



Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis

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ABSTRACT

Background: Secondhand smoke (SHS) exposure can trigger asthma exacerbations in children. Different studies have linked increased asthma symptoms, health care use, and deaths in children exposed to SHS, but the risk has not been quantified uniformly across studies.

Objective: To perform a systematic review and meta-analysis to evaluate and quantify asthma severity and health care use from SHS exposure in children.

Methods: A systematic review was undertaken to assess the association between asthma severity and SHS in children. Inclusion criteria included studies that evaluated children with SHS exposure and reported outcomes of interest with asthma severity including exacerbations. Random effect models were used to combine the outcomes of interest (hospitalization, emergency department or urgent care visits, severe asthma symptoms, wheeze symptoms, and pulmonary function test results) from the included studies.

Results: A total of 1,945 studies were identified and 25 studies met the inclusion criteria. Children with asthma and SHS exposure were twice as likely to be hospitalized for asthma (odds ratio [OR] 1.85, 95% confidence interval [CI] 1.20–2.86, $P = .01$) than children with asthma but without SHS exposure. SHS exposure also was significantly associated with emergency department or urgent care visits (OR 1.66, 95% CI 1.02–2.69, $P = 0.04$), wheeze symptoms (OR 1.32, 95% CI 1.24, 1.41, $P < .001$), and lower ratio of forced expiratory volume in 1 second to forced vital capacity (OR –3.34, 95% CI –5.35 to –1.33, $P = .001$).

Conclusion: Children with asthma and SHS exposure are nearly twice as likely to be hospitalized with asthma exacerbation and are more likely to have lower pulmonary function test results.

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Introduction

Asthma is a leading cause of chronic disease in children, with an increasing prevalence of disease persistence and acute attacks over time.^{1–9} According to the Centers for Disease Control and Prevention, in 2012, 9.3% of US children were affected by asthma.¹⁰ Other studies have shown 300 million children are affected worldwide.^{7,11} With the increase in prevalence comes an increase in burden of disease affecting quality of life at school and during physical

activity. It also places a significant burden on the families of these children and on the health care system.^{3,12,13}

Acute asthma exacerbations are characterized by airway constriction and increased mucous production that in turn lead to symptoms of cough, wheeze, shortness of breath, and chest tightness.⁵ These acute attacks can be severe and might require emergency department (ED) visits, hospitalizations, intensive care unit admissions, and even lead to death.^{2,14} Acute attacks also might lead to a decrease in pulmonary function.¹⁵ Many triggers causing acute asthma attacks have been identified, including environmental exposures such as aeroallergens, pollution, and secondhand smoke (SHS).^{4,5,16} In the early 1990s, the Environmental Protection Agency estimated that 1 million episodes of increased asthma symptoms in children were associated with environmental tobacco

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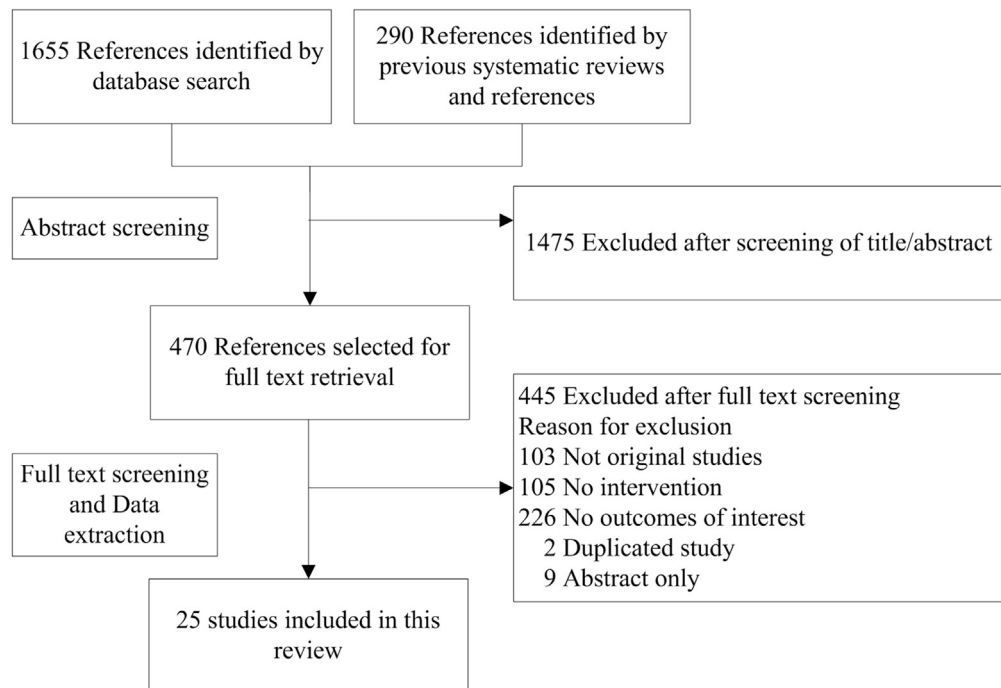


