were 1-15 years of age and for whom both outcome and exposure data had been reported. Participants with missing data on the hay fever, maternal age at birth, weight at birth, household smoking variables were excluded. | 3074 | Patients with asthma: 8.5 (4.1); Patients without asthma: 7.1 (4.2) | 49 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Neuman 2012** | Cohort study (retrospective) | Germany; Spain; Netherlands; Sweden; Denmark; UK | 1990-1999 | 4-6 years (age of children) | To assess the effect of exposure to maternal smoking during pregnancy on wheeze and asthma among preschool-age children | Participants recruited during pregnancy or in the first months after birth with at least one follow-up assessment of the outcomes of wheeze or asthma at 4 to 6 years of age, and with information on maternal smoking during pregnancy and from the first year after birth. | 21600 | NR | NR |
| **Rivas-Juesas 2021** | Cohort study (prospective) | Spain | 2018-2019 | 12 months | To compare the incidence of asthma diagnosed in infants during the first year of life according to the smoking status of their mothers during pregnancy | Babies born at term and alive in a single hospital of Valencia, Spain (2017-2018) | 648 | NR | 46 |
| **Robison 2012** | Cohort study (prospective) | USA | 1998-2010 | 6 years | To evaluate the interaction between maternal smoking and prematurity upon the development of early childhood wheezing. | Women admitted to delivery at a medical centre who delivered a singleton live infant. | 1448 | mean, SD: 3.1 (2.4) years in the non-wheezing group, 4.7 (2.3) years in the | 50 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | wheezing group | |
| **Scherman 2021** | Cohort study (prospective) | USA | 2012-2015 | 12 months | To examine the relationship between maternal chronic stress (indexed by prenatal hair cortisolconcentration), and maternally reported wheezing in children through 12 months of age among a sample of 132 US pregnant women exposed to prenatal cigarette smoke | English-speaking pregnant women at least 15 years of age, with a singleton gestation, and who reported smoking cigarettes. | 132 | NR | 48 |
| **Spanier 2011** | Cohort study (prospective) | USA | NR | 2 years | To identify the optimal measure of active and passive prenatal tobacco exposure to predict wheeze in early life | English-speaking women at 16 (+-2 weeks) gestation, living in a home built before 1979, residing within 5 Ohio counties surrounding Cincinnati, receiving prenatal care from a participating obstetrical clinic, and giving birth at a participating hospital. Women were ineligible when they were human immunodeficiency | 367 | NR | 55.3 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | virus positive, were taking anti-epileptic medication, were receiving chemotherapy, had diabetes mellitus (not gestational), had bipolar disorder, or had schizophrenia. | | | |
| **Stein 1999** | Cohort study (prospective) | USA | 1980-1984 | 11 years | To examine the effects of passive smoking on respiratory symptoms in a cohort of over 1,000 children born during 1980-1984. | Newborns (born between 1980-1984) whose parents used one of the largest health maintenance organizations in Tucson, Arizona. Premature infants were not excluded if they were healthy | 1104 | 1-10 years (depending on the follow-up year). | NR |
| **Sunde 2022** | Cohort study (prospective) | Denmark | NR | 7 years | To examine the effect of prenatal tobacco exposure and its relation to 17q12-21 genotype on a wide array of asthma and allergy-related outcomes in early childhood | Infants of mothers with history of asthma, excluding those with a severe congenital anomaly, a gestational age younger than 36 weeks, a need for mechanical ventilation, or a | 411 | NR | 51.6 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | lower respiratory tract infection | | | |
| **Svanes 2016** | Cohort study (prospective) | Norway, Sweden, Iceland, Denmark, Estonia | 1991-2012 | NR | To examine whether parental exposure to smoking and welding, including exposure prior to conception, influenced asthma risk in offspring, with a particular focus on exposures in fathers. | Random population samples of men and women born in 1945–73. | 26945 | 22 (range: 2-51) | NR |
| **Tabuchi 2015** | Cohort study (prospective) | Japan | 2001-2009 | 8 years | To assess whether and how parental smoking behaviours, combined with indoor smoking status at home, were associated with the development and severity of childhood asthma from very young ages up to 8 years of age, using data from a large nationally representative birth cohort study. | All infants born in Japan during the periods January 10–17, 2001, and July 10–17, 2001. The analysis was limited to cases where both parents lived together with the subjects at the time of the first survey. | 42768 | NR | 48 |
| **Tanaka 2008** | Cohort study (prospective) | Japan | 2001-2003 | 24 months | To evaluate the association between maternal smoking during pregnancy and postnatal exposure to ETS and the development of wheeze, asthma, and | Pregnant women were who lived in Neyagawa City (Osaka Prefecture) | 763 | NR | 47.0 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | atopic eczema in Japanese infants | | | | |
| **Tanaka 2017** | Cohort study (prospective) | Japan | 2007-2008 | 2 years | To examine the association between prenatal and postnatal tobacco smoke exposure during the first year of life and the risk of wheeze in Japanese children aged 23 to 29 months. | Women who became pregnant in one of seven prefectures on Kyushu Island or Okinawa Prefecture between April 2007 and March 2008. | 1354 | NR | 52.3 |
| **Tanaka 2020** | Cohort study (prospective) | Japan | 2007-2008 | 3 years | To investigate the association between prenatal and postnatal tobacco smoke exposure and the risk of asthma in Japanese children | Women who became pregnant in one of seven prefectures on Kyushu Island or Okinawa Prefecture between April 2007 and March 2008 | 1304 | NR | 52.7 |
| **Tariq 2007** | Cohort study (prospective) | UK | 1989-1990 | 4 years | To examine the influence of ETS on the development of asthma symptoms and allergen sensitisation during early childhood. | Consecutive births (January 1989 - February 1990) over the whole of the Isle of Wight. Exclusion of perinatal deaths, adoptions and moves | 1218 | NR | NR |
| **Thacher 2014** | Cohort study (prospective) | Sweden | 1994-1996 | 16 years | To examine the role of prenatal and postnatal second-hand tobacco smoke exposure on asthma, | Parents of newborn children (1994-1996), living in Stockholm. | 3798 | NR | 49 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | rhinitis, and eczema development up to 16 years of age. | Exclusion criteria: the family planned to move within 1 year of the study start; insufficient knowledge of the Swedish language; the family had a seriously ill child; or an older sister or brother was already included in the study. | | | |
| **Thacher 2018** | Cohort study (prospective) | Netherlands; Germany; Sweden; | 1990-1999 | 14 to 16 years | To examine the association of exposure to parental smoking during foetal life, infancy, childhood and adolescence with the onset, progression, and persistence of asthma and rhinoconjuntivitis during childhood and adolescence. | Participants of cohorts with (i) relevant information on maternal smoking during pregnancy or secondhand smoking exposure during the first year of life, (ii) follow-up between 14 and 16 years of age; and (iii) suitable outcome assessments from three predefined age intervals (4–6, 8–10, and 14–16 years) were included. | 10603 | NR | 50 |
