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Short-term exposure to pollen and the risk of allergic and asthmatic manifestations: A systematic review and meta-analysis

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ABSTRACT

Background Several studies have assessed effects of short-term exposure to pollen on asthmatic and allergic manifestations. The evidence is inconclusive, and no meta-analysis has been published.

Objective To synthesize the evidence on the relations between short-term pollen exposure and the risk of allergic and asthmatic manifestations.

Methods We performed a systematic literature search of PubMed and Scopus databases up to the end of August 2018. In addition, we reviewed the reference lists of relevant articles. Two authors independently evaluated the eligible articles and extracted relevant information in a structured form. We calculated summary effect estimates (EE) based on the study-specific odds ratios and regression coefficients (β) by applying both fixed- and random-effects models.

Results 26 studies met the *a priori* eligibility criteria, and 12 of them provided sufficient information for the meta-analysis. The summary EE related to 10 grains per m^3 increase in pollen exposure showed an 1% increase (EE=1.01 95% CI 1.00 to 1.02) in the risk of lower respiratory symptoms and a 2% increase (EE=1.02 95% CI 1.01 to 1.03) in the risk of any allergic or asthmatic symptom. Correspondingly, the risk of upper respiratory symptoms and ocular symptoms increased 7% (EE=1.07 95% CI 1.04 to 1.09) and 11% (EE= 1.11 95% CI 1.05 to 1.17), respectively, in relation to such pollen exposure. Short-term exposure to pollen did not show any significant effect on daily lung function levels.

Conclusion: Our results provide new evidence that short-term pollen exposure significantly increases the risks of allergic and asthmatic symptoms.

Strengths and limitations of this study

- Identification of individual studies based on a clearly defined and extensive (including secondary references) search strategy based on a priori set inclusion and exclusion criteria.
- The study-specific effect estimates were converted into comparable common effect estimates for exposure corresponding to 10 pollen grains increase per cubic meter**.**
- Publication bias was assessed by visual inspection of the funnel plots and application of Begg's and Egger's tests.
- For the first time, it is shown quantitatively using meta-analytic approach that short-term exposure to pollen grains increases the risks of allergic and/or asthmatic symptoms.
- The number of studies available for the sub-analyses investigating various outcomes was quite low.

Keywords

Allergy; asthma; panel study; pollen exposure; systematic review; meta-analysis

INTRODUCTION

Allergy and asthma are common diseases and consequently, of public health importance globally. Approximately 500 million people suffer from allergic rhinitis worldwide and more than 300 million people have asthma.[1-3] The prevalence of rhinitis and/or rhinoconjunctivitis varies globally between 1% and 45%[4] and that of asthma between 1% and 21%.[5] In Western Europe, the prevalence of allergic rhinitis and/or rhinoconjunctivitis ranges from 17% to 29%[6] and the prevalence of asthma from 6% to 18%.[7] Respectively, the prevalence of rhinitis and/or rhinoconjunctivitis and asthma are 12–30%[8] and 5-10% in the U.S.[9]

The majority of individuals suffering from allergic rhinitis experience seasonal symptoms when exposed to pollen.[10] Correspondingly, exposure to pollen grains increases the risk of asthma exacerbations among asthmatic persons.[11] Clinically meaningful threshold levels for pollen exposure have varied between 30 and 60 pollen grains per cubic meter of air.[12,13] However, exposures to relatively low levels of pollen (6-9 grains/m^3) have been associated with asthma symptoms among those who already have this disease.[14] Pollen allergy has been found in 80–90% of children suffering from asthma and in 40–50% of adult-onset asthmatics.[15]

Several panel studies have suggested an association between short-term exposure to pollen and asthmatic/allergic manifestations, although the magnitude and statistical significance of such estimated relations have varied.[16-20] Lung function levels have not been found to clearly associate with pollen exposure.[21-25] However, the amount of exhaled nitric oxide (NO)[21,26] and asthma and/or allergy medication use[17,23] seem to increase during pollen season. Caillaud et al.[27] reviewed qualitatively three panel studies that provided some evidence on a relation between daily counts of atmospheric pollen and occurrence of health outcomes.

The panel studies on pollen exposure and manifestations of asthma or allergy have provided somewhat conflicting results.[22,28] To our knowledge there are no previous systematic reviews with meta-analysis that have assessed the effects of short-term pollen exposure on the risk of allergic and asthmatic symptoms and lung function. Therefore, we conducted a systematic review and meta-analysis to summarize the existing evidence on the relations between short-term exposure to pollen and the occurrence of various asthmatic and allergic symptoms and/or lung function manifestations.

METHODS

This systematic review and meta-analysis is based on a review protocol accessible online (http://www.oulu.fi/cerh/node/50459).

Search strategy and eligibility criteria

We performed a systematic literature search of PubMed and Scopus databases up to the end of August 2018, as shown in figure 1. In the first phase, we used the search terms “panel study” and “pollen”. In order to have a more extensive data search, we included the terms “pollen exposure”, “asthma”, “cohort study”, “longitudinal study”, “follow-up study”, “case-control study” and “cross-sectional study” in the second search.

Studies that met the following *a priori* eligibility criteria were included in this systematic review: the study (1) was an original study; (2) was a panel study where a group of people were followed longitudinally over a certain time period; (3) included asthmatic or allergic symptoms or measurements of lung function as the outcome; (4) included a study population of children or adults or both; and (5) reported on relations between daily mean airborne pollen exposure and manifestations of asthma and/or allergies.

Articles that were obviously irrelevant were excluded applying title screening. Articles that did not meet our *a priori* inclusion criteria were excluded by reading the abstract or full text. Reference lists of the articles that fulfilled the eligibility criteria were also reviewed and additional 14 articles fulfilling the criteria were included. Seven duplicate studies were excluded. The final number of the articles included in the systematic review was 26; 12 studies of them were included in the quantitative meta-analyses (see figure 1). Table 1 displays the characteristics of the 26 eligible studies.[13,14,16,18-20,22-26,28,45-58]

Table 1 Characteristics of the eligible studies included in the systematic review and meta-analysis (n = 26).

Reference (Region, country)	Study population	Study size (number of participants)	Follow-up (length and rate, %)	Outcomes	Method for pollen exposure assessment	NOS quality score [a]
Caillaud et al., 2012[45] (France and Switzerland)	Adults with hay fever sensitized to grass pollen	106	17 weeks; 71.1%	Self-reported ocular, nasal and lower respiratory symptoms	Regional monitoring by a volumetric pollen trap	4/9
Caillaud et al., 2014a[16] (France and Switzerland)	Adults with seasonal rhinitis sensitized to ragweed pollen	16 in 2009, 22 in 2010, a total of 30	11 weeks; 96.8%	Self-reported daily SAR symptoms: ocular (itching and/or tear flow and/or conjunctival redness), nasal (sneezing and/or runny nose and/or blocked nose) and respiratory (cough and/or wheezing and/or asthma) symptoms, use of medication	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level	6/9
Caillaud et al., 2014c[46] (France and Switzerland)	Adults with seasonal rhinitis sensitized to birch pollen	61	8 weeks; 85.9%	Self-reported daily SAR symptoms: ocular (itching and/or tear flow and/or conjunctival redness), nasal (sneezing and/or runny nose and/or blocked nose) and respiratory (cough and/or wheezing and/or asthma) symptoms	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level	5/9
Delfino et al., 1996[49] (US)	9-18 years old subjects with physician-diagnosed asthma	12	6 weeks; 80.0%	Asthma symptoms (wheeze, cough, sputum production, shortness of breath, chest tightness) and use of as-needed beta-agonist inhalers	Regional monitoring by a volumetric pollen trap located 10 meters above the ground level	4/9
Delfino et al., 1997[22] (US)	9-46 years old subjects with physician-diagnosed asthma sensitized to tree, grass or weed pollen	22	8 weeks; 91.7%	Self-reported daily asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness), each evening and morning three PEF blows and daily asthma medication use (i.e. beta-agonist inhaler)	Regional monitoring by a volumetric pollen trap located 4 meters above the ground level	5/9

Delfino et al., 2002[19] (US)	9-19 years old subjects with physician-diagnosed asthma	22	8 weeks; 88.0%	Self-reported daily asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness)	Regional monitoring by a volumetric pollen trap located 4 meters above the ground level	5/9
DellaValle et al., 2012[14] (US)	4-12 years old children with physician-diagnosed asthma	430	24-26 weeks during the years 2000-2004; 92.3%	Self-reported daily asthma symptoms (wheeze, night symptoms, shortness of breath, chest tightness, and persistent cough), use of asthma medication	Personal pollen exposure assessment based on modeling	5/9
Djukanović et al., 1996[50] (United Kingdom)	20-49 years old adults with atopic asthma	17	15 weeks; 94.1%	Self-reported asthma symptoms (nocturnal wheeze, nocturnal cough, morning chest tightness, day-time wheeze, subjective worsening of asthma due to exercise, cold air or fumes), self-reported morning and evening PEF values, FEV1	Not specified	1/9
Dominguez-Vilches et al., 1995[51] (Spain)	Patients with pollen induced allergic rhinitis	70 in 1991 and 23 in 1992	12 weeks in 1991 and 12 weeks in 1992; 70.0% in 1991 and 46.0% in 1992	Daily conjunctival, nasal and respiratory symptoms	Regional monitoring by a volumetric pollen trap placed on the roof of a university building	2/9
Feo Brito et al., 2007[47] (Spain)	Subjects with mild to moderate seasonal asthma sensitized to grass and/or olive pollen	137	6 weeks; 90.1%	Self-reported symptoms of asthma, self-reported morning and evening PEF values	Regional monitoring by a volumetric pollen trap	4/9
Feo Brito et al., 2010[13] (Spain)	10-51 years old patients with seasonal rhinitis and/or asthma, mono-sensitized to grass pollen	27	52 weeks; 100%	Self-reported symptoms / symptom and medication scores (including nasal obstruction, runny nose, sneezing/congestion, itching of the eyes, asthma attacks, use of medication)	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level	2/9
Feo Brito et al., 2011[48] (Spain)	10-51 years old patients with seasonal rhinitis or asthma mono-sensitized to olive pollen	20	52 weeks; 100%	Self-reported symptoms (including conjunctival, nasal and respiratory symptoms)	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level	3/9

