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Ambient pollen concentrations and asthma hospitalization in children and adolescents: a systematic review and meta-analysis

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ABSTRACT

Objective: We aimed to conduct a systematic review examining the association between outdoor pollen and childhood asthma hospitalizations.

Data Source: A systematic search of articles in MEDLINE, EMBASE, CINAHL, ProQuest Central, Web of Science and Google Scholar published to 18 July 2019.

Study selection: Studies that presented data on pollen exposure and childhood asthma hospitalization were included and evaluated for potential risk of bias by two independent authors. Random effects meta-analysis was performed where possible.

Results: A total of 1048 records were identified, and twelve studies included in the review. The synthesis suggested possible associations between outdoor pollen, especially for grass and birch and childhood asthma hospitalization. However, the results varied widely across geographical areas and settings for other pollen taxa. The meta-analysis of the case-crossover studies showed a positive association between grass and childhood asthma hospitalization, an increase in 10 grass pollen grains/m³ was associated with a 3% increase in childhood asthma admission (OR = 1.03; 95%CI:1.01, 1.04), but the pooled estimate was not significant for timeseries studies. The meta-analysis of the timeseries studies for birch pollen showed an increase in 10 pollen grains/m³ being significantly associated with a Mean Percentage Change (MPC) in childhood asthma admissions (MPC= 0.85; 95%CI:0.40, 1.30).

Conclusion: Globally, grass and birch pollen are important triggers of childhood asthma hospitalization, but the association could not be ascertained for other pollen taxa. Pollen is a major environmental trigger of asthma exacerbations and more focus on early interventions to reduce this burden needs to be considered.

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Introduction

Asthma is a global chronic public health problem that affects people of all age groups (1,2), but the burden of disease is greatest in children. The International Study of Asthma and Allergies in Childhood (ISAAC) showed that the global prevalence of severe asthma was 6.9% among 13 to 14 year old adolescents (3). Childhood asthma presentations and subsequent admissions during peak seasonal periods such as winter and spring are a huge burden on children and families (4) and limits their participation in school, extra-curricular activities and necessitates parents to take time off work. Care and management of asthma demands significant support from the carers/families and health care resources.

Environmental factors such as pollutants such as Particulate Matter (PM_{2.5}), Ozone and Nitrogen

Dioxide (NO₂) (5–7); and Human rhinoviruses (HRV) infections (8) can act as triggers for asthma exacerbations requiring hospitalizations. Increasingly, studies are focusing on outdoor pollen concentrations as primary triggers, but the evidence is inconsistent for different pollen species and the results vary over different geographical regions (9). In the Southern Hemisphere, grass pollen has been recognized as an important aeroallergen triggering serious asthma symptoms among children (10,11). In other areas, the evidence for other pollen taxa such as weed, and tree is inconsistent (12–15).

Our recent systematic review showed that outdoor pollen was a trigger for child and adolescent asthma emergency department presentations (16). Despite the emerging evidence linking pollen with asthma exacerbations requiring hospitalizations in children and

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adolescents, no systematic review has been conducted to integrate the existing evidence and to determine whether the findings are consistent across differing populations and geographical regions. Pollen seasons are likely to prolong or increase in intensity in the future because of changing climatic conditions (17,18). The devastation caused by the Thunderstorm asthma epidemic in Australia in November 2016 during the peak grass pollen season was so severe hundreds of people were impacted and unprepared for such serious events (19). It is timely to identify the current gaps in our knowledge and to address this, we sought to conduct a systematic review and meta-analysis of current studies of pollen as a trigger of childhood asthma exacerbations requiring a hospital admission.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20) was used when conducting this review (online [Supplementary Table 1](#)). We also registered the protocol for the review with PROSPERO (registration number: CRD42018097311).

Eligibility criteria

To be eligible for inclusion, all studies needed to be published in English comprising study population as children aged below 18 years. If a study included both children and adults, we excluded the articles that only reported overall effect size estimates without age-specific estimates. However, articles that did conduct age-stratified analysis with estimates for children reported then they were included. Asthma outcome was defined as the ICD diagnosis of asthma at admission either in hospital or health institutional database. We only included studies that present asthma admissions as the outcome. Those children who were admitted at emergency department or short-stay units for some hours were not included. In addition, only those studies that had measured pollen as the primary exposure variable were included in this review.

Search strategy

Two researchers (SKS and KL) independently conducted and replicated the literature search. The relevant literature was searched in MEDLINE, CINAHL, EMBASE, ProQuest central, Web of science and Google scholar up to page 10 published till 18 July 2019. Additionally, the reference lists of relevant

articles were further checked. The search strategy used a combination of the following terms: “pollen” interchangeable with grass or weeds or trees (exposure); “asthma” as asthma hospital*, asthma admiss*, asthma readmiss*, asthma emergency (outcome); and children as a child*, infant, young, adoles*, pediatric, pediatric (population).

The relevant articles were identified, and duplicates were removed after initial screening of the title, author and publication date. At initial screening, the abstracts were reviewed by both authors (SKS and KL) to determine whether they were relevant and met the inclusion criteria. Both authors independently prepared the list of probable articles for full manuscript review and any disagreement between them were discussed with third author (BE). All search results were managed with Endnote software X7.

Quality assessment of all included studies

Two researchers (SKS and KL) independently performed quality assessment of the included articles using a validated quality assessment tool for observational studies (21). This tool is useful for quality assessment of all study types including observational ecological studies used in quality assessment of articles in other systematic reviews (16).

Any discrepancies in the assessment between the two researchers were addressed through mutual consensus or with the third author (BE). The quality benchmark was set for assessing quality of the article based on the median quality score of all included studies (22). We set the benchmark of 75% and above as high-quality and below 75% as low-quality.

Data extraction

Information on the first author, publication date, study design, place the study occurred, study settings, date of study, age range and total number of children/ participants, study duration, instrument for measurement of pollen exposure, exposure data, outcome (asthma) definition and measurement, effect size estimates and 95% confidence interval (CI), lagged effects analysis, adjustment for confounders and any subgroup analysis and/or effect modification were extracted from all included studies.