| **Vanker 2017** | Cohort study (prospective) | South Africa | 2012-2015 | 1 year | To investigate antenatal and postnatal exposure | Pregnant women were enrolled at 20–28 weeks' | 1065 | 0-1 year | 49 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | to indoor air pollution or environmental tobacco smoke, and its association with lower respiratory tract illness or wheezing illness in a South African birth cohort study. | gestation at two public primary health clinics serving different populations. Participants who were younger than 18 years, who did not attend study clinics for postnatal care, or who were intending to move out of the district within 2 years after the infant's birth were excluded | | | |
| **Vardavas 2016** | Cohort study (prospective) | 19 European countries (European birth cohorts) | 1990-2008 | NR | To examine the association between maternal passive smoking during pregnancy and wheeze in children up to the age of 2 years. | Newborns (recruited during pregnancy or shortly after birth) for which there was information of maternal and infant exposure to active and passive smoking, and on the development of wheeze before the age of 2 years. | 27993 | NR | 48.4 |
| **Wada 2021** | Cohort study (prospective) | Japan | 2011-2014 | 13 years | To investigate the effect of maternal exposure to tobacco | Pregnant women residing in one of the study areas at | 90210 | NR | 49 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | smoke on wheeze/ asthma development at 1 year of age in her offspring using data from the nationwide birth cohort study in Japan | the time of recruitment, with expected delivery date after August1, 2011, and capable of comprehending the Japanese language and completing the self-administered questionnaires. | | | |
| **Weitzman 1990** | Cross-sectional | USA | 1981 | N/A | To study the relationship between maternal smoking and (1) the prevalence of childhood asthma, (2) the likelihood of taking asthma medication, (3) the age of onset of children's asthma, and (4) the number of hospitalizations among children with and without asthma. | Civilian noninstitutionalized population of the United States, with assessment of one randomly chosen child in each eligible household. | 4331 | NR | NR |
| **Werhmeister 2015** | Cohort study (prospective) | Brazil | 1993-2009 | 15 years | To evaluate the association between parental smoking during pregnancy and wheezing during childhood/adolescence (11 and 15 years of age) in individuals from a prospective | All hospital live births in the city - New-borns whose mothers lived in the urban area were included. | 5249 | NR | 50.3 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | birth cohort in southern Brazil. | | | | |
| **Wu 2014** | Cohort study (prospective) | Taiwan | 1999-2001 | 6 years | To investigate the interactions among GSTM1 genotype, gender, and prenatal ETS regarding childhood asthma development. | Parents of children were prenatally recruited in the Kaohsiung Chang Gung Memorial Hospital by a study nurse to enroll the birth cohort. | 756 | NR | NR |
| **Wu 2019** | Cohort study (prospective) | Taiwan | NR | 6 years | To investigate whether parental tobacco smoke exposure was associated with the offspring's asthma and correlated to epigenetic methylation of potential tobacco-related immune genes | Newborns at a single centre hospital | 1629 | NR | 46.9 |
| **Young 2000** | Cohort study (prospective) | Australia | 1987-1991 | 12 months | To assess the influence of infant gender, parental history of asthma, and parental antenatal smoking on respiratory function during the first year of life using prospective longitudinal lung function data. | Full-term gestation (>36 weeks), an absence of perinatal health problems, and no major congenital anomalies. | 237 | NR | 43 |
| **B. Post-natal environmental exposure to combustion smoking** | | | | | | | | | |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Alati 2006** | Cohort study (prospective) | Australia | 1981-1984 | 14 years | To evaluate the link between maternal smoking during pregnancy and parental smoking soon after birth and the development of asthma symptoms in adolescence | Birth cohort study of mothers and children enrolled at the first antenatal visit at a single hospital. | 3915 | 14 | 48 |
| **Carlsten 2012** | Cohort study (prospective) | Canada | NR | 7 years | To compare questionnaire-based ETS estimates with bio-markers of ETS, on associated risk for recurrent wheeze, physician-diagnosed asthma, and measures of bronchial hyperresponsiveness. | Having, according to parental report, at least one first-degree relative with asthma or two first-degree relatives with other IgE-mediated allergic disease (atopic dermatitis, seasonal or perennial allergic rhinitis, or food allergy). | 545 | NR | NR |
| **Ciaccio 2014** | Cohort study (retrospective) | USA | October 2008-November 2011 | NA | To determine the association of second-hand ETS in the home environment with childhood asthma, wheeze, and oral corticosteroids use. | Families with a child that has been diagnosed with asthma, chronic respiratory symptoms, chronic allergy symptoms, or other chronic symptoms affected by a home | 382 | 8.3 (4.1) asthma group, 7.1 (4.6) no asthma group; 7.9 (4.3) wheeze group, 7.7 (4.3) no | 45 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | environment; were living in the Kansas City area; were staying at the same home at least 4 nights/week; had lived in the same home for the past 6 months; planned to live in the same home for the next 12 months; and were from families with a total family income < 80% of the Kansas City median family income. | | wheeze group | |
| **Cunningham 1996** | Cross-sectional | USA and Canada | 1988-1990 | N/A | To examine the relationship between current and past exposure to maternal, paternal, and nonparental ETS in home and several measures of asthma and wheeze in school-aged children from 24 communities across the United States and Canada | Fourth and fifth grade students from eighteen communities in the United States and six communities in Canada (selected on the basis of their ambient air pollution and demographic characteristics) were identified and invited to participate. | 11534 | NR | 51 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Dai 2016** | Cohort study (prospective) | Australia | 1990-1994 | 18 years | To investigate the association between perinatal ETS with lung function, lung function growth and asthma in children up to the age of 18 years. | Having one or both parents or any sibling(s) having either atopic dermatitis, asthma, hay fever, or severe adverse reactions to food. | 620 | NR | 48.9 |
| **Den Dekker 2015** | Cohort study (prospective) | The Netherlands | 2002-2012 | 6 years | To examine the associations of maternal and paternal smoking in different periods of pregnancy and childhood with airway resistance, airway inflammation, wheezing patterns, and physician-diagnosed asthma in school-aged children | Pregnant women and their children. Eligible mothers were those who were resident in the study area at their delivery date and had a delivery date from April 2002 until January 2006. | 6007 | 6 years | 49.3 |
| **Fergusson 1985** | Cohort study (prospective) | New Zealand | 1977-1983 | 6 years | To examine the association between parental smoking and the onset of asthma and the frequency of asthmatic attacks during early childhood. | Birth cohort of children born in the Christchurch (New Zealand) urban region in mid-1977 | 1115 | NR | NR |
| **Fernández-Plata 2016** | Cohort study (prospective) | Mexico | 1996-2002 | 6 years | To determine whether ETS at home in schoolchildren aged 8-17 years is associated with a | Students at the selected schools who were eight years of age at the beginning of the study and | 1819 | 8.7 (0.8) | 51 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | reduction in the growth of pulmonary function or with an increase in respiratory symptoms and infections, and whether there is a gender-related differential effect and an additive effect with air pollution. | residing at 2,240 m above sea level. | | | |