Figure 1. Literature search and selection of studies for systematic review.

smoke exposure.^{5,17,18} Previous studies have shown that the specific environmental trigger of SHS leads to increased phlegm, wheezing, and breathlessness in children.⁴ In 2006, the US Surgeon General noted a causal relation between SHS from parents and early childhood wheeze.^{19,20} There also was evidence linking SHS to childhood asthma, but the evidence was not sufficient for a causal relation to be determined.^{3,21} Children are perhaps more likely to be affected by cigarette smoke exposure compared with adults; this is hypothesized to be due to the immaturity of their respiratory and immune systems.^{5,18} It is known that cells in the lung continue to divide, with lung growth occurring until adolescence. Toxins such as SHS slow lung growth rates; although details of how this occurs are not entirely known, SHS does affect the respiratory system in children.²² Similarly, in 1997, it was determined that 1.8 million asthma outpatient visits and 14 deaths from asthma in children were linked to SHS in the United States. In 2004, similar results were noted worldwide linking SHS and asthma-related deaths.^{5,21}

The current literature related to asthma severity and SHS has elicited discordant results. Some studies have linked SHS exposure to increased asthma prevalence, poorer asthma control, and, as described earlier, increased symptoms.^{2,3,7,23–25} However, most studies have not been able to quantify the strength of this association.²⁶ Therefore, the authors conducted a systematic review and meta-analysis to evaluate relevant literature pertaining to asthma severity in children exposed to SHS.

Methods

This study followed the standard procedures developed by the Cochrane Collaboration²⁷ and a protocol was developed that defined the inclusion and exclusion criteria, search strategy, outcomes, and analysis plan. The reporting of this systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.²⁸

Search Strategy

A comprehensive literature search was conducted of Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE,

Ovid EMBASE, and Ovid Cochrane Database of Systematic Reviews from 2003 to week 3, 2015 (January 12, 2015) using database-appropriate terms: *passive smoking, second hand smoking, smoke exposure, tobacco smoke pollution, parental smoke, environmental smoke, asthma, child, infant, and pediatric*. Search terms were broad without language and country restrictions. The detailed search strategy is available in [eAppendix 1](#). Studies published in and before 2003 were identified through a systematic review included in the Surgeon General's report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke*.¹⁹ Relevant systematic reviews identified during the search also were used to find additional eligible studies. An experienced librarian developed and implemented the search strategy, with input from the authors.

Inclusion and Exclusion Criteria

To be included in this systematic review, studies had to meet each of the following criteria: (1) children (<18 years old); (2) evaluating exposure to SHS; and (3) reporting outcomes related to asthma severity (ie, hospitalization, ED or urgent care visits, medication use including oral steroids, clinical symptoms, acute exacerbations, and pulmonary function measurements, ie, forced expiratory volume in 1 second [FEV₁] and forced vital capacity [FVC]). Studies without original data (clinical reviews, editorials, letters, or errata) and studies that did not report outcomes of interest were excluded. Studies published only in abstract form also were excluded.