Meta-analysis

A meta-analysis was conducted if there were at-least two similar studies that reported an effect size and

95% CI for the outcome and a particular pollen taxon. We conducted a meta-analysis of studies including grass and birch pollen using a random effects model, as the conservative effect estimate to allow for variations within included studies (23); however, weeds and other tree pollen were excluded from the meta-analysis due to substantial heterogeneity and unavailability of at-least two similar studies to pool the results. We also checked for heterogeneity of the pooled estimates using the I^2 statistic. The meta-analysis was conducted using Stata SE 14.1 (StataCorp, College Station, Texas).

Results

Search results

A total of 1691 articles were identified in a search that comprised of 1675 articles from the electronic search and an additional 16 articles identified from a manual search of the references of relevant articles. After removing the duplicate articles ($n=643$), a total of 1048 articles were independently reviewed by two authors to examine relevancy and inclusion. After review, 959 articles were found to be irrelevant or not meeting the inclusion criteria, while 89 articles were identified for full review. Of these, 12 articles were selected for inclusion in the final review that fulfilled the inclusion criteria. Five studies were included in the meta-analysis for grass pollen and two studies for birch pollen (Figure 1).

Characteristics of included studies

Out of the twelve studies included, three studies were from the UK (24–26) and Australia (11,27,28) and two studies from the USA (5,29) and one study from Canada (30), Mexico (31), Sweden (32) and Belgium (33). The age of the children ranged from 0 to 18 years. The studies spanned the periods of 1987 to 2018 (Table 1).

Time-series (ecological) studies were the most common type of studies used to assess any associations between pollen exposure and the outcome. Eight out of twelve studies were time-series studies (5,24–26,29–31,33), two studies were based on a case-crossover study design (11,28), one included both time-series and a case-crossover design (27) and one was a register based cohort study (32) (Table 1).

There were wide differences in how the results were presented across the various studies. Four studies presented MPC in daily asthma hospitalizations (5,24,30,33) and another four studies with odds ratio of asthma hospitalization (11,27,28,32). One study each with mean deviation in residuals of explanatory

variables (31), simple correlations between pollen and daily asthma hospital admissions (29), change in residual variation of pollen against the chi-square distribution (25) and relative risk of asthma admission (26) (Table 1).

Quality assessment and risk of bias

Seven of the twelve studies were rated as high-quality studies (11,25,27,28,30,32,33). The average quality score of the included articles was 75.58% [95% CI: 71.12%, 80.03%] with the highest score of 85% and lowest score of 63.2% (Table 2). The studies included in the review had several limitations and risk of bias. The risk of exposure (pollen) misclassification due to a single pollen measuring station was prominent in most studies (5,11,24–29,32,33). Inclusion of children below 2 year where ascertaining asthma is difficult could be problematic for validity of outcome measurement (24,26,27,29–33), while few studies did not exclude the asthma readmission cases (27,29) (Table 2).

The possibility of confounding bias due to failure to adjust for important climatic variables and pollutants (26) and time-trend bias (31) was present in some studies.

Synthesis of findings

Case-crossover studies

All three case-crossover studies were from Australia (11,27,28). Both the studies from Melbourne (28) and Sydney (11) reported significant associations between increased outdoor grass pollen and increases in childhood asthma exacerbations requiring hospitalization. The multi-year study from Sydney (11) also reported positive associations with weeds and unclassified pollen as well as significant interactions between age groups and conifer, total tree and total pollen. The risk of asthma admission was higher for younger children aged 2–5 years and 6–12 years children compared to the older adolescents aged 13–18 years for conifer, total tree and total pollen. An association between increased total ambient pollen and increased asthma hospitalization in the cool season (April to September months) in Adelaide, Australia was shown by Chen et al (27). The authors did not report pollen specific associations, limiting comparison with the other two studies from Australia.

Time series studies

Larger variations were seen in the results of the time-series studies. Guilbert et al. (33) using large hospital