| **Fuentes-Leonarte 2015** | Cohort study (prospective) | Spain | 2003-2008 | 1 year | To assess the effects of prenatal and postnatal exposure on the risk of respiratory outcomes during the first year of life of infants from a Spanish multicentre cohort study | Women with at least 16 years of age, singleton pregnancy, and enrolment at 10–13 weeks of gestation, no assisted conception, delivery scheduled at the reference hospital, and no communication handicap. Exclusion of women who had a spontaneous abortion or foetal loss. | 2039 | NR | 49 |
| **Gilliland 2003** | Cohort study (prospective) | USA | 1993-not reported | 8 years | To investigate effects of early onset asthma and in utero exposure to maternal smoking on | Volunteer schoolchildren except those in special classes for gifted or | 5933 | NR | 51.6 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | childhood lung function | learning-disabled students. | | | |
| **Haberg 2007** | Cohort study (prospective) | Norway | 2000-2004 | 18 months | To assess the effects of prenatal and postnatal smoking on early childhood respiratory health. | Clinical birth cohort of a University Hospital, with exclusion of stillbirths | 39306 | NR | NR |
| **Hunt 2011** | Cohort study (prospective) | US | April 2001 and August 2002 (enrolment) | 1 year | To quantify asthma agent levels in the inner-city homes of a birth cohort whose mothers had a diagnosis of asthma. | Eligibility requirements included a documented history of maternal asthma, and an expectation of the mother remaining in the same home for at least 1 year in urban Syracuse or an adjacent urban location. Each baby alsohad to have a gestational age of 37 weeks or more, a birth weight of≥2500 g, the absence of any major congenital abnormality, andsingleton birth. | 103 mother and infant pairs completed all phases of the study. | | NR |
| **Magnusson 2005** | Cohort study (prospective) | Denmark | 1984-1987 | 8 years | To investigate the effects of maternal smoking in | All pregnant women in the two Danish cities, | 7844 | Follow-up up to the ages 14– | 48.4 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | pregnancy on asthma, hay fever, atopic eczema, and wheezing in the offspring up to the age of 14–18. | Odense and Aalborg. | | 18 years old | |
| **McConnochie 1986** | Cohort study (retrospective) | USA | 1971-1980 | Not reported | To explore the effects of passive smoking and non-breast feeding on wheezing in children aged 6 to 10 years | Patients of a five-paediatrician group practice in a suburb of Rochester (New York) born between November 1971 and August 1975. Subjects with a history of bronchiolitis or with a medical condition that might predispose them to respiratory illness were excluded. | 223 | 8.4 | 31 |
| **Neuman 2012** | Cohort study (retrospective) | Germany; Spain; Netherlands; Sweden; Denmark; UK | 1990-1999 | 4-6 years (age of children) | To assess the effect of exposure to maternal smoking during pregnancy on wheeze and asthma among preschool-age children | Participants recruited during pregnancy or in the first months after birth with at least one follow-up assessment of the outcomes of wheeze or asthma at 4 to 6 years of age, and with information on maternal | 21600 | 4-6 years | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | smoking during pregnancy and from the first year after birth. | | | |
| **Ramadas 2007** | Cohort study (prospective) | UK | 1989-1990 | 10 years | To examine the impact of ETS on the asthma risk-conferring abilities of the IL1RN polymorphism | Children born on the Isle of Wight (UK) between January 1989 and February 1990 | 921 | NR | |
| **Robison 2012** | Cohort study (prospective) | USA | 1998-2010 | 6 years | To evaluate the interaction between maternal smoking and prematurity upon the development of early childhood wheezing. | Women admitted to delivery at a medical centre who delivered a singleton live infant. | 1448 | mean, SD: 3.1 (2.4) years in the non-wheezing group, 4.7 (2.3) years in the wheezing group | 50 |
| **Sherrill 1992** | Cohort study (prospective) | New Zeeland | Between 1975 and 1990 | 15 years | To examine the longitudinal effects of ETS on lung function in a cohort of New Zealand children | Children of a birth cohort in New Zealand whose mothers were residents of Dunedin and that born in the city maternity hospital between April1, 1972 and March 31, 1973. | 634 | NR | 51 |
| **Snodgrass 2015** | Cohort study (prospective) | Singapore | 2009–2010 | 2 years | To quantify respiratory morbidity in young children | Pregnant women aged ≥18 years attending their | 1236 | NR | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | exposed to second-hand smoke and to identify potentially modifiable factors. | first trimester antenatal dating ultrasounds clinic at any of the Singapore's two major public maternity units, between June 2009 and September 2010. The participants approached were Singapore citizens or permanent residents of Chinese, Malay or Indian ethnicity with homogeneous parental ethnic background, and who had the intention of delivering in Singapore maternity units and residing in Singapore for the next 5 years. | | | |
| **Stein 1999** | Cohort study (prospective) | USA | 1980-1984 | 11 years | To examine the effects of passive smoking on respiratory symptoms in a cohort of over 1,000 children born during 1980-1984. | Newborns (born between 1980-1984) whose parents used one of the largest health maintenance | 1104 | 1-10 years (depending on the follow-up year) | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | organizations in Tucson, Arizona,. Premature infants were not excluded if they were healthy | | | |
| **Svanes 2016** | Cohort study (prospective) | Norway, Sweden, Iceland, Denmark, Estonia | 1991-2012 | NR | To examine whether parental exposure to smoking and welding, including exposure prior to conception, influenced asthma risk in offspring, with a particular focus on exposures in fathers. | Random population samples of men and women born in 1945–73. | 26945 | 22 (range: 2-51) | NR |
| **Tabuchi 2015** | Cohort study (prospective) | Japan | 2001-2009 | 8 years | To assess whether and how parental smoking behaviours, combined with indoor smoking status at home, were associated with the development and severity of childhood asthma from very young ages up to 8 years of age, using data from a large nationally representative birth cohort study. | All infants born in Japan during the periods January 10–17, 2001, and July 10–17, 2001. The analysis was limited to cases where both parents lived together with the subjects at the time of the first survey. | 42768 | NR | 48 |
| **Tanaka 2008** | Cohort study (prospective) | Japan | 2001-2003 | 24 months | To evaluate the association between maternal smoking during pregnancy and postnatal | Pregnant women who lived in Neyagawa City (Osaka Prefecture) | 763 | NR | 47.0 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | exposure to ETS and the development of wheeze, asthma, and atopic eczema in Japanese infants | | | | |
| **Tanaka 2017** | Cohort study (prospective) | Japan | 2007-2008 | 2 years | To examine the association between prenatal and postnatal tobacco smoke exposure during the first year of life and the risk of wheeze in Japanese children aged 23 to 29 months. | Women who became pregnant in one of seven prefectures on Kyushu Island or Okinawa Prefecture between April 2007 and March 2008. | 1354 | NR | 52.3 |
| **Tanaka 2020** | Cohort study (prospective) | Japan | 2007-2008 | 3 years | To investigate the association between prenatal and postnatal tobacco smoke exposure and the risk of asthma in Japanese children | Women who became pregnant in one of seven prefectures on Kyushu Island or Okinawa Prefecture between April 2007 and March 2008 | 1304 | NR | 52.7 |