Study Selection

Independent reviewers, working as pairs and in duplicate, screened the titles and abstracts of potentially eligible studies. Studies were eligible for full-text screening when deemed relevant by either of the reviewers. Then, the full text of relevant studies was retrieved for further review. All conflicts were resolved through discussion and consensus.

Data Extraction

Independent reviewers, working as pairs and in duplicate, extracted study details using a standardized pilot-tested form.

Table 1Twenty-five studies included in systematic review and meta-analysis reported by citation number^a

Study	Country	Study design	Sample size	Mean age (y)	Race	Male, %	Ways of ETS exposure	Reporting of ETS	ETS testing	Asthma severity
Mitchell et al. ²⁰	Worldwide	cohort study	421, 543	6–7, 13–14	NR	68.2	parental	parental 6–7 y; child 13–14 y	NR	NR
van den Bosch et al. ²	Netherlands	case–control study	230	5.2	white 64.3%	53.2	home		NR	NR
Akuete et al. ³²	USA, Puerto Rico, Mexico	case–control study	295	10.5	black 11%, Mexican 42%, Puerto Rican 46%	NR	parental	parental	NR	intermittent 34.2%, persistent 65.8%
Rabinovitch et al. ³³	USA	cohort study	44	10.1	African American 66%	64	parental	parental	cotinine measurement	NR
Radic et al. ³⁴	Serbia	cross-sectional study	231	10.6	NR	48.9	parental	parental	NR	NR
Lawson et al. ³⁵	Canada	case–control study	98	NR	NR	66	NR	parental	cotinine measurement	NR
Gerald et al. ³⁶	USA	prospective study	240	11	black 90%	58	inside and outside home	parental		mild persistent 15%, moderate persistent 80%, severe persistent 5%
Forbes et al. ³⁷	UK	case–control study	1412	Median 8.5	NR	61.5	home/same room	parental	cotinine measurement	NR
Vargas et al. ³⁸	USA	cohort study	954	1.4	white 16.5%, black 59%, Hispanic 22.3%, other 2.2%	61	home	parental	NR	mild 60%, moderate 36%, severe 4%
Wang et al. ³⁹	USA	cohort, retrospective study	355	5.5	white, Latino, African American, other	60	home	NR	NR	NR
Murray et al. ⁴⁰	UK	case–control study	84	NR	white ethnicity 84.5%	NR	parental		NR	NR
Everhart et al. ⁴¹	USA	cohort study	133	13	Latino, African American, non-Latino white	NR	home	parental	NR	NR
Cinar et al. ⁴²	Turkey	cohort study	345 families	1.8	NR	NR	parental	parental	NR	NR
Yamasaki et al. ⁴³	Japan	cohort study	282	6.9	NR	73.1	parental/home	parental	NR	no symptoms 55.9%, <1 mild symptom/ wk 24.9%, >1 mild symptom/wk but no attack 10.2 %, >1 symptom and/or attack 9%
Jin et al. ⁴⁴	USA	cross-sectional study	5686	5.5	NR	50.3	home	parental	NR	NR
Chilmonczyk et al. ⁴⁵	USA	prospective study/ cross-sectional study	199	7.5	NR	71	home or daycare	household and daycare smoking questionnaire; parental	urine	NR
Abd Elmoneim et al. ⁴⁶	Egypt	observational	178	6.1	white	64.6	home	child and parental	NR	NR
Lang et al. ⁴⁷	USA	prospective study	265	11.4	non-Hispanic 84–94%	69	home	parental	NR	poorly controlled
Azizi et al. ⁴⁸	Malaysia	case–control study	359	3.03	Malaysian 57–69%	57	home/indoor	parental	NR	NR
Ehrlich et al. ⁴⁹	USA	case–control study	107	7.29	Hispanic 60–66%	61.5	maternal caregiver	parental	cotinine measurement	acute 67.3%, nonacute 32.7%
Evans et al. ⁵⁰	USA	cohort study	276	9.9	Hispanic 55%, non-Hispanic black 38%, others 7%	60	home	parental	NR	NR
Leson and Gershwin ⁵¹	USA	retrospective cohort study	300	7.2–7.7	black 55%, white 23%, Hispanic 16%, Asian 5%, American Indian 1%	55	parents, other family members or roommates	parental	NR	mild 49%, moderate 39%, severe 12%
Mannino et al. ⁵²	USA	cross-sectional study	539	11	white 66%, non-white 33%	64	home	child and parental	cotinine measurement	mild 73.3%, moderate 10.2%, severe 16.5%
Howrylak et al. ⁵³	USA	cohort	619	6.43	white 32%, African American 57.4%, multiracial 9.69%, others 0.96%	65.3	home	parental	serum and salivary cotinine levels	NR
Ciaccio et al. ⁵⁴	USA	retrospective analysis	308	8.3	African American 39.9%, Hispanic 19.2%, Caucasian 30.8%, others 2.1%	58.1	home	parental	NR	NR