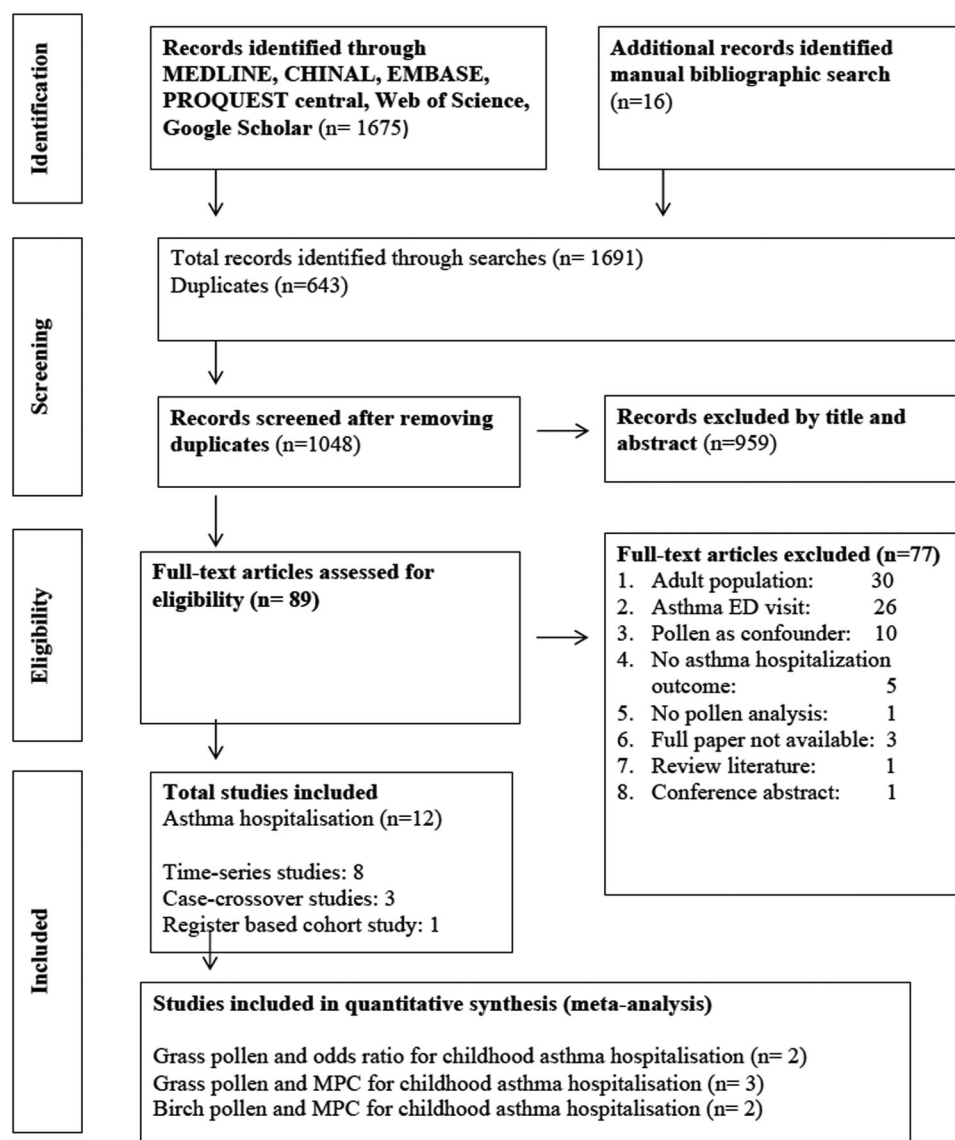


Figure 1. Flow diagram of the systematic review process.

admission dataset from Brussels found significant cumulative percentage change (CPC) in asthma hospitalization associated with increased hornbeam and birch pollen with no evidence of associations with grass pollen. Similarly, a five-year study by Anderson et al. (24) in London showed a significant positive MPC in childhood asthma hospitalization associated with increased birch pollen. They reported a negative association between asthma hospitalizations and both grass and oak pollen, while showing a positive correlation between grass pollen and ozone, and SO₂ suggesting some confounding. Weed, tree and grass pollen were not significantly associated with daily MPC for boys aged less than 13 years in a large 10 city study in Canada (30). However, tree pollen was found to be a significant predictor of asthma hospitalizations in girls.

A study in Washing DC reported no significant association between same day grass and tree pollen on childhood asthma hospitalizations but an increase in weed pollen was associated with increase in daily asthma admissions (5). Similarly, Im et al. (29) reported associations between weed pollen and daily asthma hospital admissions in New Jersey, USA, where a 3-day lag weed pollen concentration explained 5.8% of the total hospital admission such that an increase of 13 grains/m³ of weed pollen increased 1 case of daily asthma hospital admission in children.

A study done by Rosas et al. (31) in Mexico City found grass to be a major predictor of asthma admissions during both the dry and wet seasons. Using the Log linear auto-regression model, Newson et al. (26) in England examined the association between previous

Table 1. Data extraction (characteristics of included studies).

Author, study design, sampling and analysis methods	Age group, total sample/daily mean visits, location and time period	Exposure (Pollen); measurement instrument and other settings	Outcome (Asthma) definition	Control for confounding	Possible Bias
Case-crossover studies: Shrestha et al. (2018); Case-crossover; Population; Conditional logistic regression	2-18 years; Total sample (n)=2098; Sydney, Australia; May 1, 2008 and May 31, 2013	Grass (Poaceae); Weed (<i>Plantago</i> , <i>Echium plantagineum</i> and <i>Parietaria</i>); Tree (<i>Cupressus</i> , <i>Casuarina</i> , <i>Eucalyptus</i> , conifer and <i>Platanus</i>) and “unclassified pollen”; Burkard volumetric spore trap	Asthma Hospitalization (ICD10-AM; SNOMED CT-AU; ICD-9)	Climatic conditions (Maximum temperature and mean humidity), and pollutant (PM _{2.5})	Pollen exposure misclassification; Confounding by respiratory viruses or pollen sensitization
Chen et al. (2016); Case-crossover and time-series study; Population; Log-linear quasi-Poisson and Conditional logistic regression	0-17 years; Total sample (n)= 36024; Adelaide, Australia; 2003-2013	Total pollen; Hirst automatic volumetric spore trap; Cool Season	Hospitalizations including the *ICD-10 codes J45 (asthma) and J-46 (status asthmaticus)	Climatic conditions and pollutants	Outcome measurement bias: <i>Asthma in less than 2 years children</i> ; Pollen exposure misclassification
Erbas et al. (2015); Case-Crossover study; Population; Population averaged conditional regression;	2-17 years; Total Sample (n)=644; Melbourne, Australia; Sep 2009 to Dec 2011	Grass; Measurement instrument: <i>Not given</i>	Principal diagnosis of asthma at hospitalization	Climatic conditions and pollutants	Pollen exposure misclassification.
Time-series studies: Guilbert et al. (2018); Time series; Population; Quasi-Poisson regression model	0-14 years; 35% of 5094 (≈1783) Brussels, Belgium; 2008-2013	11 pollen taxa (alder, hazel, yew, Cupressaceae, ash, hornbeam, birch, oak, plantin, grasses and mugwort); Hirst-type volumetric spore sampler (Burkard Manufacturing Co., Ticknamsworth, UK)	Asthma admissions (ICD-9 code 493)	Seasonal and long-term trends, day of weeks and Public holiday Mean; Climatic temperature Relative humidity	Outcome measurement bias: <i>Asthma in less than 2 years children</i> Pollen exposure misclassification
Babin et al. (2007); Time-series; Population; Poisson Regression model	5-12 years; Sample size: <i>Not given</i> ; Washington, USA; 2001-2004	Grass, Weeds, Trees; Measurement instrument: <i>Not given</i>	Hospital visit records in which one of the first three of nine possible diagnosis fields listed an asthma code (ICD-9) who were subsequently admitted. Discharge records with ICD-9 code 493	Seasonal factors	Pollen exposure misclassification
Cakmak et al. (2005); Time series; Population; Generalized Additive models.	0-13 years; Total sample (n)= 356605; 10 cites of Canada; April 1993- March 2000	Grass; Rotational Impaction methods		Climatic and pollutants.	Outcome measurement bias: <i>Asthma in less than 2 years children</i> .
Im et al. (2005) Time series; Population; Pearson cross-correlation and multiple regression analysis	0-14 years; Total sample (n)=17,905; New Jersey, USA; 1993-1995	Tree, Grass, Weed, and ragweed; Burkard Trap Device	Primary diagnosis of asthma (ICD-9 codes 493.0, 493.90, and 493.91)	Seasonal factors and pollutants.	Outcome measurement bias: <i>Asthma in less than 2 years children</i> . <i>Not excluded readmission data</i> Pollen exposure misclassification

(Continued)

Table 1. Continued.