Grammer et al., 1990[52] (US)	Patients with history of ragweed rhinitis	29	10 weeks; 100%	Self-reported daily symptoms / symptom medication scores (nasal congestion, nasal discharge, sneezing, ocular pruritus, cough, use of medication)	Not specified; A rotating arm impactor and weekly pollen data were used	2/9
Jantunen et al., 2012[53] (Finland)	8-70 years old persons with physician-diagnosed birch pollen allergy (rhinoconjunctivitis)	28 in 2009 and 33 in 2010	8 weeks; 95.3%	Self-reported symptoms (conjunctival symptoms [itchy, swollen, watery, or sore eyes], nasal symptoms [sneezing, runny, itchy, or blocked nose], other allergy symptoms), use of medication	Regional pollen monitoring by a volumetric pollen trap located 14 meters above the ground level	3/9
Klabuschnigg et al., 1981[54] (Austria)	7-14 years old children with clinically-diagnosed asthma	40	6 weeks; 92.5%	Self-reported asthma symptoms, lung function (PEF, FEV1, FVC) measured every second day, use of medication	Regional pollen monitoring by a volumetric pollen trap located 12 meters above the ground level	2/9
Krämer et al., 2005[55] (Germany)	9 years old children with diagnosed allergic eczema	39	26 weeks; 69.6%	Self-reported daily eczema symptoms: itching and the extent of skin lesions	Regional pollen monitoring by a volumetric pollen trap located 12 meters above the ground level	5/9
Newhouse & Levetin, 2004[28] (US)	9-64 years old patients with physician-diagnosed asthma	24	8 weeks; 63.2%	Self-reported asthma symptoms, morning and evening PEF values	Regional pollen monitoring by a volumetric pollen trap located on the roof of a university building	3/9
Ostro et al., 2001[20] (US)	8-13 years old children with physician-diagnosed asthma	138	13 weeks; 90.2%	Self-reported daily asthma symptoms (shortness of breath, cough, and wheeze)	Pollen monitoring by a Rotorod device (taking a sample for 30 seconds every 10 minutes)	5/9
Petersen & Sandberg, 1981[56] (Denmark)	Patients suffering from diagnosed pollen allergy	78	36 weeks; 83.2%	Daily scoring of symptoms and use of medication; before, during and after pollen season	Regional pollen data	3/9
Roberts et al., 2004[26] (United Kingdom)	7-16 years old children with mild to moderate seasonal allergic asthma and rhinoconjunctivitis sensitized to grass pollen	44	10 weeks; 100%	Exhaled NO –measurements and FEV1	Regional pollen monitoring by a volumetric pollen trap	4/9
Roberts et al., 2005[18]	6-17 years old children with seasonal allergic	84	12 weeks; 100%	Self-reported weekly pediatric allergic disease quality based on life	Regional pollen monitoring by a volumetric pollen trap	3/9

(United Kingdom)	rhinoconjunctivitis, asthma and/or eczema sensitized to grass pollen			questionnaire, symptoms (chest, nasal, ocular, cutaneous and other symptoms) and emotional problems		
Ross et al., 2002[23] (US)	5-49 years old subjects with asthma	40	26 weeks; 67.8%	Self-reported morning and evening PEF, symptom score, occurrence of asthma attacks and frequencies of asthma medication use	Local pollen monitoring by Rotorod devices located 2 meters above the ground level	4/9
Scarlett et al., 1996[24] (United Kingdom)	7-11 years old children with and without asthma	154	6 weeks; 100%	Daily lung function measurements (FEV0.75, FVC, FEV0.75/FVC)	Regional pollen monitoring, pollen counts were derived from the local monitoring site	6/9
Schäppi et al., 1998[57] (Australia)	17-50 years old volunteers with moderate to severe hay fever sensitized to grass pollen	21	3 weeks; 75.0%	Nasal (blockage, discharge or itching) and eye symptom scores (itching, swelling or running)	Regional pollen monitoring by a volumetric pollen trap located 14 meters above the ground level	3/9
Studnicka et al., 1995[25] (Austria)	7 years old and older children with and without asthma	47 in panel 1, 45 in panel 2, 41 in panel 3	3 weeks; 88.7%	Daily lung function measurements (FEV1, FVC, PEF)	Regional pollen monitoring by a volumetric pollen trap located 10 meters above the ground level	7/9
Taudorf & Moseholm, 1988[58] (Denmark)	16-47 years old pollinotic (hay fever) patients sensitized to birch pollen	15	16 weeks in 1983 and 16 weeks in 1984; 75.0%	Nose and eye symptom scores, use of medication	Regional pollen monitoring by a volumetric pollen trap	3/9

SAR, Seasonal allergic rhinitis. PEF, Peak expiratory flow. FEV1, Forced expiratory volume in the first second. FVC, Forced vital capacity. NO, Nitric oxide. FEV0.75, Forced expiratory volume at 3/4 of a second. [a] For panel studies, the maximum score is 7/9.

Outcome and exposure definitions

The outcome of interest was occurrence of asthma and/or allergy manifestations. The definitions of asthma and allergy manifestations included self- or parent-reported symptoms (lower and upper respiratory tract symptoms, ocular symptoms, skin symptoms and/or symptom scores), lung function measurements (Peak expiratory flow, PEF, Forced expiratory volume, FEV, Forced vital capacity, FVC, Exhaled nitric oxide, NO), and use of asthma and/or allergy medications. The exposure of interest was exposure to pollen, expressed as the amount of pollen grains per cubic meter of air sampled (grains/m^3). The eligible definition of exposure included exposure to mean daily total airborne pollen or exposure to mean daily airborne pollen of distinct types (including birch, grass, ragweed, mugwort, olive, elm and/or hazel/alder pollen).

Data extraction and quality assessment

Eligible studies were examined and their relevant characteristics recorded in a standardized data extraction form independently by two authors (M.A.K. and D.R.Y.). Any disagreements were discussed together with additional two authors (T.T.H. and J.J.K.J.) until a consensus was achieved. Table 1 displays the main characteristics of the eligible studies. The study quality was assessed applying the Newcastle-Ottawa Scale (NOS) with the maximum score of 9.

In one study, the occurrence of asthmatic and allergic symptoms in relation to pollen exposure was investigated by recruiting a group of study subjects in two consecutive years.[16] There was some overlap among the study subjects, so that seven individuals (23% of participants) were included in both of these study groups. These two groups provided independent effect estimates (EE) for our meta-analysis. In another study, subjects were recruited in three distinct but successive periods of time within the pollen season.[25] These three groups also provided three independent effect estimates for the meta-analyses. The protocol was conducted according to PRISMA guidelines.[29]

Statistical methods

In the meta-analysis, we calculated summary effect estimates (EEs) from the study-specific odds ratios (OR) or regression coefficients (β) by using fixed- and random-effects models. When available, we preferred the adjusted EEs to the crude estimates. The summary EE from the fixed-effects model is presented when the study-specific EEs were homogenous, whereas the summary EE from the random-effects model is presented when moderate or substantial heterogeneity was

observed between the study-specific estimates. Heterogeneity was evaluated using the Q- and I^2-statistics. I^2-statistic >50% indicates high, 25-50% moderate and <25% low heterogeneity. Publication bias was assessed by visual inspection of the funnel plots and application of Begg's and Egger's tests.[30,31] Individual studies included in the meta-analysis assessed their EEs in relation to different levels of pollen exposure. Because of this, individual EEs were converted into a common pollen concentration, i.e. as 10 pollen grains increase per cubic meter of air, before estimating the summary effect.

Because of only a small number of studies or inadequacy of data in the existing studies, we were not able to analyze potential relations between pollen exposure and skin symptoms, forced vital capacity (FVC), exhaled NO or asthma and/or allergy medications. The panel studies with asthmatic and/or allergic populations examined usually asthma- and allergy-related symptoms as outcomes. In panel studies including general populations, the outcomes were lung function measurements. We used the "metan" command of the Stata 11 statistical program to analyze the fixed and random effects (StataCorp, College Station, Tex).

Patient and public Involvement

Due to nature of systematic review and meta-analysis, there was no patient and public involvement in this study.

RESULTS

Literature search

A step-by-step approach of the literature search is presented in figure 1. Twenty-six studies met the *a priori* inclusion criteria and were included in the systematic review, while 12 studies were included in the meta-analysis. Ten of the 26 studies specifically investigated the relation between total pollen exposure and asthmatic and/or allergic manifestations. Thirteen reported on grass (*Poaceae*), 5 on birch (*Betula*), 5 on ragweed (*Ambrosia*), 3 on hazel/alder (*Corylus/Alnus*), 3 on olive (*Olea*), 2 on elm (*Ulmus*), and 1 on mugwort (*Artemisia*) exposure and asthma and/or allergy manifestations.

Characteristics of included studies

Characteristics of the 26 eligible studies are shown in table 1. In 13 studies subjects were asthmatics, in 11 studies subjects were sensitized to pollen (i.e. positive Skin prick test, SPT or

Allergen-Specific Immunoglobulin E Test, IgE test) and in 8 studies subjects had hay fever (i.e. allergic rhinitis, pollen allergy, pollinosis). One study investigated subjects with eczema. In 2 studies, subjects with and without asthma were analyzed together without taking into account the prior disease status. Ten studies investigated children, four adults, and 9 both children and adults. In 3 studies, authors did not specify the age of the subjects. Six studies applied logistic regression, 9 studies linear regression, 2 studies Poisson regression, and 2 studies time series regression for the analyses.

The studies defined the outcomes in different ways. Sensitization based on SPT or IgE analysis was the most common criterion used for the definition of allergy. Current presence of asthma, previous history of asthmatic symptoms, and/or physician (i.e. clinical) diagnosis were also frequently included as an outcome in the studies. We systematically categorized outcomes into any symptom, lower respiratory tract symptoms, upper respiratory tract symptoms, ocular symptoms, skin symptoms, symptom scores, lung function measurements (PEF, FEV, FVC and exhaled NO), and use of asthma and/or allergy medications.

Pollen monitoring used for exposure assessment was based on regional sampling in 21 studies, on local sampling in 2 studies, and on personal exposure modelling in one study. In 2 studies, authors did not specify the type of pollen sampling. The height of the pollen sampler varied between 2-15 meters above the ground level. Thirteen of the studies did not give the height information for pollen sampler. Twenty-five studies expressed the mean pollen concentration as pollen grains per cubic meter of air per 24 h. In 3 studies, daily pollen counts were converted into weekly pollen sums, and consequently, the relations between weekly pollen counts and weekly symptoms were presented. In 2 studies, hourly/bihourly pollen counts were presented in addition to daily counts. Main outcomes for the studies that were not included into the meta-analysis are presented in table 2.

Table 2 The main findings in articles not included into the meta-analysis (n = 14)

Reference	Main findings
Delfino et al. 1996[49]	Pollen exposure was not associated with either asthma symptom scores or as-needed beta-agonist inhaler use.
Delfino et al. 1997[22]	Pollen exposure was not associated with asthma symptom severity, morning or evening peak expiratory flow rate (PEFR), or β-agonist inhaler use.
Djukanovic et al. 1996[50]	The peak pollen season was associated with a significant increase in asthma symptoms.
Dominguez-Vilches et al. 1995[51]	A greater seasonal pollen intensity was associated with a higher occurrence of daily symptoms.
Feo Brito et al. 2010[13]	A significant positive association was found between the presence of symptoms and pollen grains.
Grammer et al. 1990[52]	The peak pollen periods were associated with a twofold increase in symptom-medication scores among a subset of patients.
Jantunen et al. 2012[53]	The number of subjects with allergy symptoms increased significantly with the daily pollen concentrations.
Klabuschnigg et al. 1981[54]	Two hourly pollen counts or daily pollen counts were not associated with the frequency of asthma attacks. In contrast, consecutive 10-day mean symptom scores (assessing asthma attacks) associated with the total pollen counts. No associations were found between pollen exposure and lung function measurement (including PEF, FEV1 and FVC).
Krämer et al. 2005[55]	Pollen exposure had no significant effect on skin symptom severity among children with winter type eczema. In contrast, grass-pollen exposure showed a significant effect on the severity of skin symptoms among children with summer type eczema.
Newhouse & Levetin 2004[28]	*Ambrosia* pollen concentrations were significantly correlated with composite asthma scores, rhinitis scores and several individual symptoms. *Chenopodiaceae/Amaranthaceae* pollen concentrations showed significant associations with composite asthma scores. *Ulmus, Chenopodiaceae/Amaranthaceae* and *Poaceae* pollen concentrations showed significant correlations with composite rhinitis scores. Pollen concentrations significantly influenced morning (but not evening) PEF values measured in the following day.
Petersen & Sandberg 1981[56]	There was a positive association between the appearance of pollen grains in the air and the symptom-medication score.
Roberts et al. 2004[26]	Fractional exhaled nitric oxide (FENO) levels increased significantly during the grass pollen season. There were no apparent associations between pollen counts and other lung function measurements.
Schäppi et al. 1998[57]	The grass pollen counts associated significantly with the average nasal and eye symptom scores
Taudorf & Moseholm 1988[58]	Occurrence of symptoms and daily medication increased during the season with a constant pollen load.