Abbreviations: ETS, environmental tobacco smoke; NR, not reported.

^aYear of publication, location and type of study, clinical features of children included, and ETS exposure are included. End outcomes of each study are noted.

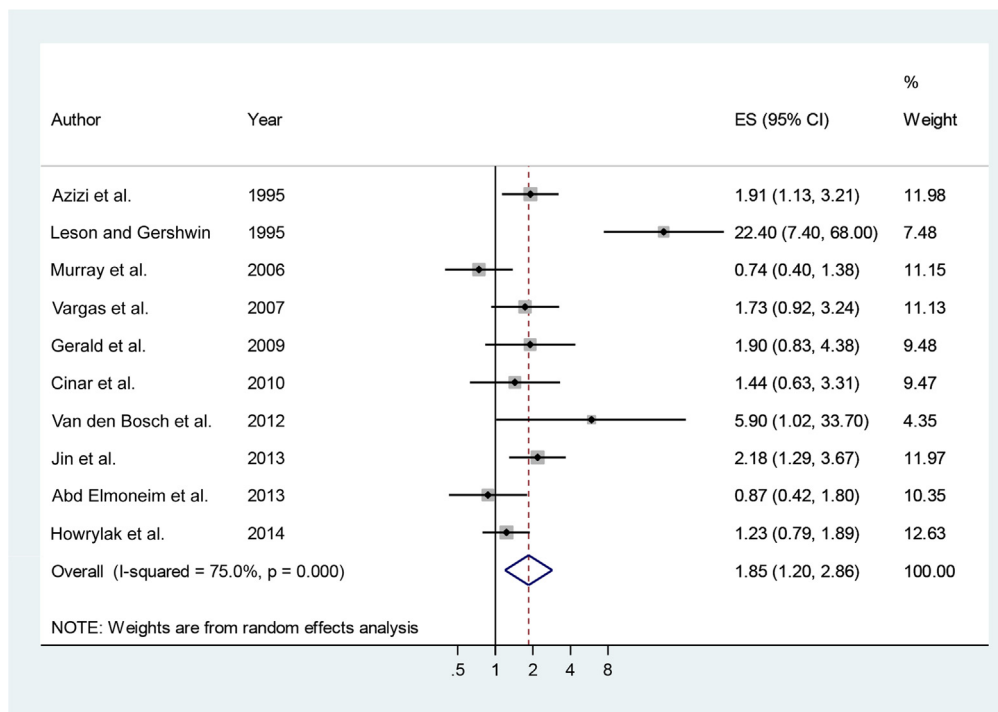


Figure 2. Pooled odds ratios of hospital admissions owing to asthma exacerbations. Vertical line indicates no effect, squares and horizontal lines indicate odds ratio and associated 95% confidence interval (CI) for each study, and diamonds indicate pooled odds ratios. ES, effect size.

Conflicts were resolved by discussion and consensus. The following data were extracted: contributing authors, year of publication, country, study design, age, race or ethnicity, types of smoking exposure, reporting method of smoking exposure, testing and severity of smoking exposure, and outcomes of interest (hospitalization, ED visit/urgent care visit, FEV₁%, FEV₁/FVC ratio, wheeze symptom, severe asthma, and asthma attack).