Author, study design, sampling and analysis methods	Age group, total sample/daily mean visits, location and time period	Exposure (Pollen); measurement instrument and other settings	Outcome (Asthma) definition	Control for confounding	Possible Bias
Anderson et al. (1998); Time-series; Population; Poisson Regression model	0-14 years; Sample size not given (Daily mean admission: 45.4 cases) London, UK; 1987-1992	Grass, Birch, Oak; Burkard Volumetric Trap; Warm season	ICD-9 493 coded at discharge	None	Outcome measurement bias: <i>Asthma in less than 2 years children</i> ; Pollen exposure misclassification
Rosas et al. (1998); Time series study; Population; Generalized linear models with Poisson distribution and log link	0-15 years; Total sample (n)=903; Mexico City, Mexico; 1991	Tree, Grass and Weed; Burkard Volumetric Trap; Wet and dry seasons	ICD-9 code 493	Controlled for climatic conditions;	Outcome measurement bias: <i>Asthma in less than 2 years children</i> . Time trend bias Pollen exposure misclassification.
Newson et al. (1997) Time series; Population; Log linear auto-regression model	0-14 years; Total sample (n)=not given; England; 1990-1994	Grass; Volumetric Trap; Effect measure of previous high grass count for moderate positive and exceptionally high spheric densities.	Asthma admission record taken from Hospital Episodes System (HES)	Public holiday, Weekly cycle, Season of year, long term trend,	Outcome measurement bias: <i>Asthma in less than 2 years children</i> . Exposure measurement: <i>Missing or inconsistent data on pollen measurement due to instrument failure</i> ; <i>Pollen misclassification</i> Not controlled for the climatic factors and pollutants.
Khot et al. (1988) Time series study; Population; Series of Poisson regression models.	18 months to 16 years; Total sample (n)=768; Brighton; England; 1988	Grass pollen; Burkard 7-day volumetric spore trap;	Asthma admitted to Royal Alexandra Hospital for sick children	Controlled for linear trend, day-of-week effect, weather variable, spores	Pollen misclassification; Confounding due to viral infection and seasonal patterns.
Cohort study Lowe et al. (2012) Register based cohort study; Population; Logistic regression model.	Less than one year; Total sample (n)=110381; Stockholm, Sweden; 1988-1995	All pollen species; Burkard Trap; Pollen exposure measured during first and last 12 weeks of pregnancy and first 12 weeks of infancy and risk of asthma hospital admission in the first year of life.	ICD-9 coded 493	Controlled for season and year of birth, air pollutants, temperature and humidity.	Outcome measurement bias: <i>Asthma in less than 2 years children</i> . Pollen misclassification; Aggregated pollen species count taken as the exposure.

*ICD = International Classification of Disease.

Table 2. Quality assessment checklists and summary.

Study	Study design	Population density	Population description	Time points	Entire sampling or probability sampling	Eligibility criteria	Exposure measures				Outcome measures				Statistical test suitable	Adjustment for confounders	Bias discussed	Bias not covered
							Validity		Reliability		Validity		Reliability					
Guilbert et al. 2018	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	
Shrestha et al. 2018	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	×	
Chen et al. 2016	✓	✓	×	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	×	
Erbas et al. 2015	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	
Babin et al. 2007	✓	✓	×	✓	✓	✓	✓	×	×	×	×	✓	✓	×	✓	✓	×	
Cakmak et al. 2005	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Im et al. 2005	✓	✓	×	✓	✓	✓	✓	×	×	×	×	✓	✓	✓	✓	✓	×	
Anderson et. 1998	✓	✓	×	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	×	
Rosas et al. 1998	✓	✓	×	✓	✓	✓	✓	×	✓	✓	×	✓	✓	✓	×	×	×	
Newson et al. 1997	✓	✓	×	✓	✓	✓	✓	×	×	×	×	✓	✓	✓	×	×	×	
Khot et al. 1988	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	
Lowe et al. 2012	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	

Key: ✓: criteria satisfied; T: criteria not satisfied.

day high grass pollen count on childhood asthma admission compared to zero/low pollen count during sferic (thunderstorm with lightning flashes) and non-sferic days. The study showed that presence of high pollen counts significantly increased risk of asthma hospitalization in sferic days but the association was not significant in non-sferic days (26).

A much earlier study from Brighton (25) found no significant association between 1-day lagged grass pollen concentrations and asthma admissions among children (Table 3).

Cohort studies

A large register based cohort study in Sweden (32) examined the association between exposure to high pollen counts during pregnancy and the first 12 weeks of infancy, and risk of childhood asthma hospitalization in first year of life. The study showed that increase in pollen exposure during late pregnancy was associated with increased risk of asthma hospitalization among infants. In addition, a protective effect of pollen exposure during infancy was observed for childhood hospitalization but only among the children of mothers who were heavy smokers (Table 3).

Meta-analysis

Pooling of the results from the included studies was difficult due to substantial heterogeneity related to the pollen species, method of analysis used to estimate the effect size and the differences in lagged day effects considered for the analysis. However, we were able to conduct a meta-analysis for grass, separately for studies reporting the odds ratios (11,28) and studies reported the MPC (5,24,33) and for birch pollen presenting estimated effects as MPC of childhood asthma admissions (24,33). We converted the estimated effect per 10 pollen grains/m³ increase in pollen level for consistency across different studies to pool the studies for meta-analysis.

An increase in 10 pollens/m³ concentrations was significantly associated with 1.03 times odds of childhood asthma hospital admissions (OR = 1.03; 95%CI: 1.01, 1.04) and measure of heterogeneity was near to zero ($I^2=0\%$, $p=0.339$) (Figure 2), based on case crossover studies (11,28) presenting the same day pollen effect. However, no significant pooled association was shown between grass pollen levels and mean percentage change in childhood asthma hospitalization (MPC= 0.85; 95%CI: -3.24, 4.95) (Figure 3). The heterogeneity was higher ($I^2=54.0\%$, $p=0.114$) as two included studies (5,24) reported the same day effect

Table 3. Results and findings from included studies.