PEFR, Peak expiratory flow rate = PEF, Peak expiratory flow. FEV1, Forced expiratory volume in the first second. FVC, Forced vital capacity. FENO, Fractional exhaled nitric oxide.

Relations between pollen exposure and asthma- and allergy-related symptoms among allergic / asthmatic subjects

The summary EE for the relation between pollen exposure and any symptoms was statistically significantly increased at 1.02 (95% confidence interval (CI): 1.01-1.03) from the random effects model (figures 2, 3 and Supplementary File, figure 1). The study-specific estimates showed high heterogeneity. This estimate was based on 6 studies (providing 9 EEs). The funnel plot and the results from the Begg's (z= -1.25; P value= 0.211) and Egger's tests (Bias coefficient .0457453; 95% CI -.0048418-.0963324; P value= 0.070) on short-term pollen exposure and any symptoms provided no indication of publication bias (Supplementary File, figure 2).

A total of 6 studies (9 EEs) provided study-specific EEs for pollen exposure and lower respiratory symptoms. The summary EE from the random effects model was 1.01 (95% CI: 1.00-1.02). The study-specific estimates showed high heterogeneity.

The summary EE for pollen exposure and upper respiratory symptoms, based on 3 studies (4 EEs), was significantly increased at 1.07 (95% CI: 1.04-1.09) from the random effects model. There was moderate heterogeneity between the study-specific estimates.

The relation between pollen exposure and ocular symptoms was reported in 3 studies (4 EEs). The summary EE from the random-effects model was 1.11 (95% CI: 1.05-1.17). The study-specific estimates showed high heterogeneity.

The relation between pollen exposure and symptom scores was based on 4 studies applying linear regression modelling (giving regression coefficients). The summary EE was significantly elevated (1.003; 95% CI: 1.001-1.004). The study-specific estimates showed high heterogeneity.

Relations between pollen exposure and lung function among general population

The relation between pollen exposure and peak expiratory flow (PEF) was assessed in 2 studies (giving 4 EEs), resulting in a summary EE of 0.98 for 10 pollen grains increase per cubic meter of air (95% CI: 0.95-1.01) in the random effects model based on linear regression modelling. The study-specific estimates showed large heterogeneity.

Two studies estimated the relation between pollen exposure and forced expiratory volume (FEV). One study used forced expiratory volume in the first second, FEV1 as the outcome and the other forced expiratory volume at 3/4 of a second, FEV0.75. Different FEV estimates were combined in the analysis. Meta-analysis gave the summary EE of 1.00 for 10 pollen grains increase

per cubic meter of air (95% CI: 0.99-1.01) in the fixed effects model based on linear regression modelling. There was little heterogeneity between the studies.

Relations between pollen exposure and use of asthma and/or allergy medication

In 2 studies, the use of asthma and/or allergy medication was combined with information on asthma and/or allergy symptoms (in forming symptom-medication score). In 5 studies that investigated the relation between pollen exposure and the use of medication, pollen exposure increased the use of medication. In contrast, 3 studies did not show any association between pollen exposure and use of allergy/asthma medication.

DISCUSSION

Main findings

This systematic review and meta-analysis provides new evidence that short-term pollen exposure significantly increases the risk of asthmatic and allergic symptoms. The summary EE for a 10 grains /m³ increase in pollen exposure showed on average a 2% increase in the risk of any asthmatic or allergic symptom. The corresponding increases in the risk of upper respiratory symptoms and ocular symptoms were 7% and 11%, respectively. All summary EEs were statistically significant. This meta-analysis did not show any statistically significant relations between pollen exposure and lung function measurements. The summary EE for 10 grains /m³ increase in pollen exposure indicated a 2% decrease in PEF values, while no change was detected in relation to FEV values.

Risk of bias across the studies

In the majority of studies, exposure assessment was based on single stationary regional sampler located on the roof level (table 1). Although it has been suggested that different types of pollen sampling can be used to get a rough estimate of pollen exposure,[32] many of the approaches may not capture in satisfactory detail daily individual exposures at the breathing level. In 2013, we monitored grass pollen concentrations at 16 sites in the cities of Helsinki and Espoo during the peak pollen season by using rotorod-type samplers at the breathing height.[33] We identified substantial variation in exposure concentrations at breathing height according to urbanity of the site and time of the day within areas covered by our roof level monitoring stations. Most valid estimates of pollen exposure could be obtained by using personal pollen sampling. There were also other potential sources of heterogeneity in the exposure measured by these studies linked to

variation in weather/climatic conditions, period of monitoring, nature of pollen season, daily activities/time spent outdoors by the study subjects, and pollen types monitored.

In all studies, selection of study subjects was based on predefined and justified eligibility criteria. Due to the study design including inference based on within-individual variation of health outcome, the risk of selection bias is rather small. Also the relatively high follow-up rates (varying from 46.0 to 100%) across studies reduce the risk of selection bias. However, there was substantial diversity in the type and measurement of outcomes, which resulted in difficulties in forming the major outcome groups for the meta-analyses. Status of asthma and/or allergic diseases varied from mild to moderate or from moderate to severe.

The studies could be divided roughly into two major groups on the basis of what kind of adjustment was applied for confounding. The first group of studies provided only descriptive results without any or only with very basic statistical analyses. The second group performed extensive statistical analyses, including controlling for a few or several confounders. Due to study design where individuals act as their own controls on days with no (major) exposure, individual characteristics are not potential confounders. In contrast, environmental factors, such as temperature and air pollution can be potential confounders. A significant number of the studies adjusted for temperature (13) and other meteorological parameters (12), as well as for air pollution (4). Other potential sources of heterogeneity include variation in the studied time lags between the exposure and the outcome (varying from 0 to 14 days), potential differences in allergen content of pollen of interest, and different characteristics and size of the study populations (varying from 12 to 430 subjects). In 24 studies, the study focused on asthmatics and/or subjects with allergies, whereas two studies included both healthy and non-healthy subjects.[24,25]

Validity of results

The strengths of our study include identification of individual studies based on a clearly defined search strategy. In addition to the primary PubMed and Scopus database searches, we also used secondary references that were cited by the articles and reviews identified in the primary search to achieve as complete set of studies as possible. Two reviewers checked independently the eligibility of the studies according to *a priori* set inclusion and exclusion criteria and identified the most appropriate effect estimate.

The present systematic review and meta-analysis focused on panel studies mainly with relatively brief follow-up periods. The follow-up periods in the studies varied from 3 weeks to 52 weeks. However, pollen related asthmatic and allergic symptoms are usually induced after only a few hours or days of exposure.[34,35] Thus, variable and/or relatively short follow-up periods are probably not problematic when assessing the relationship between pollen exposure and outcomes of interest in this study.

Our statistical analyses included 12 studies, because only 12 studies out of a total of 26 presented the exact mean or interquartile range (IQR) values of pollen grains per cubic meter. Information on the mean and IQR values were needed to convert the study-specific effect estimates into common effect estimates for exposure corresponding to 10 pollen grains increase per cubic meter. The aim of this transformation was to make studies containing different pollen concentration values comparable. Although the total number of panel studies was reasonable, the numbers of studies available for the sub-analyses investigating various outcomes were quite low. Therefore, the conclusions based on results of the sub-analyses should be interpreted with caution.

"Any exposure" was applied in the analyses due to the heterogeneity of exposure assessment. Total daily mean pollen concentration values were preferred, but when such were not available, information on the mean daily airborne concentration of distinct pollen types (birch, grass, ragweed, mugwort, olive, elm and/or hazel/alder) was used as the measure of exposure in the analyses. This should not cause any problem, because the pollen seasons of different pollen types commonly overlap, so individuals can react to exposure to several pollen types. Consequently, the reaction to pollen exposure is likely to be a combined reaction to a sum of various pollen types.[36] It is not always possible to define exactly which specific pollen type caused the symptoms. Therefore, the exact separation of distinct pollen types in health effect studies is somewhat artificial and thus, unnecessary.

Synthesis with previous knowledge

Our results indicated that short-term pollen exposure increases the risk of any respiratory or other allergic symptom, lower and upper respiratory symptoms and ocular symptoms among asthmatic and/or allergic subjects. In a recent systematic review and meta-analysis of 14 studies,[37] the mean number of emergency department attendance among children and adolescents with asthma increased 1.88% (95% CI = 0.94%-2.82%) in relation to a 10 grass pollen grain increase per cubic

meter. These results are in line with a recent ecologic study from Japan, where a positive association was observed between cedar and cypress pollen counts and the prevalence of symptoms of allergic rhinoconjunctivitis and asthma in school children.[38] Similarly, our results are also in line with the register-based time-series analysis among Belgian population, where a positive association was observed between pollen exposure and allergy medication sales.[39] A time-stratified case-crossover study showed a positive association between tree and weed pollen exposure and emergency department visits due to asthma exacerbations among 13-17 year- old U.S. asthmatics.[40]

According to our results, the effect of pollen exposure was stronger in upper respiratory tract than in lower respiratory tract. This could be explained by the large size of the pollen grain. Generally, the size of pollen varies between 20 and 100 micrometers in diameter.[41] Therefore, particles of pollen grain size do not penetrate well into the lower respiratory tract.[42] Pollen grains are likely to adhere and release their allergenic content already in the upper respiratory tract. As a consequence of this, the majority of the direct allergic inflammatory effects caused by pollen may be experienced in the region of the upper respiratory tract.

Our systematic review did not detect any major effect of pollen exposure on lung function. The results may be explained by the fact that the study population for lung function effects included healthy people in addition to asthmatic and allergic subjects. If these studies would only include asthmatic and/or allergic persons, more pronounced effects might be detected. In the Swedish cohort-based study, exposure to grass pollen during the preceding day was associated with a reduced forced expiratory volume in relation to an increase in three pollen counts (/m^3) among the 8-year-old children.[43] This association was more pronounced among children who were sensitized to pollen allergens. In line with those results, another study of Swedish adults showed that pollen exposure resulted in significantly increased concentration of nitric oxide in exhaled air, which suggested increased airway inflammation among these asthmatics compared to the healthy controls.[44]

Conclusions

This systematic review and meta-analysis provides new evidence that short-term exposure to pollen grains increases any respiratory symptoms, as well as specifically upper respiratory and ocular symptoms among asthmatic and allergic subjects. It is important that clinicians take into account, when working with allergic and asthma patients that even relatively short-term exposure

to pollen can induce for them symptoms of allergies and asthma. Clinicians should advice allergic and asthmatic subjects to avoid spending much time outdoors during the (main) pollen periods, and to use adequate allergy and asthma medications when such exposures cannot be avoided. Future studies should use personal exposure assessment and it would be important to find out how the variation in pollen exposure affects the health of allergic and asthmatic subjects.