Quality Assessment

The modified Newcastle–Ottawa quality assessment scale²⁹ was used to assess risk of bias using the following items: assessment and clear ascertainment of outcome, adjustment of exposure, adjusting for confounders, attrition bias or loss to follow-up, and representativeness of study patients.

Statistical Analysis

The odds ratio (OR) was calculated or extracted from the included studies for dichotomized outcomes (hospitalization, ED or urgent care visit). DerSimonian and Laird³⁰ random effect models with heterogeneity assessed from the Mantel–Haenszel method were used to determine pooled logarithmically transformed ORs. For continuous outcomes (FEV₁%, FEV₁/FVC), the weighted mean difference was combined using the same DerSimonian and Laird random effect models.

Heterogeneity across included studies was evaluated using the I^2 index, where I^2 greater than 50% suggests high heterogeneity. The authors were unable to evaluate publication bias owing to the small number of studies included in each outcome or large heterogeneity.³¹ All statistical analyses were conducted using STATA 13.1 (StataCorp, College Station, Texas).

Results

A total of 1,945 studies were identified through the database search and reference mining, of which 470 studies were retrieved

for full-text screening. Twenty-five studies met the inclusion criteria and were included in this systematic review (Fig 1).

Characteristics of the included studies are listed in Table 1.^{2,20,32–54} All studies were observational studies; no quasi-experimental or experimental design was identified. Fourteen studies were conducted in the United States, 1 in Canada, 4 in Asia, 2 in Europe, 2 were multinational, and 2 in other countries (Table 1). Overall, 434,737 patients were included, with a mean age of 7.6 years (range 1.4–13.1 years), and 61.4% were male. Seventeen studies reported the patients' races or ethnicities (16.4% were white, 30% were black, 0.3% were Asian, and 9.1% were Hispanic). Most studies (96%) investigated smoking exposure at home or by parents; 8% investigated exposure outside the home. Only 7 studies (28%) reported testing for SHS, whereas others relied on parent- or caregiver-reported exposure.

The methodologic quality of the included studies was generally low owing to the observational nature of the studies (eFig 1 and eAppendices 1 and 2). Most studies had a high or unknown risk of bias for exposure ascertainment and attrition bias. However, all studies provided a clear ascertainment of the outcome and most studies had an adjustment for the confounders. Assessment of potential publication bias was not done owing to the small number of studies included in each outcome and/or high heterogeneity observed ($I^2 > 50\%$) in the studies.

Figure 2 shows the pooled ORs of hospital admissions owing to asthma flares, with 10 cohorts reporting hospital admissions. Children exposed to SHS were significantly more likely to be admitted to the hospital than were children without SHS (OR 1.85, 95% confidence interval [CI] 1.20–2.86, $P = .01$, $I^2 = 75.0\%$). Smoking exposure also was significantly associated with ED or urgent care visits (OR 1.66, 95% CI 1.02, 2.69, $P = .04$; Table 2) and wheeze (OR 1.32, 95% CI 1.24–1.41, $P < .001$). The authors did not find a statistically significant difference in frequency of asthma exacerbation ($P = .88$). With regard to pulmonary function testing, the FEV₁/FVC ratio was significantly lower in children with smoking exposures (OR -3.34 , 95% CI -5.35 to -1.33 , $P = 0.001$), but there was no significant difference in FEV₁%.

Table 2
Pooled outcomes of the included studies

Outcome	Cohorts, n	Effect size (95% CI)	P value	I ²
ED or urgent care visit	6	OR 1.66 (1.02–2.69)	.04	66.3%
FEV ₁ %	4	–3.53 (–7.86 to 0.79)	.11	60.0%
FEV ₁ /FVC	3	–3.34 (–5.35 to –1.33)	.001	0.0%
Wheeze symptoms	5	OR 1.32 (1.24–1.41)	<.001	46.3%
Asthma exacerbation	6	OR 0.93 (0.38–2.29)	.88	87.8%

Abbreviations: CI, confidence interval; ED, emergency department; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio.