Author	Results	Findings
Case-crossover studies:		
Shrestha et al. (2018)	Odds ratio for asthma hospitalization: (<i>grass per 9 grains/m²; Plantago, Eucalyptus and Unclassified pollen 5 grains/m²; Platanus, Other weeds, and Casuarina 4 grains/m²; Cupressus 24 grains/m²; conifer 7 grains/m², total tree 46 grains/m² and total pollen 64 grains/m²</i>) 2 to 18 years children (Lag 0) Grass 1.037 (1.005 to 1.070) Plantago 1.003 (0.962 to 1.045) Other weeds 1.053 (1.009 to 1.098) Cupressus 1.007 (0.986 to 1.027) Casuarina 1.004 (0.992 to 1.015) Eucalyptus 0.991 (0.962 to 1.022) Conifer 1.015 (0.987 to 1.017) Platanus 1.002 (0.987 to 1.017) Unclassified pollen 1.034 (1.010 to 1.058) Total tree 1.015 (0.988 to 1.042) Total pollen 1.026 (0.992 to 1.060) 2 to 18 years children (Cumulative Lag: Lag0, Lag1, Lag2, Lag 3) Grass 1.005 (0.995 to 1.015) Plantago 0.994 (0.983 to 1.005) Other weeds 1.002 (0.990 to 1.015) Cupressus 1.001 (0.994 to 1.008) Casuarina 1.003 (0.997 to 1.009) Eucalyptus 0.995 (0.986 to 1.005) Conifer 1.004 (0.995 to 1.012) Platanus 0.996 (0.991 to 0.999) Unclassified pollen 1.008 (1.001 to 1.015) Total tree 1.002 (0.993 to 1.010) Total pollen 1.002 (0.992 to 1.013) 2-5 years children (Lag0) Grass: 1.047 (95%CI 1.005 to 1.091) Other weeds: 1.075 (95%CI 1.024 to 1.129) Platanus: 1.017 (95%CI 1.003 to 1.032) Unclassified pollens: 1.059 (95%CI 1.027 to 1.091) 6-12 year old children (Lag0) Conifer: 1.051 (95%CI 1.011 to 1.092) Odds ratio for the asthma hospitalization: (<i>per 10 grains/m²</i>) Total pollen: OR = 1.042 (95%CI 1.022 to 1.061)	Same day (Lag0) Grass, Other weeds (<i>Echium plantagineum</i> & <i>Parietaria</i> pollen) and Unclassified pollen significantly associated with childhood asthma hospitalization among 2-18 years children. Cumulative lag (Lag0 to Lag3) Unclassified pollen associated with asthma hospitalization among 2-18 years children. Conifer (Lag 0) was significantly associated with asthma hospitalization among 6-12 years children. Evidence of interaction between pollen and age groups was observed for conifer ($P=0.008$), total tree ($P=0.004$) and total pollen ($P=0.004$).
Chen et al. (2016)	Odds ratio for asthma hospitalization: (<i>per 50 grains/m²</i>) Grass: OR = 1.11 (95%CI 1.003 to 1.22)	Significant association between the total pollen and asthma hospitalization found in cool season.
Erbas et al. (2015)	Odds ratio for asthma hospitalization: (<i>per 50 grains/m²</i>) Grass: OR = 1.11 (95%CI 1.003 to 1.22)	High level of grass associated with asthma admission for boys but not for girls. Girls sensitized to food were higher risk of asthma hospitalization.
Time-series studies:		
Guilbert et al. (2018)	Cumulative (Lag 0-6 days) percentage change: (<i>Alder 9 grains/m³, Hazel 4 grains/m³, Yew Cupressaceae 49 grains/m³, Ash 4 grains/m³, Hornbeam 1 grain/m³, Birch 40 grains/m³, Oak 22 grains/m³, Plantain 1 grain/m³, Grass 12 grains/m³, Mugwort 1 grain/m³</i>) Age 0-14 years Alder: -1.0 (-3.7, 1.7) Hazel: -0.1 (-3.3, 3.2) Yew Cupressaceae: -3.9 (-8.8, 1.4) Ash: -0.1 (-0.6, 0.5) Hornbeam: 0.7 (0.1, 1.3) Birch: 3.3 (1.1, 5.5) Oak: -5.7 (-11.6, 0.5) Plantain: 7.4 (-9.9, 11.5) Grass: 5.2 (-0.9, 11.5) Mugwort: 1.3 (-4.8, 7.9)	Asthma hospitalization significantly associated with Hornbeam and Birch pollen concentrations among 0-14 years children.
Babin et al. (2007)	MPC for daily asthma hospitalization: (<i>grass and weed per 10 grains/m³ and tree per 100 grains/m³</i>) Age 1-17 years Grass Lag0: MPC = 0.7 (95%CI -7.4 to 9.5) Weed Lag0: MPC = 7.7 (95%CI 0.7 to 15.2) Tree Lag0: MPC = 1.5 (95%CI -0.3 to 3.3)	Significant effects of weed pollen for asthma hospitalization for age group 1-17 years and 5-12 years but not for grass and tree.

(Continued)

Table 3. Continued.