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Contributors

JJ and TH conceived the study; MK, DRY and TH reviewed the articles, NS and MK analyzed the data under supervision of JJ; MK, TH, MJ, and JJ wrote the manuscript, all authors contributed to the intellectual content and approved the final version

Data sharing statement

No additional data available.

Patient consent

Not required

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Competing Interests None declared.

Legends to the figures

Figure 1 Flow diagram showing searches and study selection.

Figure 2 Forest plot for the relation between pollen exposure and any symptom (Weights are from random effects analysis).

Figure 3 A Forest plot for the relation between pollen exposure and lower respiratory symptoms (Weights are from random effects analysis). **B.** Forest plot for the relation between pollen exposure and upper respiratory symptoms. **C.** Forest plot for the relation between pollen exposure and ocular symptoms (Weights are from random effects analysis). **D.** Forest plot for the relation between pollen exposure and symptom score (Weights are from random effects analysis).

Supplementary File, Figure 1 A. Forest plot for the relation between pollen exposure and peak expiratory flow (PEF; Weights are from random effects analysis). **B.** Forest plot for the relation between pollen exposure and forced expiratory volume (FEV).

Supplementary File, Figure 2 Funnel plot with pseudo 95% confidence limits for the relation between short-term pollen exposure and any symptom.

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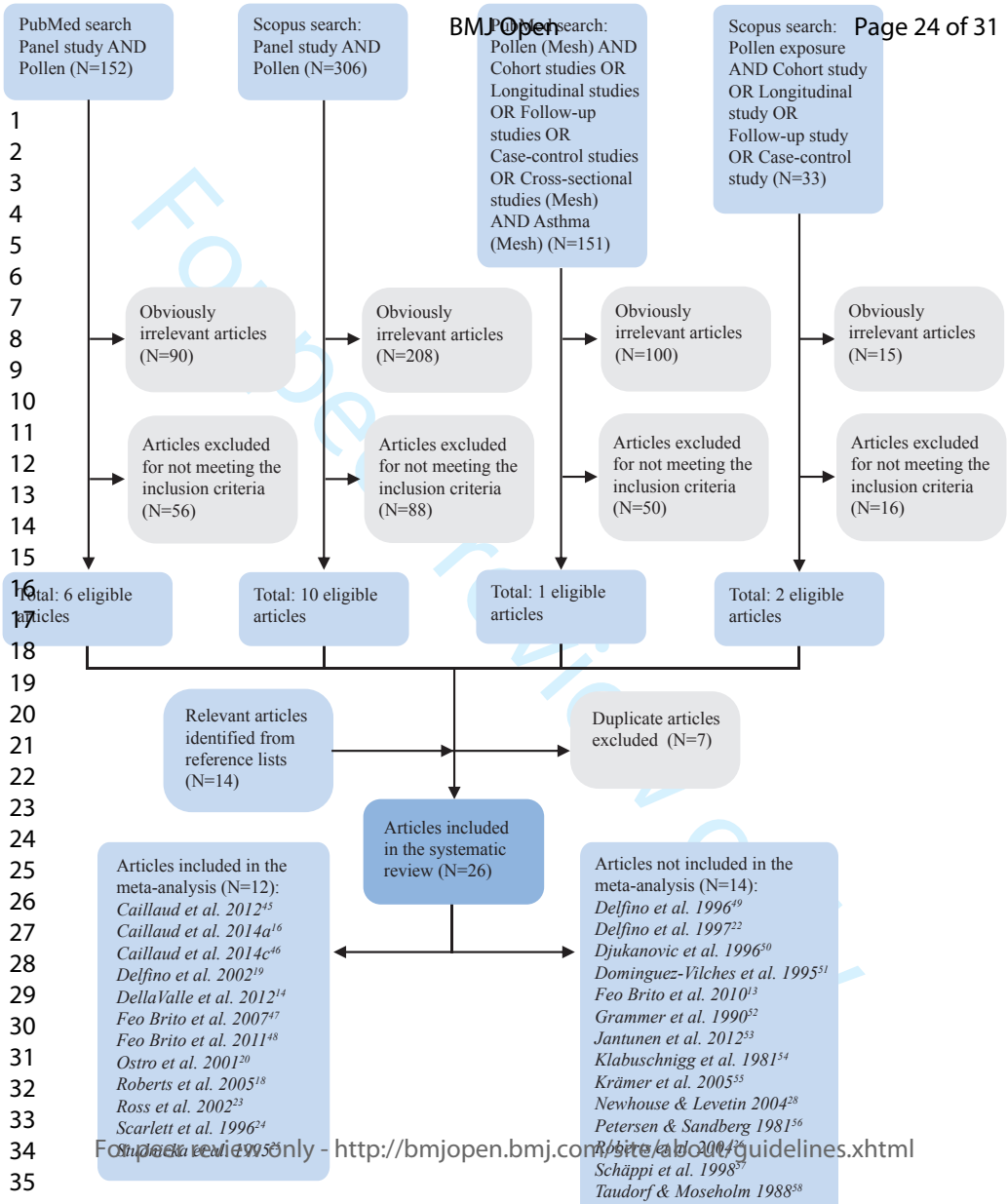