Discussion

Previous studies have linked SHS exposure with asthma prevalence, increased symptoms, and poorer control. However, research evaluating SHS related to asthma severity in children has yielded mixed results, and therefore this systematic review was needed. This systematic review and meta-analysis assessed asthma severity, specifically hospitalization, ED or urgent care visits, severe asthma symptoms, wheeze, and pulmonary function in children with SHS exposure according to standard procedures developed by the Cochrane Collaboration. It shows a nearly 2-fold increase in risk of hospitalization for an asthma exacerbation in children with asthma and SHS exposure. This is the first time this risk has been quantified and will enable health care providers to convey the harmful effects of SHS to parents about aggravation of asthma. Of note, a previous systematic review of 8 European birth cohorts consisting of nearly 21,000 children found that exposure to maternal smoking only during pregnancy and not after birth increased the risk of wheezing and asthma at 4 to 6 years of age.⁵⁵

This 2-fold difference in risk of hospitalization is a significant difference related to disease severity, because hospitalizations for asthma increase the likelihood of fatal asthma and poorer asthma control.^{56–59} It also illustrates the increased burden of disease on the health care system with increased rates of hospitalizations.

There are several limitations to the present systematic review. Substantial heterogeneity was observed for most outcomes and the authors were unable to evaluate potential publication bias. The methodologic quality of the included studies also was generally low owing to the observational nature of the included studies. Therefore, using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework, the overall quality of this evidence is low owing to heterogeneity and risk for bias.⁶⁰ In addition, most studies included were performed in westernized countries without adequate representation of third-world countries, where the risk of SHS is believed to be higher. The authors were unable to assess for a dose–response relation, as seen with previous studies,⁶¹ because most studies did not have an objective measurement of SHS (it was a self-reported exposure). Only 7 studies obtained objective data for nicotine exposure with cotinine measurements.

Of note, a recent retrospective matched case–control study noted that children with asthma exposed to SHS had lower FEV₁/FVC ratio and FEV₁ compared with children with asthma who were not exposed to SHS (Pyle et al, unpublished observations). This is congruent to the present findings that showed a lower FEV₁/FVC ratio in children with SHS exposure.

Future studies are still needed to investigate the relation between SHS exposure and asthma. These would include standardized assessment and reporting of smoke exposure and delineation of smoke exposure from parents and other people living in the house or other environments, and objective measurements of tobacco exposure (urine and salivary cotinine measurements, etc). In addition, large studies assessing symptoms using validated scoring systems and objective data with pulmonary function testing should be done. It has been well documented that tobacco cessation is cost

effective. Studies assessing severity and health care cost in these children after tobacco cessation is initiated would be helpful.

This systematic review noted worsened severity of asthma in children exposed to SHS compared with controls and the most impressive is the increase in hospitalization.

Assessment of SHS (subjective and objective measurements) should be an integral part of asthma care in children. This will help address and eliminate modifiable risk factors and improve the overall health of children with asthma.

Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2015.08.005>.

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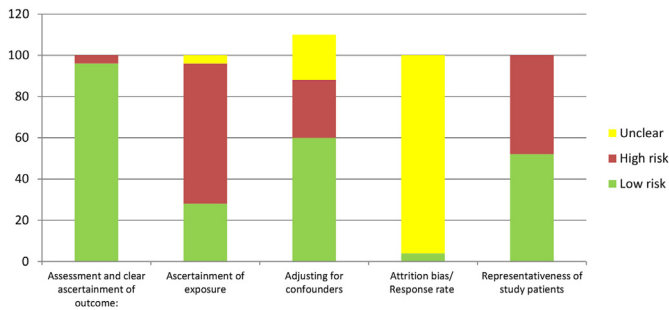


Figure 1. Risk of bias for included studies.