Author	Results	Findings
	Age 5-12 years Grass Lag0: MPC = 1.8 (95%CI -9.4 to 14.5) Weed Lag0: MPC = 10 (95%CI 0.5 to 20.5) Tree Lag0: MPC = 1.8 (95%CI -0.8 to 4.4)	
Cakmak et al. (2005)	MPC for daily hospitalization: (<i>grass per 10grains/m³; tree per 125grains/m³ and weeds per 33 grains/m³</i>) Male: Grass: MPC = 1.3(95%CI -1.9 to 4.5) Tree: MPC = 2.1 (95%CI -5.4 to 9.6) Weeds: MPC = 4.8 (95%CI -2.0 to 11.6) Female: Grass: MPC=-3.6 (95%CI -12.6 to 5.5) Tree: MPC = 7.8 (95%CI 2.5 to 13.1) Weeds: MPC=-1.5 (95%CI -4.9 to 1.9)	No significant association between grass, weeds and trees on asthma hospitalization for boys. For girls, trees pollen concentration was associated with asthma hospitalization. In young age group (less than 13 years) male more susceptible but in older age (greater than 13 years), female more at risk but the test for interaction not presented.
Im et al. (2005)	Percentage of daily asthma hospital admissions: Three-day lag weed pollen explained 5.8% of daily asthma hospital admission, adjusted $R^2=0.58$, $F(1,274)=17.830$, $p<0.001$.	Only weed pollen significantly associated with children's hospital admissions for asthma.
Anderson et al. (1998)	Mean percentage change (MPC) for daily hospitalization: (<i>per 10 grains/m³</i>) Grass (Lag0): -1.13 (95%CI -1.96 to 0.0) Trees (Oak) (Lag0): -1.62 (95%CI -3.21 to 0.0) Trees (Birch) (Lag2): 0.9 (95%CI 0.14 to 1.67)	2-day lagged concentration of Birch pollen significantly associated with asthma hospitalization among children. Grass and Oak tree pollen had a significant same day protective effect on asthma hospitalization.
Rosas et al. (1998)	Mean deviance on residual on asthma admission: Mean deviation on residual (degree of freedom): 1.86 (179).	Grass was the major factor for the asthma emergency admission both on the dry and wet seasons.
Newson et al. (1997)	Relative asthma excesses associated with previous high (50 Grains/m ³ /day or more) grass pollen counts compared to zero/low pollen count. Ratio (with/without sferics): 1.16 (95%CI 1.03, 1.31) Without sferics: 1.00 (95% CI: 0.94 to 1.07) With sferics: 1.16 (95% CI: 1.04 to 1.31)	Previous high five-day moving average pollen counts were associated with increased risk of asthma hospitalization but when segregated, the effect size is significant and greater during the sferics compared to non-sferics days.
Khot et al. (1988)	Change in residual variation against the Chi-squared distribution. Grass (Lag period of 1 day): Contribution: 5.4 (1 degree of freedom)	No association observed for grass pollen and asthma admission.
Cohort study Lowe et al. (2012)	Odds ratio for asthma hospitalization: The risk of asthma hospitalization in infancy (1 st year of life) associated with interquartile range increase in pollen exposure during first 12 weeks and last 12 weeks of pregnancy, and the first 12 weeks of infancy. <i>Effect per inter-quartile range increase in pollen exposure:</i> First trimester: 0.98 (95% CI: 0.89, 1.08) Last trimester: 1.18 (95% CI: 1.00, 1.38) Infancy: 0.80 (95% CI: 0.65, 0.97)	Exposure to high levels of pollen during late pregnancy was associated with increased risk of asthma hospitalization for children during infancy. High pollen exposure in infancy had protective effect on asthma hospitalization in children within 1 year of age. However, the effect was only apparent in children of mothers who were heavy smokers (≥ 10 cigarettes/ day).

but the other study reported cumulative (lag 0–6) percentage change (33).

Two studies (24,33) were included in the meta-analysis pooling association between birch pollen and childhood asthma admission. Anderson et al. presented estimated effect for 2 days lagged pollen concentration and Guilbert et al. presented the cumulative (lag 0–6) percentage change (Figure 4). The meta-analysis showed a statistically significant increase in MPC of childhood asthma admission associated with increase of 10 birch pollen grains/m³

($I^2=0\%$, $p=0.88$; MPC = 0.85; 95%CI: 0.40, 1.30; $p<0.001$).

Discussion

Our systematic review of the available evidence suggests an association between outdoor pollen, especially for grass and birch, and increased risk of asthma exacerbations requiring hospitalization for children and adolescents. In the meta-analysis of case-crossover studies for grass pollen where results were presented

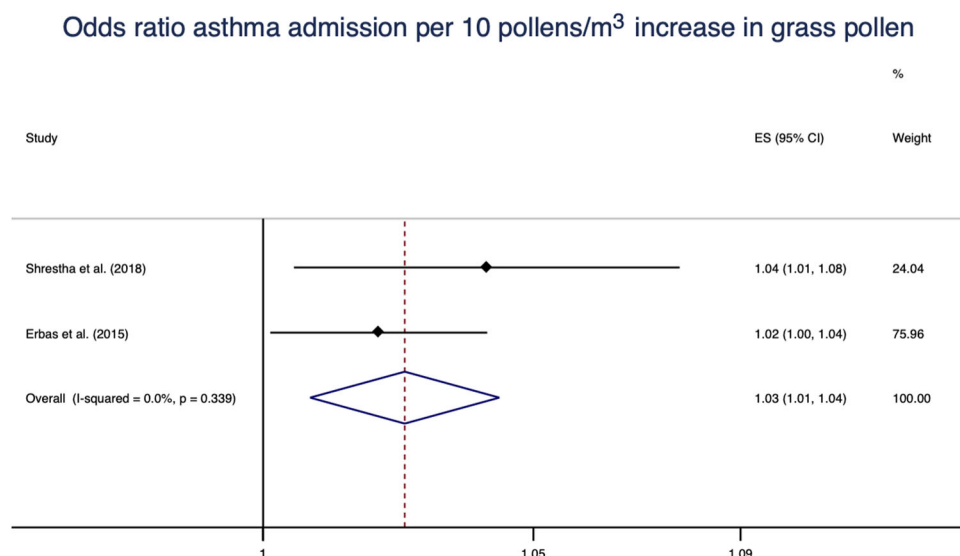


Figure 2. Odds ratio of childhood asthma admission associated with 10 pollens/m³ increase in grass pollen (meta-analysis).