| **Tashking 1984** | Cohort study (prospective) | USA | 1973-1977 | NR | To evaluate the effect of passive smoking on the lung function of children, by means of a respiratory questionnaire and lung function tests performed in the Los Angeles area. | Households in which one or both parents were regular smokers or life-time non-smokers. Households in which one or both parents were former smokers were excluded. Children were | 971 | NR | 49 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | excluded if thet were non-white or had a Spanish surname. Children who were known ever-smokers or had physician-diagnosed asthma, bronchitis, or other reported lung disease, were excluded from the main analysis. | | | |
| **Thacher 2014** | Cohort study (prospective) | Sweden | 1994-1996 | 16 years | To examine the role of prenatal and postnatal second-hand ETS on asthma, rhinitis, and eczema development up to 16 years of age. | Parents of newborn children (1994-1996), living in Stockholm. Exclusion criteria: the family planned to move within 1 year of the study start; insufficient knowledge of the Swedish language; the family had a seriously ill child; or an older sister or brother was already included in the study. | 3798 | NR | 49 |
| **Vanker 2017** | Cohort study (prospective) | South Africa | 2012-2015 | 1 year | To investigate antenatal and | Pregnant women were at 20–28 | 1065 | 0-1 year | 49 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | postnatal exposure to indoor air pollution or environmental tobacco smoke, and its association with lower respiratory tract illness or wheezing illness in a South African birth cohort study. | weeks' gestation at two public primary health clinics serving different populations. Participants who were younger than 18 years, who did not attend study clinics for postnatal care, or who were intending to move out of the district within 2 years after the infant's birth were excluded | | | |
| **Vardavas 2016** | Cohort study (prospective) | 19 European countries (European birth cohorts) | 1990-2008 | NR | To examine the association between maternal passive smoking during pregnancy and wheeze in children up to the age of 2 years. | Newborns (recruited during pregnancy or shortly after birth) for which there was information of maternal and infant exposure to active and passive smoking, and on the development of wheeze before the age of 2 years. | 27993 | NR | 48.4 |
| **Wu 2013** | Cohort study (prospective) | UK | 1995-1997 | 3 years | To investigate interactions between | Parents screened at antenatal visits | 807 | NR | 44.9 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | GST variants and maternal smoking in relation to the development of wheezing during childhood and whether any such interaction changes with time. | (during the first 8–10 weeks of pregnancy) by using skin-prick testing and a structured questionnaire. | | | |
| **Wu 2014** | Cohort study (prospective) | Taiwan | 1999-2001 | 6 years | To investigate the interactions among GSTM1 genotype, gender, and prenatal ETS regarding childhood asthma development. | Parents of children were prenatally recruited in the Kaohsiung Chang Gung Memorial Hospital by a study nurse to enroll the birth cohort. | 756 | NR | NR |
| **Wu 2019** | Cohort study (prospective) | Taiwan | NR | 6 years | To investigate whether parental tobacco smoke exposure was associated with the offspring's asthma and correlated to epigenetic methylation of potential tobacco-related immune genes | Newborns at a single centre hospital | 1629 | NR | 46.9 |
| **Zhang 2018** | Cohort study (prospective) | USA | 2003-2014 | NR | To evaluate the difference in the trends of passive tobacco smoke exposure levels over time among US | Data from six consecutive cycles of the 2003–2014 NHANES on | 8064 | NR | 48 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | children ages 3–11 years using NHANES | children aged 3–11 years. | | | |
| **C. Combined pre-natal and post-natal exposure to combustion smoking** | | | | | | | | | |
| **Accordini 2018** | Cohort study (prospective) | Australia; Belgium; Denmark; Estonia; France; Germany; Iceland; Italy; Norway; Spain; Sweden; United Kingdom | 1991-2013 | NR | To examine the pattern of associations between tobacco smoking and asthma across three generations (grandparents, parents, offspring) during different developmental stages within those generations | Subjects who had participated in ECRHS I and III, and who had reported at least one offspring at the ECRHS III clinical interview | 8858 | Offspring in maternal line: 26 years; Offspring in paternal line: 24 years | 50 |
| **Alati 2006** | Cohort study (prospective) | Australia | 1981-1984 | 14y | To evaluate the link between maternal smoking during pregnancy and parental smoking soon after birth and the development of asthma symptoms in adolescence | Birth cohort study of mothers and children enrolled at the first antenatal visit at a single hospital | 3915 | 14 | 48 |
| **Cunningham 1996** | Cross-sectional | USA and Canada | 1988-1990 | N/A | To examine the relationship between current and past exposure to maternal, paternal, and nonparental ETS in the home and several measures of asthma and wheeze in school-aged children from 24 communities across | School-aged children aged 8-11 years | 11534 | NR | 51 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | the United States and Canada | | | | |
| **Gilliland 2003** | Cohort study (prospective) | USA | 1993-not reported | 8 years | To investigate effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function | Volunteer schoolchildren except those in special classes for gifted or learning-disabled students. | 5933 | NR | 51.6 |
| **Gilliland 2006** | Cohort study (prospective) | USA | 1993-1996 | 8 years | To determine whether regular smoking was associated with the new onset of asthma during adolescence. | Children with no lifetime history of asthma or wheezing who were recruited from fourth- and seventh-grade classrooms and followedannually in schools in 12 southern California communities | 1489 | NR | 50 |
| **Haberg 2007** | Cohort study (prospective) | Norway | 2000-2004 | 18 months | To assess the effects of prenatal and postnatal smoking on early childhood respiratory health. | Clinical birth cohort of a University Hospital, with exclusion of stillbirths | 39306 | NR | NR |
| **Harju 2016** | Cohort study (retrospective) | Finland | 1989-2008 | 4.2 years | To evaluate the association between maternal and paternal smoking during pregnancy, and asthma among offspring. | Population-based birth cohort that recruited pregnant women resident in Avon, UK with expected dates of delivery from April 1991 to December 1992. | 8002 | NR | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Keil 2009** | Cohort study (prospective) | Germany | 1990-not reported | 10 years | To examine the interaction of passive smoking and an allergic predisposition regarding allergic sensitization, allergic airway symptoms and respiratory infections during the first 10 years of life | Children with: (i) available umbilical cord blood immunoglobulin (IgE) values; (ii) 37 weeks of pregnancy; and (iii) 3rd percentile of birth weight. Those with: severe complications during birth; treatment on intensive care unit; or families with insufficient knowledge of the German language were excluded | 958 | NR | NR |
| **Lannero 2006** | Cohort study (prospective) | Sweden | February 1994-November 1996 | 22 months | To assess the possible effects of exposure to cigarette smoking in utero on lower respiratory disease in children up to two years of age. | Newborn infants born in Stockholm at their first visit to the Child Health Centre. Infants were excluded if they had a serious disease or if the families planned to move within a year, had insufficient knowledge of Swedish or had an already enrolled older sibling. | 3790 | NR | 49.4 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Magnusson 2005** | Cohort study (prospective) | Denmark | 1984-1987 | 8 years | To investigate the effects of maternal smoking in pregnancy on asthma, hay fever, atopic eczema, and wheezing in the offspring up to the age of 14–18. | All pregnant women in the two Danish cities, Odense and Aalborg. | 7844 | follow-up at age 14–18 | 48.4 |