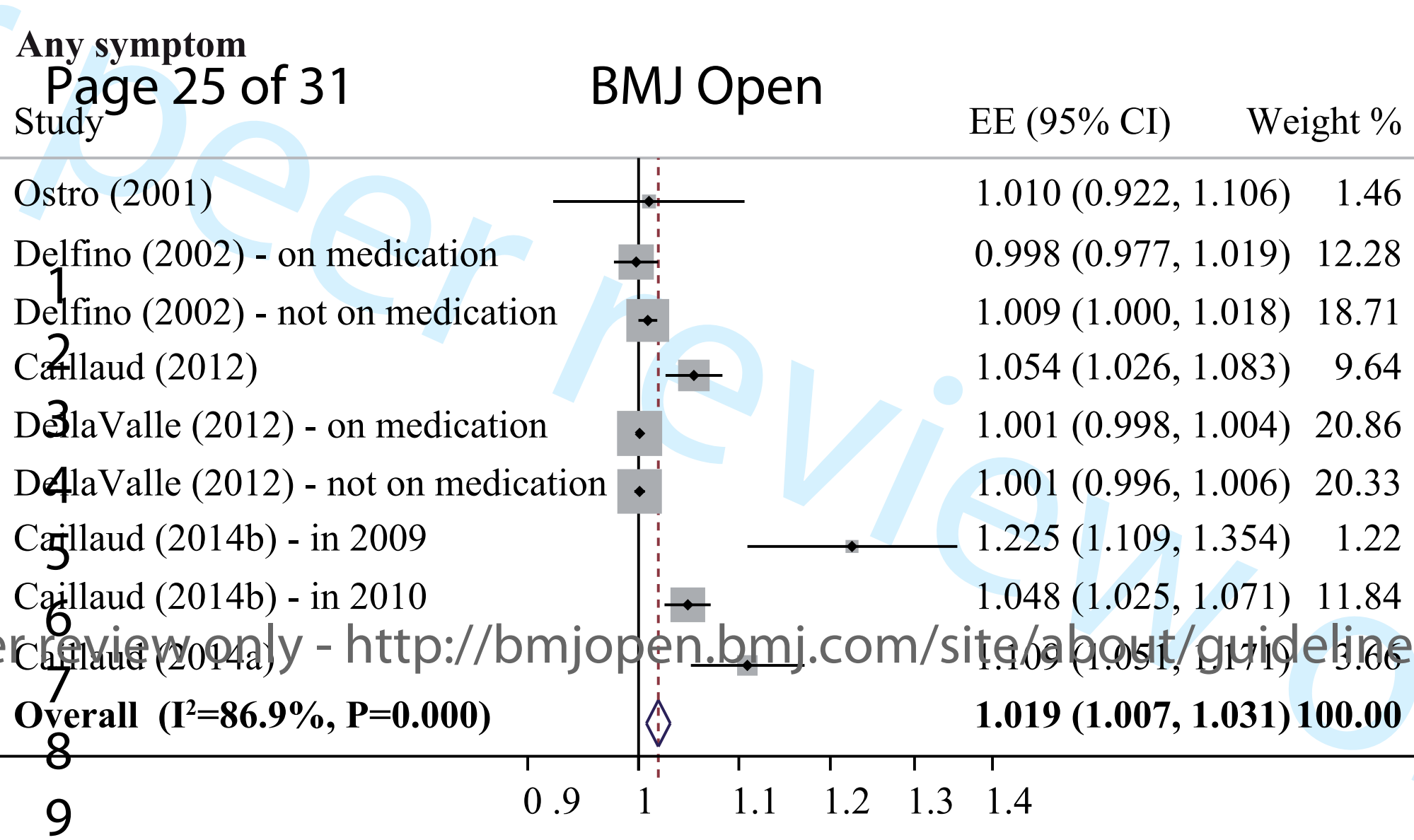

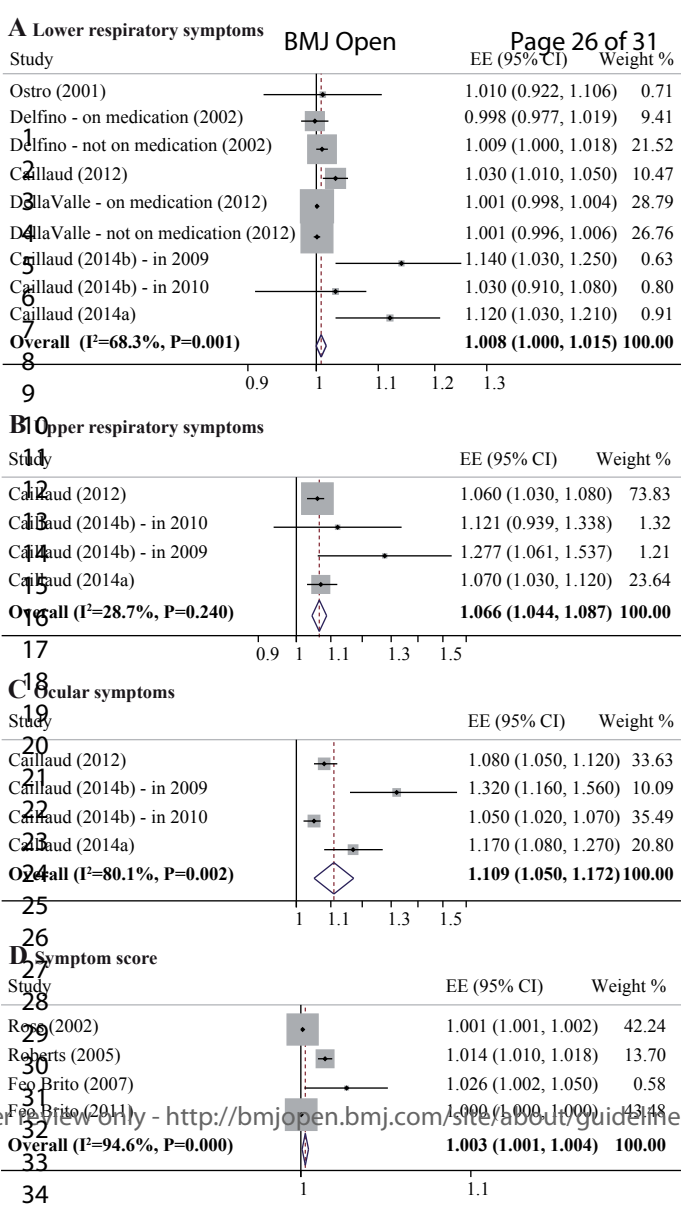

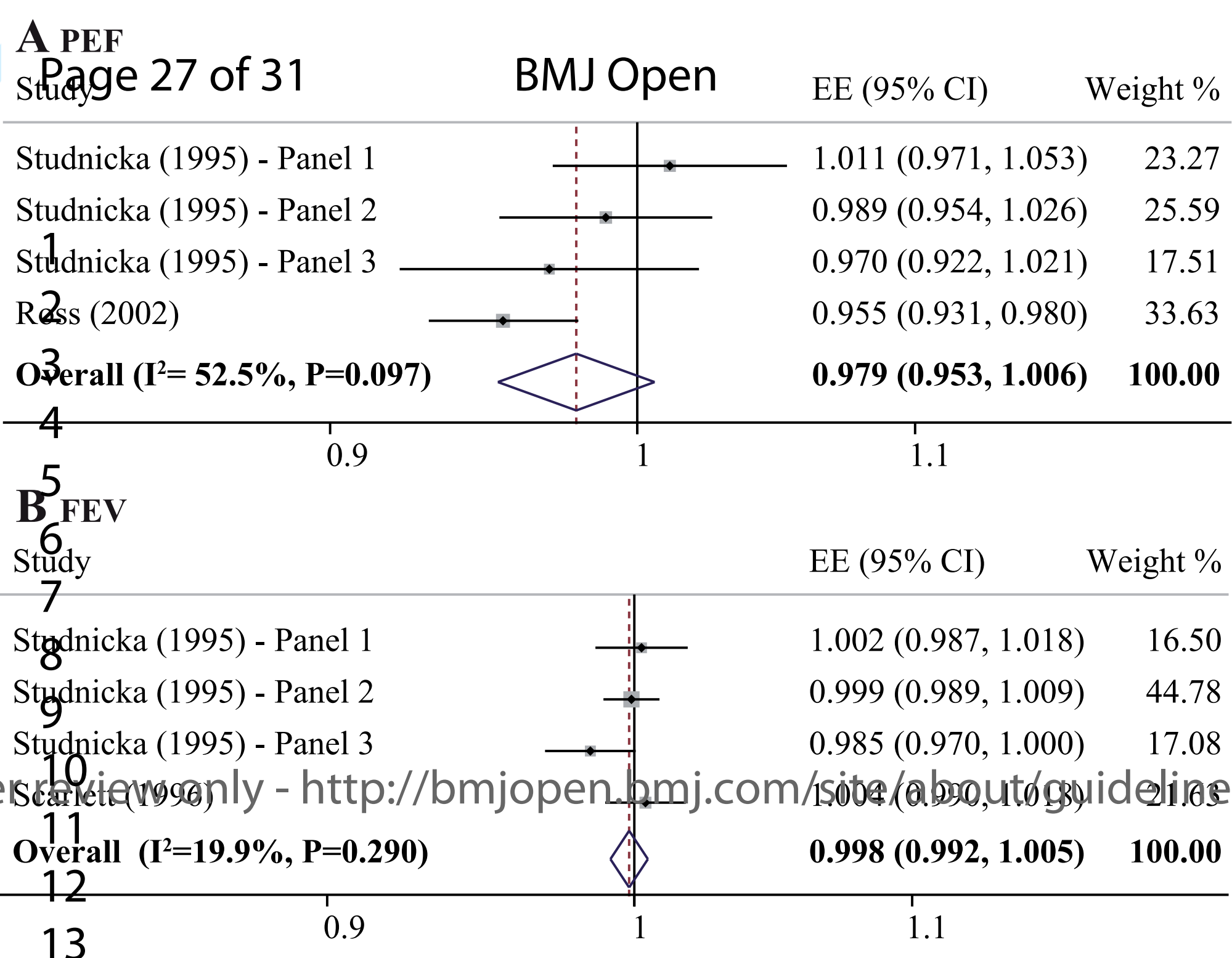

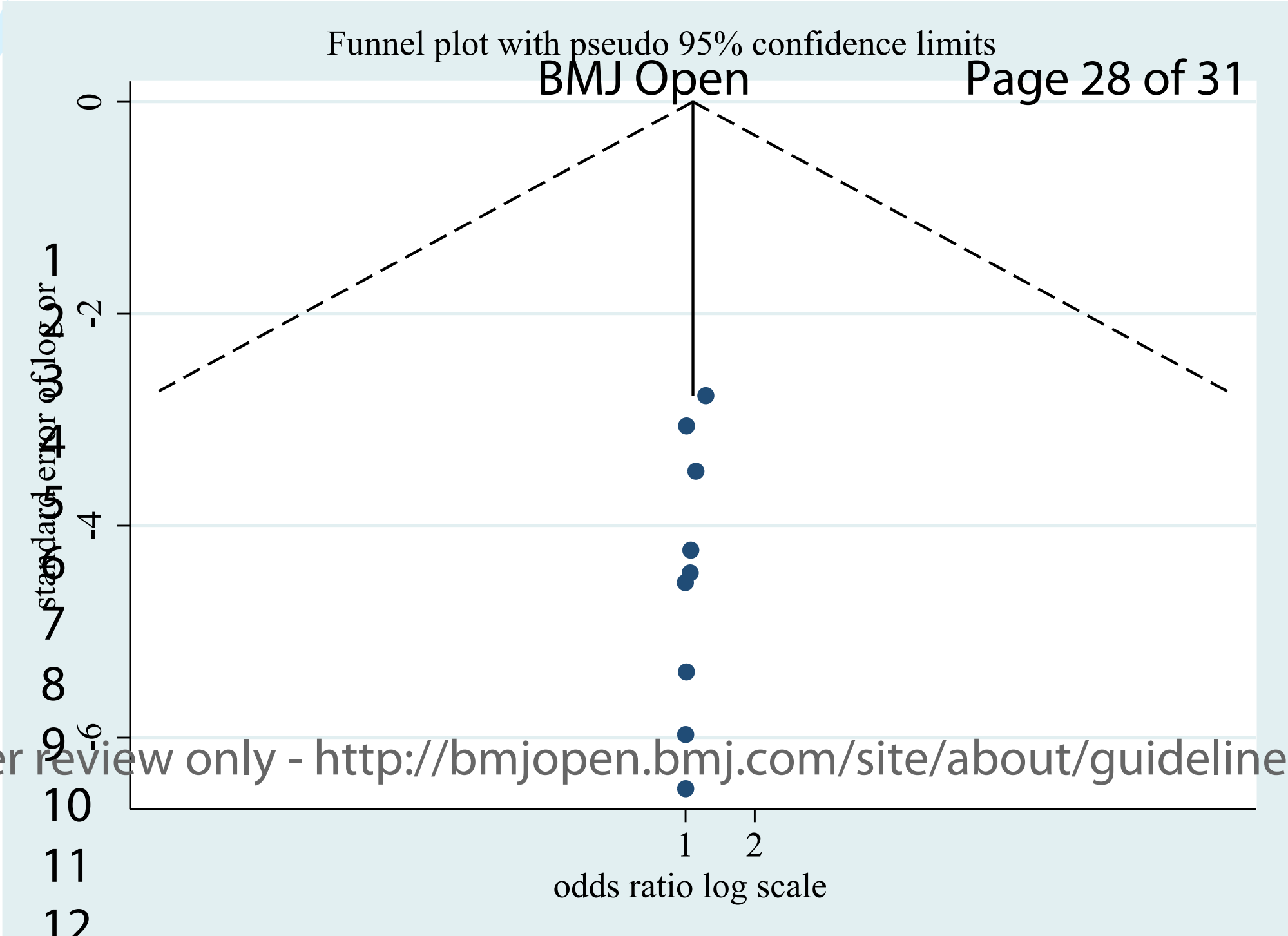

PRISMA 2009 Checklist

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.	2
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
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.	4
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	9, FIG1
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.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	study protocol
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.	14
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
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.	9

PRISMA 2009 Checklist

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).	14
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.	10
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.	Table 1
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).	Table 1
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.	FIG2-FIG3, Suppl Fig1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	FIG2-FIG3, Suppl Fig1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
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).	14
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).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
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.	18

PRISMA 2009 Checklist

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BMJ Open

Short-term exposure to pollen and the risk of allergic and asthmatic manifestations: A systematic review and meta-analysis

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Short-term exposure to pollen and the risk of allergic and asthmatic manifestations: A systematic review and meta-analysis

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ABSTRACT

Background Several studies have assessed effects of short-term exposure to pollen on asthmatic and allergic manifestations. The evidence is inconclusive, and no meta-analysis has been published.

Objective To synthesize the evidence on the relations between short-term pollen exposure and the risk of allergic and asthmatic manifestations.

Methods We performed a systematic literature search of PubMed and Scopus databases up to the end of August 2018. In addition, we reviewed the reference lists of relevant articles. Two authors independently evaluated the eligible articles and extracted relevant information in a structured form. We calculated summary effect estimates (EE) based on the study-specific odds ratios and regression coefficients (β) by applying both fixed- and random-effects models.

Results 26 studies met the *a priori* eligibility criteria, and 12 of them provided sufficient information for the meta-analysis. The summary EE related to 10 grains per m^3 increase in pollen exposure showed an 1% increase (EE=1.01 95% CI 1.00 to 1.02) in the risk of lower respiratory symptoms and a 2% increase (EE=1.02 95% CI 1.01 to 1.03) in the risk of any allergic or asthmatic symptom. Correspondingly, the risk of upper respiratory symptoms and ocular symptoms increased 7% (EE=1.07 95% CI 1.04 to 1.09) and 11% (EE= 1.11 95% CI 1.05 to 1.17), respectively, in relation to such pollen exposure. Short-term exposure to pollen did not show any significant effect on daily lung function levels.

Conclusion: Our results provide new evidence that short-term pollen exposure significantly increases the risks of allergic and asthmatic symptoms.

Strengths and limitations of this study

- Identification of individual studies based on a clearly defined and extensive search strategy based on a priori set inclusion and exclusion criteria.
- Also, secondary references were included
- The study-specific effect estimates were converted into comparable effect estimates for exposure corresponding to 10 pollen grains increase per cubic meter**.**
- Publication bias was assessed by visual inspection of the funnel plots and by applying Begg's and Egger's tests.
- The number of studies available for the sub-analyses investigating effects on various outcomes was quite low.