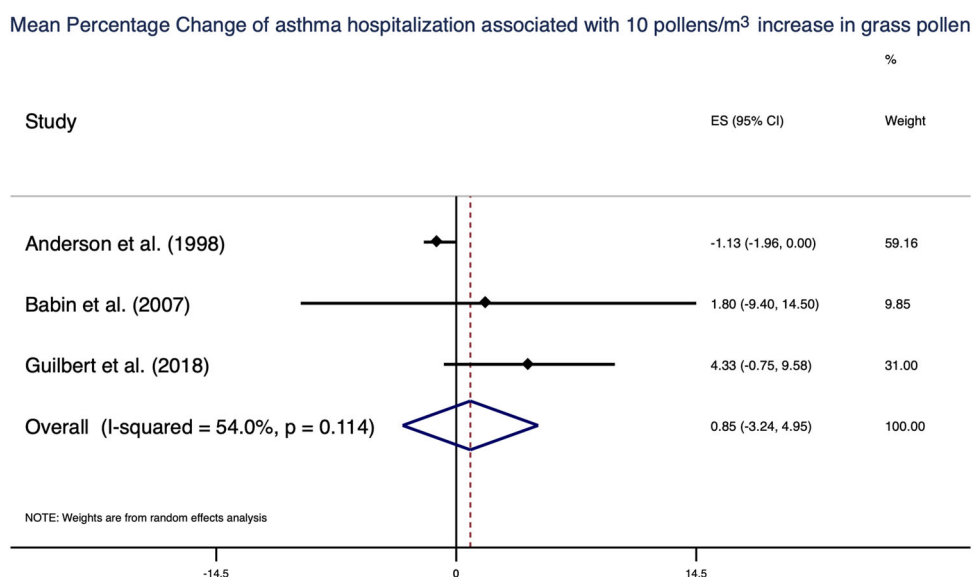


Figure 3. Mean percentage change of childhood asthma admission associated with 10 pollens/m³ increase in grass pollen (meta-analysis).

as the odds ratio, we found that an increase in 10 pollen grain/m³ of grass was associated with 3% increase in asthma hospitalization, but the pooled estimate was not significant for timeseries studies. An extreme pollen day (>100 grains/m³) could therefore see an increase in pediatric asthma hospitalizations of 30%. Birch pollen was also found to be associated with asthma hospitalizations among children. An increase in birch pollen concentration of 10 grains/m³ was associated with a mean increase of 0.88 (95% CI: 0.40, 1.30) cases of childhood asthma hospitalization. We could not perform meta-analysis for other pollen taxa because no two studies have presented estimated

effects for same pollen types and the outcome measurement.

Grass pollen was found to be an important trigger for asthma hospitalization in the meta-analysis of studies reporting ORs, however, the pooled estimate was not significant when results were pooled from studies presenting MPC as the outcome. It is important to note that both studies included in the meta-analysis presenting ORs were case-crossover studies, while other three studies pooled in meta-analysis of MPCs were time-series studies. The case-crossover design, where an individual “case” acts as its own “control”, controls for all potential bias that arises due

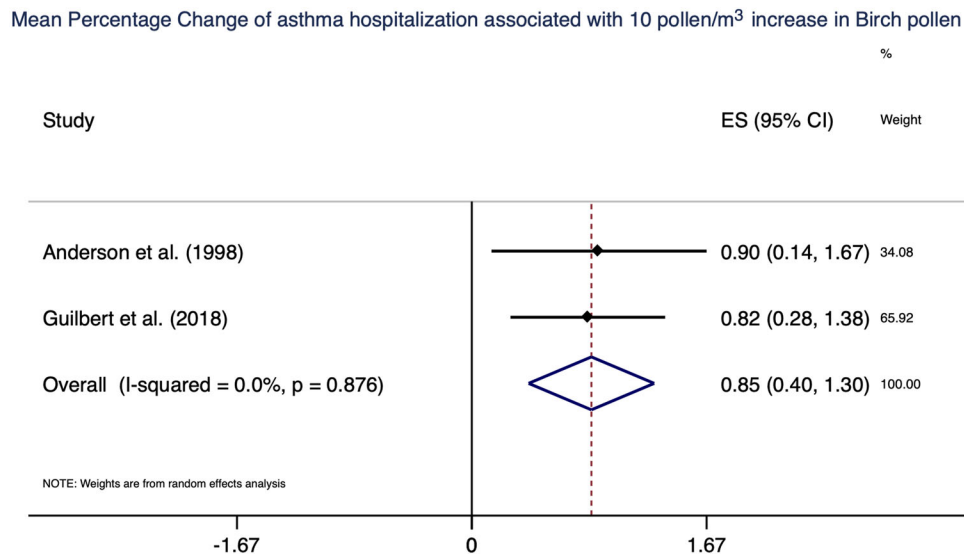


Figure 4. Mean percentage change of childhood asthma admission associated with 10 pollens/m³ increase in Birch pollen (meta-analysis).

to individual differences when selecting different controls (34). Therefore, one possibility could be that pooling the results from studies with more robust designs could have increased the precision of the study findings underpinning the association. The measure of heterogeneity across studies pooled for meta-analysis in case-crossover studies was much lower ($I^2=0\%$, $p=0.339$) compared to the timeseries studies ($I^2=54.0\%$, $p=0.114$).

Moreover, all three case-crossover studies (11,27,28), including two studies included in the meta-analysis of grass (11,28), were from Australia. This reconfirms pollen, especially grass, as an important trigger for asthma exacerbations in young populations in the region. The time-series studies examining association between grass pollen and asthma exacerbation provided mixed results. The findings differed substantially across different study settings, possible differences in climatic conditions, inclusion of confounders and adjustments. The methodological variations including the statistical analysis used in different studies further complicated our effort to summarize the findings.

Only few studies reported sex differences on the effect of grass on childhood asthma hospitalizations (11,28,30). Both case crossover studies from Australia showed increased risk among boys with grass pollen exposure (11,28), while the study in Canada (30) showed increased risk of tree pollen among girls under 13 years of age but not in boys. This latter finding is surprising since boys are usually considered greater risk of asthma exacerbation, particularly before puberty (35). Most studies have either ignored or failed to

report sex stratified analysis. As a result, there exists substantial gap in evidence understanding sex differences and additional studies are needed to further verify the findings and explore the mechanisms.

The effect of weeds on childhood asthma admission varied across different geographical regions. Weeds were found to be an important risk factor for childhood asthma hospitalization in the USA (5,29). *Echium Plantagineum* and *Parietaria* were also associated with childhood asthma hospitalization in Australia (11). In contrast, the time-series study from Canada failed to detect any significant effect of weed (30). The differences in pollen counts during pollen seasons considered in the analysis, pollen types and synergistic effects between local pollutants and pollen combinations could explain some of the variations across these different studies.