| **Neuman 2012** | Cohort study (retrospective) | Germany; Spain; Netherlands; Sweden; Denmark; UK | 1990-1999 | 4-6 years | To assess the effect of exposure to maternal smoking during pregnancy on wheeze and asthma among preschool-age children | Participants recruited during pregnancy or in the first months after birth with at least one follow-up assessment of the outcomes of wheeze or asthma at 4 to 6 years of age, and with information on maternal smoking during pregnancy and from the first year after birth. | 21600 | 4-6 years old | NR |
| **Neuspiel 1989** | Cohort study (prospective) | UK | 1970 | 10 years | To examine the relationship of cigarette smoking by either one or both parents with reporting of post-infancy wheezing in a large, representative British national cohort. | All births in Great Britain during the week of April 5-11, 1970. | 11776 | NR | 48.6 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| **Stein 1999** | Cohort study (prospective) | USA | 1980-1984 | 11 years | To examine the effects of passive smoking on respiratory symptoms in a cohort of over 1,000 children born during 1980-1984. | Newborns whose parents used one of the largest health maintenance organizations in Tucson, Arizona. Premature infants were not excluded if they were healthy | 1104 | 1-10 years (depending on the follow-up year). | NR |
| **Svanes 2016** | Cohort study (prospective) | Norway, Sweden, Iceland, Denmark, Estonia | 1991-2012 | NR | To examine whether parental exposure to smoking and welding, including exposure prior to conception, influenced asthma risk in offspring, with a particular focus on exposures in fathers. | Random population samples of men and women born in 1945–73. | 26945 | 22 (2-51) mean (range) | NR |
| **Tanaka 2017** | Cohort study (prospective) | Japan | 2007-2008 | 2 years | To examine the association between prenatal and postnatal tobacco smoke exposure during the first year of life and the risk of wheeze in Japanese children aged 23 to 29 months. | Women who became pregnant in one of seven prefectures of Kyushu Island or Okinawa Prefecture between April 2007 and March 2008. | 1354 | NR | 52.3 |
| **Vardavas 2016** | Cohort study (prospective) | 19 European countries (European birth cohorts) | 1990-2008 | NR | To examine the association between maternal passive smoking during pregnancy and wheeze in children | Newborns (recruited during pregnancy or shortly after birth) for which there was information of | 27993 | NR | 48.4 |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age (mean, SD) | % women |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | up to the age of 2 years. | maternal and infant exposure to active and passive smoking, and on the development of wheeze before the age of 2 years. | | | |
| **Wang 2008** | Cohort study (prospective) | USA | 1993-1996 | Not reported | To investigate the joint effects of in utero and childhood second-hand tobacco smoke exposure and two well-characterized functional single-nucleotide polymorphisms (Arg16Gly and Glu27Gln) of β2-adrenergic receptor gene on asthma and wheezing | Volunteer schoolchildren except those in special classes for gifted or learning-disabled students. | 3128 | 11.3 (2.3) | 53.4 |

ECRHS: European Community Respiratory Health Survey; ETS: Environmental tobacco smoking; NA: Not applicable; NHANES: National Health and Nutrition Examination Survey; NR: Not reported; SD: Standard-deviation

**Table S4. Description of individual studies included in the SR on the impact of ETS (combustion or e-cigarette) on asthma-related outcomes**

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Akinbami LJ 2013** | Time series | USA | 2003-2010 | 12 months | To assess the current impact of ETS exposure on children with asthma | Children with asthma from the NHANES | 925 | Children and teenagers | 6 to 19 | 46.6 | Mild to severe |
| **Boskabady MH. 2022** | Cohort study (prospective) | Iran | 1998-2000 | 3 years | To examine the effect of 3-year parental smoking on respiratory symptoms, drug use and functional tests in their children with asthma | Children with asthma seen in a hospital clinic | 90 | Children (<12 years) | Non-smokers: 8.19 (3.28); Smokers: 8.45 (3.52) | 41.1 | Mild to moderate |
| **Butz 2011** | Randomized clinical trial | USA | 2006-2008 | 2 weeks | To examine the association between measures of second hand smoking and asthma morbidity outcomes among low-income, minority children with asthma residing with a smoker | Children aged 6–12 years, classified with intermittent or persistent asthma, using daily controller medication over the past 6 months, sleeping in a home 5 or more days per week and with a smoker in the home. | 126 | Children (<12 years) | 9.1 | 45 | Mild to severe |
| **Butz 2019** | Randomized clinical trial | USA | 2013-2016 | 12 months | To examine if an association exists between second hand smoking exposure, based on salivary cotinine levels, and frequency of day and night time symptoms in low-income, minority children with poorly controlled asthma. | Physician-diagnosed persistent and uncontrolled asthma having two or more ED asthma visits or ≥ 1 hospitalization over the past 12 months, and residing in the Baltimore metropolitan area. Children were excluded if they had other non-asthma respiratory conditions including cystic fibrosis, bronchopulmonary dysplasia or lung cancer | 222 | Children (<12 years) | 6.3 (2.7) | 35 | Not restricted to a specific severity level |
| **Chilmonczyk 1993** | Cohort study (retrospective) | USA | 1992 | 12 months | To examine the association between exposure to environmental tobacco smoke and exacerbations of asthma in children | Children with asthma (age: 8 months to 13 years) and the parents who accompanied them to routine visits at a large | 204 | Children (<12 years) | 7.5 (2.8) | 30 | Not restricted to a specific severity level |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | allergy-asthma practice in Portland, Maine. | | | | | |
| **Eisner 2001** | Cohort study (prospective) | USA | July 1998 and December 1999 | NR | To measure ETS exposure in a cohort of adults with asthma living in Northern California | Subjects with no current personal tobacco smoking and a positive answer to any screening question indicating potential ETS exposure | 50 | Adults (≥18 years) | 44.4 (7.9) | 72 | Not restricted to a specific severity level. Severity of asthma score= 10.7 (6.8) |
| **Eisner 2002** | Cohort study (prospective) | USA | July 1998 and December 1999 | 5 years | To examine the prevalence and short-term health impact of ETS exposure during travel among adults with asthma. | Adults with asthma recruited from physician practices in Northern California | 111 | Adults (≥18 years) | 44 (7.7) | 71 | Not restricted to a specific severity level |
| **Eisner 2002a** | Cohort study (prospective) | USA | 1998-1999 | 18 months | To assess the impact of exposure to ETS, gas stoves, and woodsmoke on health outcomes | Adults with asthma from a random sample of board-certified pulmonary specialists, allergy/immunology specialists, and family practitioners in Northern California | 349 | Adults (≥18 years) | 44.2 (7.7) | 72 | Not restricted to a specific severity level |
| **Eisner 2005** | Cohort study (prospective) | USA | Beginning 2000-2004 | N/A | To study the impact of second hand smoking exposure on asthma health outcomes | Adult members admitted to Northern California hospitals with a main discharge diagnosis code for asthma or with a secondary discharge diagnosis code for asthma and a principal code for acute asthma related respiratory conditions. Persons with a primary or secondary discharge diagnosis code for chronic bronchitis, emphysema, or chronic airway obstruction were excluded | 778 | Adults (≥18 years) | 61 (16) | 70 | Severe asthma |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gaisberger 2021** | Randomized clinical trial | Austria | 2008-2010 | 180 min | To examine whether acute, experimental ETS exposure influences asthma symptoms, lung function, and inflammatory parameters. | Non-smoking adults with mild to moderate well-controlled allergic asthma | 23 | Adults (≥18 years) | Exposed (ETS): 34 years; Unexposed (ambient air): 30 years | 65 | Mild to moderate |