Keywords

Allergy; asthma; panel study; pollen exposure; systematic review; meta-analysis

INTRODUCTION

Allergy and asthma are common diseases and consequently, of public health importance globally. Approximately 500 million people suffer from allergic rhinitis worldwide and more than 300 million people have asthma.[1-3] The prevalence of rhinitis and/or rhinoconjunctivitis varies globally between 1% and 45%[4] and that of asthma between 1% and 21%.[5] In Western Europe, the prevalence of allergic rhinitis and/or rhinoconjunctivitis ranges from 17% to 29%[6] and the prevalence of asthma from 6% to 18%.[7] Respectively, the prevalence of rhinitis and/or rhinoconjunctivitis and asthma are 12–30%[8] and 5-10% in the U.S.[9]

The prevalence of physician-diagnosed pollen-induced allergic rhinitis was 18.5% among people living in northern China.[10] The majority of individuals suffering from allergic rhinitis experience seasonal symptoms when exposed to pollen.[11] Correspondingly, exposure to pollen grains increases the risk of asthma exacerbations among asthmatic persons.[12] There are no universally accepted, clinically meaningful threshold levels for pollen exposure. In previous studies, threshold levels have varied between 30 and 60 pollen grains per cubic meter of air.[13,14] However, exposures to relatively low levels of pollen (6-9 grains/m^3) have been associated with asthma symptoms among those who already have this disease.[15] Pollen allergy has been found in 80–90% of children suffering from asthma and in 40–50% of adult-onset asthmatics.[16]

Several panel studies have suggested an association between short-term exposure to pollen and asthmatic/allergic manifestations, although the magnitude and statistical significance of such estimated relations have varied.[17-21] Lung function levels have not been found to clearly associate with pollen exposure.[22-26] However, the amount of exhaled nitric oxide (NO)[22,27] and asthma and/or allergy medication use[18,24] seem to increase during pollen season. Caillaud et al.[28] reviewed qualitatively three panel studies that provided some evidence on a relation between daily counts of atmospheric pollen and occurrence of health outcomes.

The panel studies on pollen exposure and manifestations of asthma or allergy have provided somewhat conflicting results.[23,29] To our knowledge there are no previous systematic reviews with meta-analysis that have assessed the effects of short-term pollen exposure on the risk of allergic and asthmatic symptoms and lung function. Therefore, we conducted a systematic review and meta-analysis to summarize the existing evidence on the relations between short-term exposure to pollen and the occurrence of various asthmatic and allergic symptoms and/or lung function manifestations.

METHODS

This systematic review and meta-analysis is based on a review protocol accessible online (http://www.oulu.fi/cerh/node/50459).

Search strategy and eligibility criteria

We performed a systematic literature search of PubMed and Scopus databases up to the end of August 2018, as shown in figure 1. In the first phase, we used the search terms “panel study” and “pollen”. In order to have a more extensive data search, we included the terms “pollen exposure”, “asthma”, “cohort study”, “longitudinal study”, “follow-up study”, “case-control study” and “cross-sectional study” in the second search. All languages were included in the search.

Studies that met the following *a priori* eligibility criteria were included in this systematic review: the study (1) was an original study; (2) was a panel study where a group of people were followed longitudinally over a certain time period; (3) included asthmatic or allergic symptoms or measurements of lung function as the outcome; (4) included a study population of children or adults or both; and (5) reported on relations between daily mean airborne pollen exposure and manifestations of asthma and/or allergies.

Articles that were obviously irrelevant were excluded applying title screening. Articles that did not meet our *a priori* inclusion criteria were excluded by reading the abstract or full text.

Outcome and exposure definitions

The outcome of interest was occurrence of asthma and/or allergy manifestations. The definitions of asthma and allergy manifestations included self- or parent-reported symptoms (lower and upper respiratory tract symptoms, ocular symptoms, skin symptoms and/or symptom scores), lung function measurements (Peak expiratory flow, PEF, Forced expiratory volume, FEV, Forced vital capacity, FVC, Exhaled nitric oxide, NO), and use of asthma and/or allergy medications. The exposure of interest was exposure to pollen, expressed as the amount of pollen grains per cubic meter of air sampled (grains/m^3). The eligible definition of exposure included exposure to mean daily total airborne pollen or exposure to mean daily airborne pollen of distinct types (including birch, grass, ragweed, mugwort, olive, elm and/or hazel/alder pollen). All the available studies assessed the associations between pollen concentrations and symptoms during the same day, i.e. the duration of short-term exposure was here one day.

Data extraction and quality assessment

Eligible studies were examined and their relevant characteristics recorded in a standardized data extraction form independently by two authors (M.A.K. and D.R.Y.). Any disagreements were discussed together with additional two authors at the end of the data extraction process (T.T.H. and J.J.K.J.) until a consensus was achieved. Table 1 displays the main characteristics of the eligible studies. The study quality was assessed applying the Newcastle-Ottawa Scale (NOS) with the maximum score of 9.

In one study, the occurrence of asthmatic and allergic symptoms in relation to pollen exposure was investigated by recruiting a group of study subjects in two consecutive years.[17] There was some overlap among the study subjects, so that seven individuals (23% of participants) were included in both of these study groups. These two groups provided independent effect estimates (EE) for our meta-analysis. In another study, subjects were recruited in three distinct but successive periods of time within the pollen season.[26] These three groups also provided three independent effect estimates for the meta-analyses. The protocol was conducted according to PRISMA guidelines.[30]

Statistical methods

In the meta-analysis, we calculated summary effect estimates (EEs) from the study-specific odds ratios (OR) or regression coefficients (β) by using fixed- and random-effects models. When available, we preferred the adjusted EEs to the crude estimates. The summary EE from the fixed-effects model is presented when the study-specific EEs were homogenous, whereas the summary EE from the random-effects model is presented when moderate or substantial heterogeneity was observed between the study-specific estimates. Heterogeneity was evaluated using the Q- and I^2-statistics. I^2-statistic >50% indicates high, 25-50% moderate and <25% low heterogeneity. Publication bias was assessed by visual inspection of the funnel plots and application of Begg's and Egger's tests.[31,32] Individual studies included in the meta-analysis assessed their EEs in relation to different levels of pollen exposure. Because of this, individual EEs were converted into a common pollen concentration, i.e. as 10 pollen grains increase per cubic meter of air, before estimating the summary effect.

Because of only a small number of studies or inadequacy of data in the existing studies, we were not able to analyze potential relations between pollen exposure and skin symptoms, forced vital capacity (FVC), exhaled NO or asthma and/or allergy medications. The panel studies with

asthmatic and/or allergic populations examined usually asthma- and allergy-related symptoms as outcomes. In panel studies including general populations, the outcomes were lung function measurements. We used the "metan" command of the Stata 11 statistical program to analyze the fixed and random effects (StataCorp, College Station, Tex).

Patient and public Involvement

Due to nature of systematic review and meta-analysis, there was no patient and public involvement in this study.

RESULTS

Literature search

Reference lists of the articles that fulfilled the eligibility criteria were also reviewed and additional 14 articles fulfilling the criteria were included. Seven duplicate studies were excluded. A step-by-step approach of the literature search is presented in figure 1. Twenty-six studies met the *a priori* inclusion criteria and were included in the systematic review, while 12 studies of them were included in the quantitative meta-analysis. Table 1 displays the characteristics of the 26 eligible studies.[14,15,17,19-21,23-27,29,33-46]

Ten of the 26 studies specifically investigated the relation between total pollen exposure and asthmatic and/or allergic manifestations. Thirteen reported on grass (*Poaceae*), 5 on birch (*Betula*), 5 on ragweed (*Ambrosia*), 3 on hazel/alder (*Corylus/Alnus*), 3 on olive (*Olea*), 2 on elm (*Ulmus*), and 1 on mugwort (*Artemisia*) exposure and asthma and/or allergy manifestations.

185 **Table 1** Characteristics of the eligible studies included in the systematic review and meta-analysis (n = 26).

Reference (Region, country)	Study population	Study size (number of participants)	Follow-up (length and rate, %)	Outcomes	Method for pollen exposure assessment and the level of exposure expressed as mean daily pollen concentrations (pollen grains/m³ of air)	NOS quality score [a]
Caillaud et al., 2012[33] (France and Switzerland)	Adults with hay fever sensitized to grass pollen	106	17 weeks; 71.1%	Self-reported ocular, nasal and lower respiratory symptoms	Regional monitoring by a volumetric pollen trap; range 0-130	4/9
Caillaud et al., 2014a[17] (France and Switzerland)	Adults with seasonal rhinitis sensitized to ragweed pollen	16 in 2009, 22 in 2010, a total of 30	11 weeks; 96.8%	Self-reported daily SAR symptoms: ocular (itching and/or tear flow and/or conjunctival redness), nasal (sneezing and/or runny nose and/or blocked nose) and respiratory (cough and/or wheezing and/or asthma) symptoms, use of medication	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level; range 0-543	6/9
Caillaud et al., 2014c[34] (France and Switzerland)	Adults with seasonal rhinitis sensitized to birch pollen	61	8 weeks; 85.9%	Self-reported daily SAR symptoms: ocular (itching and/or tear flow and/or conjunctival redness), nasal (sneezing and/or runny nose and/or blocked nose) and respiratory (cough and/or wheezing and/or asthma) symptoms	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level; range 0-400-	5/9
Delfino et al., 1996[35] (US)	9-18 years old subjects with physician-diagnosed asthma	12	6 weeks; 80.0%	Asthma symptoms (wheeze, cough, sputum production, shortness of breath, chest tightness) and use of as-needed beta-agonist inhalers	Regional monitoring by a volumetric pollen trap located 10 meters above the ground level; range 4-115	4/9
Delfino et al., 1997[23] (US)	9-46 years old subjects with physician-diagnosed asthma sensitized to tree, grass or weed pollen	22	8 weeks; 91.7%	Self-reported daily asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness), each evening and morning three PEF blows and daily asthma medication use (i.e. beta-agonist inhaler)	Regional monitoring by a volumetric pollen trap located 4 meters above the ground level; range 11-611	5/9