The meta-analysis of studies evaluating the effect of birth pollen on childhood asthma hospitalization showed risk of birch pollen on asthma hospitalization. The increase in 10 pollen grain/m³ birch pollen increased 0.85 cases (95% CI: 0.40, 1.30) of childhood asthma admissions. The studies included in the meta-analysis were from Europe, UK (24) and Belgium (33). The other studies from the USA (5) and Australia (11) failed to find any significant association. In contrast, Anderson et al. (24) reported protective effects of same day oak pollen in the UK and most likely, the association could have been confounded by other pollutants and climatic factors that were not adjusted in the regression models used to assess these associations.

This review has provided valuable insights and confirmed the adverse effects of pollen on the childhood asthma burden, despite considerable complexity and heterogeneity in existing evidence. However, wide differences in the methodology and statistical methods across different studies limited direct comparison of the findings. We could not conduct meta-analysis for pollen taxa other than grass and birch pollen. Furthermore, the small number of studies included in the meta-analysis limited external validity for generalizing the results to wider geographical areas. Although we pooled the studies for the meta-analysis it is important to acknowledge that some variability due to climatic conditions may exist. The majority were from temperate climates, especially those observed for grass, but this may play a part. Moreover, although most were from urban populations, we cannot discount the contribution of differing levels of air pollutants, study periods (where prior season rain fall may contribute to pollen flowering) unstudied confounders such as socio-demographic factors, time outdoors and family history may all play a part. The studies included for review, while generally being of high quality, suffered from a variety of biases. The asthma readmission cases in children within 28 days could be as high as 21% in winter (36) and not excluding the readmission cases could potentially dilute the effect size estimation and bias the study results. The appropriateness of the pollen measurement instrument depends upon the pollen size, aerosol velocity and wind direction. Burkard spore trap generally offers the higher estimates for lower sized particulates compared to rotational impaction methods but offers superior results for particle less than 10 μm (37). The use of different types of instruments for exposure measurement is a major limitation for the comparability and consistency of exposure measurement for studies included in the review. Further, this review could not sufficiently assess effect modification by sex and age, which is limited in the current literature.

Conclusion

In summary, both grass and birch pollen are major triggers of childhood asthma exacerbation requiring hospitalization. The evidence for weed and other tree pollen taxa was inconclusive due to substantial variation across different geographical locations and methodology settings. Although there are many triggers of childhood asthma hospital admissions including viral respiratory infections, our review suggests that pollen is also important. Public health policy

could focus on strategies to minimize exposure to pollen during pollen season and communicate more broadly the elevated risk prior to the peak pollen seasons.

Declaration of interest

No potential conflict of interest was reported by the authors.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	✓ (1)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	✓ (1)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	✓ (2)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	✓ (3-4)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	✓ (3)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	✓ (3)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	✓ (3)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	✓ (3)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	✓ (3)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	✓ (3-4)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	✓ (4)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	✓ (4)



PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	✓ (4)
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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	✓ (6)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	✓ (5)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	✓ (15-19)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	✓ (20)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	✓ (22-24)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	✓ (25)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	✓ (20)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	✓ (8-11)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	✓ (10-11)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	✓ (11)
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	✓ N/A



PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Supplement 1

Quality assessment tool for ambient pollen concentration and childhood asthma hospitalization according to Zaza et al. (2000)

Reviewer name: _____ Date: _____

Paper title: _____

First author: _____

Year Published: _____ Journal: _____

#	Question	Responses	Score	Notes/Answer
1a	Where was the study done?			
1b	Population density	• Urban • Suburban • Rural • Mixed • Not reported		
2	How were outcome and other independent (or predictor) variables measured?	• Interview • Self-administered questionnaire • Hospital records • Record review • Observation • Not reported/did not assess		
3	Over what time period (include dates) and at what intervals were outcomes and other variables measured?			
4	Indicate the study design	(1) Expert opinion/ case study (2) Observational study without control group (3) Controlled observational study (4) Cohort study (5) Case control study (6) Quasi experimental study (7) Experimental study Other, specify (0) Can't tell		
5	Was the population well	Yes (1) No		

#	Question	Responses	Score	Notes/Answer
	described?	(0) N/A		
6	Were the eligibility criteria required to enter the study population well described?	Yes (1) No (0) N/A		
7	Did the authors specify the sampling frame or universe of selection for the study population?	Yes (1) No (0) N/A		
8	Was the population that served as the unit of analysis the entire eligible population or a probability sample at the point of observation?	Yes (1) No (0) N/A		
9	Were the exposure measures valid measures?	Yes (1) No (0) N/A		
10	Were the exposure measures reliable?	Yes (1) No (0) N/A		
11	Were the outcome and other independent (or predictor) variables valid measures of the outcome of interest?	Yes (1) No (0) N/A		
12	Were the outcome and other independent (or predictor) variables reliable (consistent and reproducible) measures of the outcome of interest?	Yes (1) No (0) N/A		
13	Did the authors conduct appropriate analysis by conducting statistical testing?	Yes (1) No (0) N/A		
14	Did the authors report which statistical tests were used?	Yes (1) No (0) N/A		
15	Were the statistical tests appropriate for the study design?	Yes (1) No (0) N/A		
16	Was there accounting for different levels of exposure in segments of the study population in the analysis?	Yes (1) No (0) N/A Can't tell (0)		
17	If the authors analysed group-	Yes (1) No		

#	Question	Responses	Score	Notes/Answer
	level and individual-level covariates in the same statistical model, was the model designed to handle multi-level data?	(0) N/A Can't tell (0)		
18	Were there other problems with data analysis that limit interpretation of the results of the study? If yes, describe	No (1) Yes (0) N/A Can't tell (0)		
19	Considering study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	Yes (1) No (0) N/A Can't tell (0)		
20	Did the authors identify and discuss potential biases or unmeasured/contextual confounders that may account for or influence the observed results and explicitly state how they assessed these potential confounders and biases? Describe these factors and, if possible, comment on the likely direction of bias.	Yes (1) No (0) N/A Can't tell (0)		
21	Are there are additional biases not covered in other categories that the authors did not address, if yes, list these as well.	Yes (0) No (1) N/A Can't tell (0)		