| **Gerald et al 2009** | Cohort study (prospective) | USA | 2005-2006 | 12 months | To examine the relationship between changes in ETS exposure and childhood asthma morbidity in a clinical trial of supervised asthma therapy in an urban elementary school | Physician-diagnosed persistent asthma requiring daily controller medication and ability to use a dry-powder inhaler and a peak flowmeter | 256 | Children (<12 years) | 11.0 (2.1) | 42 | Mild to severe |
| **Grarup 2014** | Cohort study (prospective) | Denmark | NR | 3 months after delivery | To investigate the effects of current and former active smoking as well as passive smoking on asthma control during pregnancy. | Pregnant women with 1) Asthma, defined according to GINA guidelines,2) At least step 1 asthma therapy, i.e., rescue bronchodilator,3) Visit 1 at the outpatient clinic within the first 18 weeks of pregnancy | 500 | Adults (≥18 years) | 30.8 | 100 | Not restricted to a specific severity level |
| **Jassal 2020** | Cohort study (prospective) | USA | 2017-2018 | 6 months | To examine how much and when does smoking reduction result in improvedenvironmental and clinical outcomes. | Children with persistentasthma (as per National Heart, Lung, and Blood Institute criteria) in pediatric pulmonary specialtyclinics and inpatient units at Johns Hopkins Children's Center | 45 | Children (<12 years) | 7 | 48.9 | Persistent asthma |
| **Keogan 2020** | Quasi-experimental study | Czechia/Ireland/Spain | 2018-2019 | NR | To assess the acute respiratory effects in lung function that result from short-term second hand smoking exposure among patients with asthma and chronic obstructive pulmonary disease | Confirmed doctor-diagnosed asthma and age of 18 years and older, | 30 | Adults (≥18 years) | 46.9 (18.7) | 64 | Not restricted to a specific severity level |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Knight 1985** | Quasi-experimental study | NR | NR | 2 days | To investigate the acute respiratory response in patients with asthma to passive cigarette smoking and to assess whether passive smoke inhalation alters bronchial sensitivity to inhaled histamine | Non-smoking adults with mild to moderate asthma | 6 | Adults (≥18 years) | NR | 33.3 | Mild to moderate |
| **Lang 2013** | Cohort study (prospective) | USA | 2007 - 2010 | 24 weeks | To describe how ETS affects gastroesophageal reflux, respiratory infections, and leukotriene production among children with poor asthma control. | Participants aged 6 to 17 years with poor asthma control despite daily treatment with an inhaled corticosteroid. Exclusion criteria: self-reported symptoms of gastroesophageal reflux requiring treatment; treatment with a proton pump inhibitor or other reflux medications; history of antireflux surgery or a previous trachea-oesophageal fistula repair; an FEV1 of less than 60% predicted; history of neonatal respiratory distress or premature birth at less than 33 weeks' gestational age; other major chronic illnesses; nonadherence; inability to take study medications, perform baseline measurements, or be contacted; or pregnancy. | 265 | Children and adolescents (6-17 years) | Home indoor smoking group: 12.8 (2.7); No home indoor smoking: 11.3 (3.0). | 37 | Poor asthma control defined based on medication use, symptoms, healthcate use of a score ≥1.25 on the Asthma Control Questionnaire. |
| **Li 2000** | Cohort study (retrospective) | USA | 1993- not reported | NR | To assess the relationships between lung function, asthma, in utero exposure to maternal smoking, and ETS exposures in boys and girls. | Fourth graders (aged 9–10 yr.), seventh graders (12–13 yr.) and tenth graders (15–16 yr.). | 5263 | Children and teenagers (boys: 7- | NR | 51 | Not restricted to a specific severity level |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 19; girls: 7-18) | | | |
| **Magnussen 1993** | Quasiexperimental study | Germany | NR | 6 days | To investigate the acute effects of ETS in children with mild asthma during rest and exercise. | Children with bronchial asthma, ranging in age from 8 to 13 years. | 13 | Children and teenagers (8- 13 years) | 10 (2) | 38.5 | Mild asthma |
| **Murray 1992** | Cohort study (prospective) | Canada | 1983 - 1990 | N/A | To investigate the effect of less exposure to cigarette smoke in the severity of asthma in children of parents who smoke. | Children (1-17 years of age) with asthma referred to an allergy clinic (1983-1990). Children who were themselves smokers, had cystic fibrosis, or gastroesophageal reflux were excluded. | 807 | Children and adolescents (1-17 years) | Children and adolescents (1-17 years) | Not reported | Not restricted to a specific severity level |
| **Newman 2010** | Cohort study (prospective) | USA | December 1994 and February 2000 | NR | To estimate the effect of active and passive household cigarette smoke exposure on asthma severity and obstetric and neonatal outcomes in pregnant women with asthma. | Pregnant women with mild and moderate-severe asthma | 1419 | Adults (≥18 years) | Smokers: 23.7 (5.6); Non-smokers/No Household ETS Exposure: 24.4 (5.9) | 100 | Mild to severe |
| **Nowak 1997** | Quasi-experimental study | Germany | NR | 2 weeks | To investigate the effect of ETS exposure in the evening on inflammatory changes in bronchoalveolar and nasal lavage fluids. | Non-smoking patients with mild bronchial asthma | 10 | Adults (≥18 years) | 25 (2) | 40 | Mild asthma |
| **Shephard 1979** | Quasi-experimental study | Canada | NR | 2 hours | To make an assessment of symptoms and objective airway responses in a group of adults with asthma passively exposed to controlled concentrations of cigarette smoke. | Volunteers with asthma attending the Asthma Clinic of The Gage Research Institute. | 14 | Adults (≥18 years) | Men: 44 (14) Women: 33 (8) | 35.7 | Not restricted to a specific severity level |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Soussan 2002** | Cohort study (prospective) | France | 1995-1998 | 3 years | To study the role of treatment compliance and parents' smoking on asthma control in children with recently diagnosed mild or moderate persistent asthma who were prescribed inhaled anti-inflammatory treatment. | Documented asthma diagnosed during the inclusion visit or no more than 12 months previously, and FEV1>60% of the predicted value at the inclusion visit. Exclusion criteria: (1) having a chronic respiratory disease other than asthma; (2) treatment with high doses of inhaled corticosteroids; and (3) having unstable asthma. | 167 | Children (<12 years) | 9.5 (2.0) | 35.9 | Mild to moderate |
| **Sunde 2022** | Cohort study (prospective) | Denmark | NR | 7 years | To examine the effect of prenatal tobacco exposure and relation to 17q12-21 genotype on a wide array of asthma and allergy-related outcomes in early childhood | Infants of mothers with history of asthma. Infants with a severe congenital anomaly, a gestational age younger than 36 weeks, a need for mechanical ventilation, or a lower respiratory tract infection were excluded | 72 | Children (<12 years) | NR | 51.6 | Not restricted to a specific severity level |
| **Sutaryono 2019** | Cohort study (prospective) | Indonesia | 2016-2017 | 12 weeks | To assess the risk impact associated with exposing children living with asthma to ETS in the family. | Asthma patients aged 12-18 years old at three hospitals (2016-2017) | 114 | Teenagers (12 to 18) | 15 (2.5) | 61.5 | Not restricted to a specific severity level |