Delfino et al., 2002[20] (US)	9-19 years old subjects with physician-diagnosed asthma	22	8 weeks; 88.0%	Self-reported daily asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness)	Regional monitoring by a volumetric pollen trap located 4 meters above the ground level; range 12-1257	5/9
DellaValle et al., 2012[15] (US)	4-12 years old children with physician-diagnosed asthma	430	24-26 weeks during the years 2000-2004; 92.3%	Self-reported daily asthma symptoms (wheeze, night symptoms, shortness of breath, chest tightness, and persistent cough), use of asthma medication	Personal pollen exposure assessment based on modeling; range 0-4187	5/9
Djukanović et al., 1996[36] (United Kingdom)	20-49 years old adults with atopic asthma	17	15 weeks; 94.1%	Self-reported asthma symptoms (nocturnal wheeze, nocturnal cough, morning chest tightness, day-time wheeze, subjective worsening of asthma due to exercise, cold air or fumes), self-reported morning and evening PEF values, FEV1	Not specified; range 0-318 (based on weekly pollen counts)	1/9
Dominguez-Vilches et al., 1995[37] (Spain)	Patients with pollen induced allergic rhinitis	70 in 1991 and 23 in 1992	12 weeks in 1991 and 12 weeks in 1992; 70.0% in 1991 and 46.0% in 1992	Daily conjunctival, nasal and respiratory symptoms	Regional monitoring by a volumetric pollen trap placed on the roof of a university building; ranges of pollen concentrations are not clearly stated	2/9
Feo Brito et al., 2007[38] (Spain)	Subjects with mild to moderate seasonal asthma sensitized to grass and/or olive pollen	137	6 weeks; 90.1%	Self-reported symptoms of asthma, self-reported morning and evening PEF values	Regional monitoring by a volumetric pollen trap; ranges 1-559 (grasses) and 0-596 (olives)	4/9
Feo Brito et al., 2010[14] (Spain)	10-51 years old patients with seasonal rhinitis and/or asthma, mono-sensitized to grass pollen	27	52 weeks; 100%	Self-reported symptoms / symptom and medication scores (including nasal obstruction, runny nose, sneezing/congestion, itching of the eyes, asthma attacks, use of medication)	Regional monitoring by a volumetric pollen trap located 5 meters above the ground level; range 0-585	2/9
Feo Brito et al., 2011[39] (Spain)	10-51 years old patients with seasonal rhinitis or asthma mono-sensitized to olive pollen	20	52 weeks; 100%	Self-reported symptoms (including conjunctival, nasal and respiratory symptoms)	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level; range 0-443	3/9

Grammer et al., 1990[40] (US)	Patients with history of ragweed rhinitis	29	10 weeks; 100%	Self-reported daily symptoms / symptom medication scores (nasal congestion, nasal discharge, sneezing, ocular pruritus, cough, use of medication)	Not specified; A rotating arm impactor and weekly pollen data were used; range 0-2100	2/9
Jantunen et al., 2012[41] (Finland)	8-70 years old persons with physician-diagnosed birch pollen allergy (rhinoconjunctivitis)	28 in 2009 and 33 in 2010	8 weeks; 95.3%	Self-reported symptoms (conjunctival symptoms [itchy, swollen, watery, or sore eyes], nasal symptoms [sneezing, runny, itchy, or blocked nose], other allergy symptoms), use of medication	Regional pollen monitoring by a volumetric pollen trap located 14 meters above the ground level; ranges 0-1970 (alders) and 0-6890 (birches)	3/9
Klabuschnigg et al., 1981[42] (Austria)	7-14 years old children with clinically-diagnosed asthma	40	6 weeks; 92.5%	Self-reported asthma symptoms, lung function (PEF, FEV1, FVC) measured every second day, use of medication	Regional pollen monitoring by a volumetric pollen trap located 12 meters above the ground level; ranges of pollen concentrations are not clearly stated	2/9
Krämer et al., 2005[43] (Germany)	9 years old children with diagnosed allergic eczema	39	26 weeks; 69.6%	Self-reported daily eczema symptoms: itching and the extent of skin lesions	Regional pollen monitoring by a volumetric pollen trap located 12 meters above the ground level; ranges 0-215 (hazel/alder), 0-1673 (birches), 0-184 (grasses) and 0-10 (mugworts)	5/9
Newhouse & Levetin, 2004[29] (US)	9-64 years old patients with physician-diagnosed asthma	24	8 weeks; 63.2%	Self-reported asthma symptoms, morning and evening PEF values	Regional pollen monitoring by a volumetric pollen trap located on the roof of a university building; ranges 1-498 (ragweeds), 0-167 (elms), 0-132 (grasses)	3/9
Ostro et al., 2001[21] (US)	8-13 years old children with physician-diagnosed asthma	138	13 weeks; 90.2%	Self-reported daily asthma symptoms (shortness of breath, cough, and wheeze)	Pollen monitoring by a Rotorod device (taking a sample for 30 seconds every 10 minutes); range 1-75	5/9
Petersen & Sandberg, 1981[44] (Denmark)	Patients suffering from diagnosed pollen allergy	78	36 weeks; 83.2%	Daily scoring of symptoms and use of medication; before, during and after pollen season	Regional pollen data; range 0-1600 (based on weekly pollen counts)	3/9

Roberts et al., 2004[27] (United Kingdom)	7-16 years old children with mild to moderate seasonal allergic asthma and rhinoconjunctivitis sensitized to grass pollen	44	10 weeks; 100%	Exhaled NO –measurements and FEV1	Regional pollen monitoring by a volumetric pollen trap; range 0-178	4/9
Roberts et al., 2005[19] (United Kingdom)	6-17 years old children with seasonal allergic rhinoconjunctivitis, asthma and/or eczema sensitized to grass pollen	84	12 weeks; 100%	Self-reported weekly pediatric allergic disease quality based on life questionnaire, symptoms (chest, nasal, ocular, cutaneous and other symptoms) and emotional problems	Regional pollen monitoring by a volumetric pollen trap; ranges of pollen concentrations are not clearly stated	3/9
Ross et al., 2002[24] (US)	5-49 years old subjects with asthma	40	26 weeks; 67.8%	Self-reported morning and evening PEF, symptom score, occurrence of asthma attacks and frequencies of asthma medication use	Local pollen monitoring by Rotorod devices located 2 meters above the ground level; range 0-1492	4/9
Scarlett et al., 1996[25] (United Kingdom)	7-11 years old children with and without asthma	154	6 weeks; 100%	Daily lung function measurements (FEV0.75, FVC, FEV0.75/FVC)	Regional pollen monitoring, pollen counts were derived from the local monitoring site; range 2-183	6/9
Schäppi et al., 1998[45] (Australia)	17-50 years old volunteers with moderate to severe hay fever sensitized to grass pollen	21	3 weeks; 75.0%	Nasal (blockage, discharge or itching) and eye symptom scores (itching, swelling or running)	Regional pollen monitoring by a volumetric pollen trap located 14 meters above the ground level; range 0-400	3/9
Studnicka et al., 1995[26] (Austria)	7 years old and older children with and without asthma	47 in panel 1, 45 in panel 2, 41 in panel 3	3 weeks; 88.7%	Daily lung function measurements (FEV1, FVC, PEF)	Regional pollen monitoring by a volumetric pollen trap located 10 meters above the ground level; ranges of pollen concentrations are not clearly stated	7/9
Taudorf & Moseholm, 1988[46] (Denmark)	16-47 years old pollinotic (hay fever) patients sensitized to birch pollen	15	16 weeks in 1983 and 16 weeks in 1984; 75.0%	Nose and eye symptom scores, use of medication	Regional pollen monitoring by a volumetric pollen trap; ranges of pollen concentrations are not clearly stated	3/9

SAR, Seasonal allergic rhinitis. PEF, Peak expiratory flow. FEV1, Forced expiratory volume in the first second. FVC, Forced vital capacity. NO, Nitric oxide. FEV0.75, Forced expiratory volume at 3/4 of a second. [a] For panel studies, the maximum score is 7/9.

Characteristics of included studies

Characteristics of the 26 eligible studies are shown in table 1. In 13 studies subjects were asthmatics, in 11 studies subjects were sensitized to pollen (i.e. positive Skin prick test, SPT or Allergen-Specific Immunoglobulin E Test, IgE test) and in 8 studies subjects had hay fever (i.e. allergic rhinitis, pollen allergy, pollinosis). One study investigated subjects with eczema. In 2 studies, subjects with and without asthma were analyzed together without taking into account the prior disease status. Ten studies investigated children, four adults, and 9 both children and adults. In 3 studies, authors did not specify the age of the subjects. Six studies applied logistic regression, 9 studies linear regression, 2 studies Poisson regression, and 2 studies time series regression for the analyses.

The studies defined the allergic and/or asthmatic manifestations in different ways. Sensitization based on SPT or IgE analysis was the most common criterion used for the definition of allergy. Current presence of asthma, previous history of asthmatic symptoms, and/or physician (i.e. clinical) diagnosis were frequently applied as inclusion criteria in the reviewed studies. We systematically categorized outcomes into any symptom, lower respiratory tract symptoms, upper respiratory tract symptoms, ocular symptoms, skin symptoms, symptom scores, lung function measurements (PEF, FEV, FVC and exhaled NO), and use of asthma and/or allergy medications.

Pollen monitoring used for exposure assessment was based on regional sampling in 21 studies, on local sampling in 2 studies, and on personal exposure modelling in one study. In 2 studies, authors did not specify the type of pollen sampling. The height of the pollen sampler varied between 2-15 meters above the ground level. Thirteen of the studies did not give the height information for pollen sampler. Twenty-five studies expressed the mean pollen concentration as pollen grains per cubic meter of air per 24 h. In 3 studies, daily pollen counts were converted into weekly pollen sums, and consequently, the relations between weekly pollen counts and weekly symptoms were presented. In 2 studies, hourly/bihourly pollen counts were presented in addition to daily counts. Main outcomes for the studies that were not included into the meta-analysis are presented in table 2.

Risk of bias across the studies

In the majority of studies, exposure assessment was based on single stationary regional sampler located on the roof level (Table 1). Although it has been suggested that different types of pollen sampling can be used to get a rough estimate of pollen exposure,[47] many of the approaches may

not have captured the daily individual exposures at the breathing level in satisfactory detail. In 2013, we monitored grass pollen concentrations at 16 sites in the cities of Helsinki and Espoo during the peak pollen season by using rotorod-type samplers at the breathing height.[48] We identified substantial variation in exposure concentrations at breathing height according to urbanity of the site and time of the day within areas covered by our roof level monitoring stations. Most valid estimates of pollen exposure could be obtained by using personal pollen sampling. There were also other potential sources of heterogeneity in the exposure measured by these studies linked to variation in weather/climatic conditions, type and period of monitoring, nature of pollen season, daily activities/time spent outdoors by the study subjects, variation in the height of monitoring and pollen types monitored.

In all studies, selection of study subjects was based on predefined and justified eligibility criteria. Due to the study design that included inference based on within-individual variation of health outcome, the risk of selection bias is rather small (Supplementary table 1). Also the relatively high follow-up rates (varying from 46.0 to 100%) across studies reduce the risk of selection bias. However, there was substantial diversity in the type and measurement of outcomes, which resulted in difficulties in forming the major outcome groups for the meta-analyses. Status of asthma and/or allergic diseases varied from mild to moderate or from moderate to severe.