Appendix 1

Search strategy

Ovid MEDLINE 1946 to week 3, 2015

#	Searches
1	exp passive smoking/
2	exp asthma/
3	("passive smoking" or "tobacco smoke pollution" or ((secondhand or "second hand" or environmental or parental) adj2 smok*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4	(1 or 3) and (exp asthma/ or asthma*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5	4 and (infant* or child* or toddler* or preschool* or pediater* or paediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 1626
6	limit to adolescence, preteen* or teen*
7	5 or 6
8	7 and (cochrane* or systematic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9	7 or 8

Embase 1988 to week 3, 2015

#	Searches, Results, Search Type
1	("passive smoking" or "tobacco smoke pollution" or ((secondhand or "second hand" or environmental or parental) adj2 smok*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2	passive smoking/
3	exp asthma/ and (1 or 2)
4	limit 3 to (to adolescence, preteen* or teen*)
5	4 and (infant* or toddler* or child* or preschool* or pediater* or paediatric*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6	4 or 5
7	6 and (systematic review/ or meta-analysis/)
8	6 or 7

EBM Reviews, Cochrane Database of Systematic Reviews 2005 to week 3, 2015

#	Searches, Results, Search Type
1	("passive smoking" or "tobacco smoke pollution" or ((secondhand or "second hand" or environmental or parental) adj2 smok*).mp. [mp=title, abstract, full text, keywords, caption text]
2	1 and (parent* or infant* or child* or preschool* or toddler* or pediater* or paediatric*).mp. and asthma*.mp. [mp=title, short title, abstract, full text, keywords, caption text]

Wos

TS=((("passive smoking" OR "second hand smok*" OR "secondhand smok*" OR "smoke exposure" OR "tobacco smoke pollution" OR "parental smok*" OR "environmental smok*") AND asthma* AND (child* OR infant* OR pediater* OR paediatric* OR preschool* OR toddler*))
 Refined by: Languages=(ENGLISH)
 Timespan=Year to date. Databases=SCI-EXPANDED.

eAppendix 2

Risk of bias of included studies

Study	Assessment and clear ascertainment of outcome	Ascertainment of exposure	Adjusting for confounders	Attrition bias and response rate	Representativeness of study patients
Mitchell et al. ²⁰	low risk	high risk	low risk	NR	low risk
van den Bosch et al. ²	low risk	high risk	low risk	NR	low risk
Akuete et al. ³²	low risk	high risk	low risk	NR	low risk
Rabinovitch et al. ³³	low risk	low risk	high risk	NR	low risk
Radic et al. ³⁴	low risk	high risk	high risk	NR	low risk
Lawson et al. ³⁵	low risk	low risk	low risk	NR	high risk
Gerald et al. ³⁶	low risk	high risk	low risk	NR	low risk
Forbes et al. ³⁷	low risk	low risk	low risk	NR	high risk
Vargas et al. ³⁸	low risk	high risk	low risk	NR	high risk
Wang et al. ³⁹	low risk	high risk	high risk	NR	high risk
Murray et al. ⁴⁰	low risk	high risk	high risk	NR	high risk
Everhart et al. ⁴¹	low risk	high risk	low risk	NR	low risk
Cinar et al. ⁴²	low risk	high risk	high risk	NR	low risk
Yamasaki et al. ⁴³	low risk	high risk	high risk	NR	high risk
Jin et al. ⁴⁴	low risk	high risk	low risk	NR	low risk
Chilmonczyk et al. ⁴⁵	low risk	low risk	NR	NR	high risk
Abd Elmoneim et al. ⁴⁶	low risk	high risk	NR	NR	high risk
Lang et al. ⁴⁷	low risk	high risk	low risk	NR	low risk
Azizi et al. ⁴⁸	low risk	high risk	low risk	NR	high risk
Ehrlich et al. ⁴⁹	low risk	low risk	low risk	NR	high risk
Evans et al. ⁵⁰	low risk	high risk	low risk	low risk	low risk
Leson and Gershwin ⁵¹	low risk	NR	high risk	NR	high risk
Mannino et al. ⁵²	low risk	low risk	NR	NR	low risk
Howrylak et al. ⁵³	low risk	low risk	low risk	NR	low risk
Ciaccio et al. ⁵⁴	high risk	high risk	low risk	NR	high risk

Abbreviation: NR, not reported.