| **Vargas 2007** | Cross-sectional | USA and Canada | 1997-1998 | NA | To determine the prevalence of ETS exposure among children presenting to the ED for acute asthma care and whether ETS exposure affects acute asthma severity or response to therapy. | Physician diagnosis of acute asthma and age 2 – 11 years. | 954 | Children (<12 years) | 6.4 (2.8) | 38.16 | Mild to severe |

ED: Emergency Department; ETS: Environmental tobacco smoking; FEV1: Forced expiratory volume at 1 second; NA: Not applicable; NHANES: National Health and Nutrition Examination Survey; NR: Not reported; SD: Standard-deviation

**Table S5. Individual studies included in the SR on the impact of active smoking (combustion or e-cigarette) on asthma-related outcomes in adolescents or adults with asthma**

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Arshad 2019** | Cohort study (prospective) | England | NR | 26 years | To determine the association of current asthma and smoking with lung function from childhood to early adult life. | All children born at one hospital on the Isle of Wight between January 1, 1989 and February 28, 1990 | 1,030 | Children and adults | NR | 54.4 | NR |
| **Boulay 2017** | Quasi-experimental study | Canada | NR | 1 hour | To investigate the impact of a 1 hour acute vaping session of nicotine-free and flavour-free e-liquid on the pulmonary function and respiratory mechanics of healthy and asthmatic individuals. | Asthmatic volunteers (no additional details available) | 10 | Adults (≥18 years) | Range:21 to 40 years | NR | NR |
| **Cerveri I 2012** | Cohort study (retrospective) | Europe | 1991–1993 and 1999–2002 | 9 years | To evaluate changes in smoking habits and their effects on lung function decline in subjects with asthma in comparison with the rest of the population, focusing on the healthy smoker effect. | Subjects without asthma and with asthma at baseline who participated in both the ECHRS I (20–44 years old in 1991–1993) and ECHRS II (1999–2002). | 17,480 | Adults (≥18 years) | Range: 20-44 years | 52 | NR |
| **Chalmers 2002** | Randomized clinical trial | UK | NR | 10 weeks | To examine the effects of active cigarette smoking on the efficacy of inhaled corticosteroid treatment in subjects with mild asthma. | Patients with asthma (reversibility to salbutamol of >10% if the FEV1 at baseline was <70% of predicted) with no history of productive cough. Patients were excluded if having a history of upper respiratory tract infection or treatment with inhaled or oral corticosteroids in the 2 months prior to attendance | 47 | Adults (≥18 years) | Non-smokers: 35.4 (9.7); Smokers: 34.6 (9.5) | 44 | Mild asthma |
| **Chauduri 2006** | Cohort study (prospective) | UK | NR | 1 year | To prospectively study smokers with asthma who successfully quit smoking and compare outcome measures | Smokers with asthma, aged 18–60 years, with baseline FEV ≤ 85% predicted, ≤ 15% reversibility of FEV after nebulized albuterol, a smoking | 20 | Adults (≥18 years) | Patients who continued smoking: | 60 | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | with smokers with asthma who continued to smoke. | history of ≥ 10 pack-years, and currently smoking ≥ 10 cigarettes/day (patients who continued smoking group). | | | 45.7 (6.8); patients who quit smoking for 6 weeks: 49.5 (9.3). | | |
| **Eisner 2007** | Cohort study (prospective) | USA | NR | 4 years | To examine the impact of cigarette smoking on asthma severity, health status, and longitudinal health care utilization for asthma. | Adult patients (aged 18 years or older) who were hospitalized at Northern California hospitals with an asthma diagnosis during a 4-year period. | 865 | Adults (≥18 years) | 60.4 (16.3) | 70 | NR |
| **Gallefoss 2002** | Randomized clinical trial | Norway | 1994-1995 | 1 year | To investigate the possible influence of smoking on lung function, quality of life and use of services in patients with asthma. | Patients with asthma (18-70 years of age) not suffering from any serious disease with a pre-bronchodilator FEV1 equal to or higher than 80% of predicted value and either a positive reversibility test (at least a 20% increase of PEF or FEV1 after inhalation of 400 µg of salbutamol), a documented 20% spontaneous variability (PEF or FEV1) or a positive methacholine test. | 78 | Adults (≥18 years) | Smoker control: 42 (9); smoker intervention: 41 (17); non-smoker control: 46 (14); non-smoker intervention: 41 (11) | 70 | NR |
| **Grarup 2014** | Cohort study (prospective) | Denmark | NR | 3 months after delivery | To investigate the effects of current and former active smoking as well as passive smoking on asthma control during pregnancy. | Pregnant women with 1) asthma, defined according to GINA guidelines, 2) At least step 1 asthma therapy, i.e., rescue bronchodilator, 3) Visit 1 at the outpatient clinic within | 500 | Adults (≥18 years) | 30.8 | 100 | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | the first 18 weeks of pregnancy | | | | | |
| **Hancox 2016** | Cohort study (prospective) | New Zealand | NR | 38 years | To investigate the effects of smoking and asthma on the development of airflow obstruction in a population-based birth-cohort followed up to age of 38 years. | Population-based cohort of 1,037 individuals born in 1972/73 primarily of New Zealand/ European ethnicity. Pregnant women were excluded. | 1,037 | Adults (≥18 years) | NR | 48 | NR |
| **James 2005** | Cohort study (prospective) | Australia | 1966-1987 and 1994-1995 | 18 years | To examine the level and rate of decline in lung function in relation to asthma and cigarette smoking in adults. | Whole-population health surveys in Busselton, Western Australia, undertaken at intervals of 3 years in adults (18 years of age) from 1966 to 1981 and in children from 1968 to 1983. Follow-up study in 1994 of all traceable subjects who had participated (as a child or as an adult) in any previous survey | 1,301 | Children and adults | Females with asthma 38.5 (14.9), Males with asthma 37.7 (15.9) | 54.8 | NR |
| **Jang 2009** | Cohort study (prospective) | Korea | NR | 1 year | To evaluate the relationship between smoking status and clinical and therapeutic parameters in patients with asthma. | Subjects with asthma from the Asthma Genome Research Center of Soonchunhyang (Korea). Exclusion criteria: FEV1/ FVC less than 70% and diffusing capacity less than 80%. | 843 | Adults (≥18 years) | Never smokers: 47.8 (0.7); current smokers: 46 (1.1); ex-smokers: 50.8 (1.2) | 42 | NR |
| **Jang 2010** | Cohort study (prospective) | Korea | NR | 3 months | To evaluate the effect of smoking cessation on lung function and quality of life in patients with asthma during corticosteroid treatment. | Subjects from the Asthma Genome Research Center (Korea). | 32 | Adults (≥18 years) | Smoking quitters: 53.3 (4.3); Current smokers: 45.6 (2.5) | 15 | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Murphy VE 2010** | Cohort study (prospective) | UK | 2004-2006 | 14.8 (3.0) | To study the clinical implications of smoking on asthma exacerbations in pregnancy | Pregnant women with physician diagnosed asthma | 80 | Adults (≥18 years) | 18-43 | 100 | NR |
| **Newman 2010** | Cohort study (prospective) | USA | December 1994 and February 2000 | NR | To estimate the effect of active and passive household cigarette smoke exposure on asthma severity and obstetric and neonatal outcomes in pregnant women with asthma. | Pregnant women with mild or moderate-severe asthma. Exclusion criteria: foetal demise, multiple gestation, gestational hypertension, congenital anomalies, pulmonary disease other than asthma, gestational age >26 weeks, or planned delivery elsewhere. | 1,419 | Adults (≥18 years) | Smokers: 23.7 (5.6); Non-smokers/ No Household ETS Exposure: 24.4 (5.9) | 100 | Mild/moderate |
| **Polosa 2011** | Cohort study (prospective) | Italy | 1990-2000 | 10 years | To investigate whether cigarette smoking could be a determinant of disease severity and poor asthma control in clinic-referred allergic subjects who developed new onset asthma. | Clinic-referred non-asthmatic adults with allergic rhinitis for whom all explanatory variables, asthma status at follow-up, and smoking history were available. Exclusion criteria: past or present history of asthma, previous asthma symptoms or asthma medication intake, and/or abnormal spirometry values at the time of their first visit. | 135 | Adults (≥18 years) | Never smokers: 28.5 (6.4); Current smokers 30.7 (5.4). | 57 | NR |
| **Shimoda 2016** | Cohort study (prospective) | Japan | NR | 6 months | To evaluate the influence of cigarette smoking on airway inflammation in patients with asthma; to compare the effect of inhaled corticosteroids between smoking and non-smoking in patients with asthma. | Patients with (1) disease reversibility with at least 12% and 200-mL improvements in FEV1 after bronchodilator therapy, (2) provocative concentrations of acetylcholine that produced a 20% fall in FEV1 8000 g/mL in a test of bronchial hyperresponsiveness to | 133 | Adults (≥18 years) | never smoker: 41 years old (sd=12); current smoker: 42 years | 70.8 | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | inhaled acetylcholine, and (3) history of wheezing and/or dyspnoea. | | | old (sd=13) | | |
| **Telenga 2013** | Cohort study (prospective) | Netherlands | NR | 12 months | To investigate whether ex-, current- and never-smokers with asthma have different inflammatory profiles and if current number of cigarettes or packyears smoked affect such profiles. | Baseline FEV1 between 50–85% predicted and reversibility of FEV1 after nebulized albuterol (2.5 mg) of 15% or more. Exclusion criteria: asthma exacerbation, use of oral corticosteroids, or a respiratory tract infection within 4 weeks before inclusion, a recent peptic ulcer, glaucoma, pregnancy, and lactation. | 114 | Adults (≥18 years) | Never-smokers: 25; Current smokers: 27 years; Ex-smokers: 38 years | 65.7 | NR |
| **Tiotiu 2021** | Cohort study (prospective) | France; Spain | 2012-2018 (France) 2013-2019 (Spain) | NR | To assess the influence of active tobacco smoking on asthma control, exacerbation rate, and lung-function parameters among patients with asthma with different smoking histories (never-smokers, ex-smokers, and current-smokers). | Asthma symptoms and either an airflow reversibility (increase in FEV1 >12% reported to baseline and 200 mL following inhalation of 400 µg salbutamol) or airway hyperresponsiveness (proved by a positive methacholine challenge test). | 176 | Adults (≥18 years) | Never-smokers: 43 (13); Ex-smokers: 46 (11); Current smokers: 46 (17) | 59.1 | NR |
| **To 2012** | Cohort study (retrospective) | Canada | 2003-2006 | 12 months | To measure the effect of changing smoking status on asthma symptom control and health services use in adults with asthma. | Patients aged 18 to 55 identified with physician-diagnosed mild to moderate asthma. Exclusion criteria: patients with unclear diagnosis of asthma, physician-diagnosed COPD, foreign body airway obstruction, congenital heart disease, bronchopulmonary dysplasia, Alzheimer's disease, | 519 | Adults (≥18 years) | Smokers: 39.1 (9.3); Ex-smokers: 42.7 (8.1); Non-smokers: 40.8 (9.8) New- | 78.4 | Mild to moderate |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | dementia, alcoholism or significant neurological deficit. | | | smokers: 35.3 (6.9) | | |
| **Tommola 2016** | Cohort study (prospective) | Finland | 1999-2013 | 12.2 years | To evaluate the effect of smoking on lung function decline in adult-onset asthma. | Inclusion criteria: Age ≥15 years and diagnosis of new-onset asthma by a respiratory specialist, confirmed by at least one of the following objective lung function measurements: FEV1 reversibility in spirometry of at least 15% and 200 mL, diurnal variability (≥20%) or repeated reversibility (≥15%/60 L/min) in PEF follow-up, a significant decrease in FEV1 (15%) or PEF (20%) in response to exercise or allergen, a significant reversibility in FEV1 (at least 15% and 200 mL) or significant mean PEF change in response to a trial with oral or inhaled glucocorticoids; symptoms of asthma. | 203 | Adults (≥18 years) | 46.0 (13.7) | 58.1 | NR |
| **Tønnesen 2004** | Randomized clinical trial | Denmark | NR | 4 months | To examine the effect of smoking reduction and cessation on asthma regulation and biomarkers of exposure to cigarette smoke. | Adult smokers (aged 18–60 years) with diagnosed asthma (allergic or nonallergic) in a stable phase. Eligible subjects had to have smoked at least 10 cigarettes per day for at least 3 years and present with an expired CO level of at least 10 ppm. Subjects had to be willing to reduce or quit smoking. At entry, subjects had to demonstrate a variation in peak flow of greater than | 110 | Adults (≥18 years) | 35 (8) | 55 | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 15% or an increase in FEV1 of at least 15% after administration of a β2-agonist. | | | | | |
| **Vignoud L 2011** | Cohort study (prospective) | France | 1991-2007 | 12 years | To assess whether active smoking among subjects with asthma influences the persistence of the disease or the 12-year evolution in lung function in children and adults | Asthma patients, first-degree relatives, and controls followed-up over 12 years. The subjects participated twice: in the first survey and in the follow-up. | 416 | Children and adults | 37.3 (3.4) | 49 | NR |
| **Westergaard 2013** | Cohort study (prospective) | Denmark | NR | N/A | To assess alterations in airway inflammation, airway hyperresponsiveness to methacholine and other disease parameters during 6 and 12 weeks of smoking cessation in young asthma patients not treated with steroids at baseline. | Inclusion criteria: (i) 18–40 years of age, (ii) current smoking with a daily consumption of at least 10 cigarettes per day within the last year, and a total consumption of at least 10 pack-years, (iii) current asthma symptoms within the last year, confirmed through interview with study physician and (iv) at least one positive objective diagnostic test suggestive of asthma. Exclusion criteria: (i) treatment with inhaled corticosteroids, (ii) lower respiratory tract infections within the last three months, (iii) chronic lung diseases, (iv) pregnancy | 46 | Adults (≥18 years) | 32 (6) | 72 | Moderate asthma |
| **Westerhof 2014** | Cohort study (prospective) | Netherlands | NR | 2 years | To identify predictors for the development of severe asthma in adults. | Recent (<1 year) diagnosis of asthma. Patients were excluded if they had a self-reported history of childhood asthma or other chronic respiratory diseases in childhood, frequent episodes | 200 | Adults (≥18 years) | 48 (15) | 50.8 | NR |

| Study | Study design | Country/ Continent | Study period | Mean follow up time | Study aim | Selection criteria | Number of participants | Age group | Age (mean, SD) | % women | Background asthma severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | of dyspnoea as a child, or use of a bronchodilator or other asthma medication in childhood. | | | | | |
| **Çolak 2015** | Cohort study (prospective) | Denmark | 2003 - unclear | 4.4 years | To test the hypothesis that in individuals with asthma, never-smokers have different characteristics and better prognosis than smokers | Individuals aged 20 to 100 years randomly selected from the national Danish Civil Registration System, reflecting the adult white Danish population of Danish descent. | 5,691 | Adults (≥18 years) | Asthmatic never smokers: 53; Asthmatic ex-smokers: 60; Asthmatic current smokers: 56 | 60.2 | NR |

COPD: Chronic obstructive pulmonary disease; ECRHS: European Community Respiratory Health Survey; ETS: Environmental tobacco smoking; FEV1: Forced expiratory volume at 1 second; FVC: Forced vital capacity; NR: Not reported; SD: Standard-deviation