The studies could be divided roughly into two major groups on the basis of what kind of adjustment was applied for confounding. The first group of studies provided only descriptive results without any or only with very basic statistical analyses. The second group performed extensive statistical analyses, including controlling for a few or several confounders. Due to study design where individuals act as their own controls on days with no (major) exposure, individual characteristics were not potential confounders. In contrast, environmental factors, such as temperature and air pollution can be potential confounders. A significant number of the studies adjusted for temperature (13) and other meteorological parameters (12), as well as for air pollution (4). Other potential sources of heterogeneity include variation in the studied time lags between the exposure and the outcome (varying from 0 to 14 days), potential differences in allergen content of pollen of interest, and different characteristics and size of the study populations (varying from 12 to 430 subjects). In 24 studies, the study focused on asthmatics and/or subjects with allergies, whereas two studies included both healthy and non-healthy subjects.[25,26]

252 **Table 2** The main findings in articles not included into the meta-analysis (n = 14)

Reference	Main findings
Delfino et al. 1996[35]	Pollen exposure was not associated with either asthma symptom scores or as-needed beta-agonist inhaler use.
Delfino et al. 1997[23]	Pollen exposure was not associated with asthma symptom severity, morning or evening peak expiratory flow rate (PEFR), or β-agonist inhaler use.
Djukanovic et al. 1996[36]	The peak pollen season was associated with a significant increase in asthma symptoms (P<0.05).
Dominguez-Vilches et al. 1995[37]	A greater seasonal pollen intensity was associated with a higher occurrence of daily symptoms.
Feo Brito et al. 2010[14]	A significant positive association was found between the presence of symptoms and pollen grains (r=0.62; P<0.001).
Grammer et al. 1990[40]	The peak pollen periods were associated with a twofold increase in symptom-medication scores among a subset of patients.
Jantunen et al. 2012[41]	The number of subjects with allergy symptoms increased significantly with the daily pollen concentrations (r= 0.35-0.36, P<0.01).
Klabuschnigg et al. 1981[42]	Two hourly pollen counts or daily pollen counts were not associated with the frequency of asthma attacks. In contrast, consecutive 10-day mean symptom scores (assessing asthma attacks) associated with the total pollen counts. No associations were found between pollen exposure and lung function measurements (including PEF, FEV1 and FVC).
Krämer et al. 2005[43]	Pollen exposure had no significant effect on skin symptom severity among children with winter type eczema (relative change in grass pollen exposure 0.98-1.00; 95% confidence limits 0.81-1.18). In contrast, grass-pollen exposure showed a significant effect on the severity of skin symptoms among children with summer type eczema (relative change in grass pollen exposure 1.16-1.19; 95% confidence limits 1.02-1.39).
Newhouse & Levetin 2004[29]	*Ambrosia* pollen concentrations were significantly correlated with composite asthma scores (r=0.263, P<0.05), rhinitis scores (r=0.513, P<0.001) and several individual symptoms. *Chenopodiaceae/Amaranthaceae* pollen concentrations showed significant associations with composite asthma scores (r=0.256, P<0.05). *Ulmus* (r=0.367, P<0.01), *Chenopodiaceae/Amaranthaceae* (r=0.458, P<0.001) and *Poaceae* (r=0.326, P<0.05) pollen concentrations showed significant correlations with composite rhinitis scores. Pollen concentrations significantly influenced morning (but not evening) PEF values measured in the following day (r=-0.261–-0.364, P<0.05-0.01).
Petersen & Sandberg 1981[44]	There was a positive association between the appearance of pollen grains in the air and the symptom-medication score.
Roberts et al. 2004[27]	Fractional exhaled nitric oxide (FENO) levels increased significantly during the grass pollen season (median change 2.9 ppb, 95% confidence interval 1.5-5.4). There were no apparent associations between pollen counts and other lung function measurements.
Schäppi et al. 1998[45]	The grass pollen counts associated significantly with the average nasal (r=0.637, P<0.001) and eye symptom (r=0.586, P<0.005) scores.
Taudorf & Moseholm 1988[46]	Occurrence of symptoms and daily medication increased during the season with a constant pollen load.

PEFR, Peak expiratory flow rate = PEF, Peak expiratory flow. FEV1, Forced expiratory volume in the first second. FVC, Forced vital capacity. FENO, Fractional exhaled nitric oxide.

Relations between pollen exposure and asthma- and allergy-related symptoms among allergic / asthmatic subjects

A total of 12 studies were included in the meta-analyses. In 8 studies [15,17,20,21,33,34,38,39] the effect estimate was based on odds ratio and in 4 studies [19, 24-26] on a regression coefficient which was or was converted to a change per 10 grains per m3 of air. The summary EE for the relation between pollen exposure and any symptoms was statistically significantly increased at 1.02 (95% confidence interval (CI): 1.01-1.03) from the random effects model (figures 2, 3 and Supplementary File, figure 1). The study-specific estimates showed high heterogeneity. This estimate was based on 6 studies (providing 9 EEs). The funnel plot and the results from the Begg's (z= -1.25; P value= 0.211) and Egger's tests (Bias coefficient .0457453; 95% CI -.0048418-.0963324; P value= 0.070) on short-term pollen exposure and any symptoms provided no indication of publication bias (Supplementary File, figure 2).

A total of 6 studies (9 EEs) provided study-specific EEs for pollen exposure and lower respiratory symptoms. The summary EE from the random effects model was 1.01 (95% CI: 1.00-1.02). The study-specific estimates showed high heterogeneity.

The summary EE for pollen exposure and upper respiratory symptoms, based on 3 studies (4 EEs), was significantly increased at 1.07 (95% CI: 1.04-1.09) from the random effects model. There was moderate heterogeneity between the study-specific estimates.

The relation between pollen exposure and ocular symptoms was reported in 3 studies (4 EEs). The summary EE from the random-effects model was 1.11 (95% CI: 1.05-1.17). The study-specific estimates showed high heterogeneity.

The relation between pollen exposure and symptom scores was based on 4 studies applying linear regression modelling (giving regression coefficients). The summary EE was significantly elevated (1.003; 95% CI: 1.001-1.004). The study-specific estimates showed high heterogeneity.

Relations between pollen exposure and lung function among general population

The relation between pollen exposure and peak expiratory flow (PEF) was assessed in 2 studies (giving 4 EEs), resulting in a summary EE of 0.98 for 10 pollen grains increase per cubic meter of air (95% CI: 0.95-1.01) in the random effects model based on linear regression modelling. The study-specific estimates showed large heterogeneity.

Two studies estimated the relation between pollen exposure and forced expiratory volume (FEV). One study used forced expiratory volume in the first second, FEV1 as the outcome and the

other forced expiratory volume at 3/4 of a second, FEV0.75. Different FEV estimates were combined in the analysis. Meta-analysis gave the summary EE of 1.00 for 10 pollen grains increase per cubic meter of air (95% CI: 0.99-1.01) in the fixed effects model based on linear regression modelling. There was little heterogeneity between the studies.

Relations between pollen exposure and use of asthma and/or allergy medication

In 2 studies, the use of asthma and/or allergy medication was combined with information on asthma and/or allergy symptoms (in forming symptom-medication score). In 5 studies that investigated the relation between pollen exposure and the use of medication, pollen exposure increased the use of medication. In contrast, 3 studies did not show any association between pollen exposure and use of allergy/asthma medication.

DISCUSSION

Main findings

This systematic review and meta-analysis provides new evidence that short-term pollen exposure significantly increases the risk of asthmatic and allergic symptoms. The summary EE for a 10 grains /m³ increase in pollen exposure showed on average a 2% increase in the risk of any asthmatic or allergic symptom. The corresponding increases in the risk of upper respiratory symptoms and ocular symptoms were 7% and 11%, respectively. All summary EEs were statistically significant. This meta-analysis did not show any statistically significant relations between pollen exposure and lung function measurements. The summary EE for 10 grains /m³ increase in pollen exposure indicated a 2% decrease in PEF values, while no change was detected in relation to FEV values.

Validity of results

The strengths of our study include identification of individual studies based on a clearly defined search strategy. In addition to the primary PubMed and Scopus database searches, we also used secondary references that were cited by the articles and reviews identified in the primary search to achieve as complete set of studies as possible. Two reviewers checked independently the eligibility of the studies according to *a priori* set inclusion and exclusion criteria and identified the most appropriate effect estimate.

The present systematic review and meta-analysis focused on panel studies mainly with relatively brief follow-up periods. The follow-up periods in the studies varied from 3 weeks to 52 weeks.

However, pollen related asthmatic and allergic symptoms are usually induced after only a few hours or days of exposure.[49,50] Thus, variable and/or relatively short follow-up periods are probably not problematic when assessing the relationship between pollen exposure and outcomes of interest in this study.

Our statistical analyses included 12 studies, because only 12 studies out of a total of 26 presented the exact mean or interquartile range (IQR) values of pollen grains per cubic meter. Information on the mean and IQR values were needed to convert the study-specific effect estimates into common effect estimates for exposure corresponding to 10 pollen grains increase per cubic meter. The aim of this transformation was to make studies containing different pollen concentration values comparable. Although the total number of panel studies was reasonable, the numbers of studies available for the sub-analyses investigating various outcomes were quite low. Therefore, the conclusions based on results of the sub-analyses should be interpreted with caution.

"Any exposure" was applied in the analyses due to the heterogeneity of exposure assessment. Total daily mean pollen concentration values were preferred, but when such were not available, information on the mean daily airborne concentration of distinct pollen types (birch, grass, ragweed, mugwort, olive, elm and/or hazel/alder) was used as the measure of exposure in the analyses. This should not cause any problem, because the pollen seasons of different pollen types commonly overlap, so individuals can react to exposure to several pollen types. Consequently, the reaction to pollen exposure is likely to be a combined reaction to a sum of various pollen types.[51] It is not always possible to define exactly which specific pollen type caused the symptoms. Therefore, the exact separation of distinct pollen types in health effect studies is somewhat artificial and thus, unnecessary.

Synthesis with previous knowledge

Our results indicated that short-term pollen exposure increases the risk of any respiratory or other allergic symptom, lower and upper respiratory symptoms and ocular symptoms among asthmatic and/or allergic subjects. Depending on the plant species, concentrations of pollen grains in the breathing air can vary between zero and thousands. Eventually, increases in pollen exposure can have a considerable effect on the well-being of allergic/asthmatic people. In a recent systematic review and meta-analysis of 14 studies,[52] the mean number of emergency department attendance among children and adolescents with asthma increased 1.88% (95% CI = 0.94%-2.82%)

in relation to a 10 grass pollen grain increase per cubic meter. These results are in line with a recent ecologic study from Japan, where a positive association was observed between cedar and cypress pollen counts and the prevalence of symptoms of allergic rhinoconjunctivitis and asthma in school children.[53] Similarly, our results are also in line with the register-based time-series analysis among Belgian population, where a positive association was observed between pollen exposure and allergy medication sales.[54] A time-stratified case-crossover study showed a positive association between tree and weed pollen exposure and emergency department visits due to asthma exacerbations among 13-17 year- old U.S. asthmatics.[55]

According to our results, the effect of pollen exposure was stronger in upper respiratory tract than in lower respiratory tract. This could be explained by the large size of the pollen grain. Generally, the size of pollen varies between 20 and 100 micrometers in diameter.[56] Therefore, particles of pollen grain size do not penetrate well into the lower respiratory tract.[57] Pollen grains are likely to adhere and release their allergenic content already in the upper respiratory tract. As a consequence of this, the majority of the direct allergic inflammatory effects caused by pollen may be experienced in the region of the upper respiratory tract.

Our systematic review did not detect any major effect of pollen exposure on lung function. The results may be explained by the fact that the study population for lung function effects included healthy people in addition to asthmatic and allergic subjects. If these studies would only include asthmatic and/or allergic persons, more pronounced effects might be detected. In the Swedish cohort-based study, exposure to grass pollen during the preceding day was associated with a reduced forced expiratory volume in relation to an increase in three pollen counts (/m^3) among the 8-year-old children.[58] This association was more pronounced among children who were sensitized to pollen allergens. In line with those results, another study of Swedish adults showed that pollen exposure resulted in significantly increased concentration of nitric oxide in exhaled air, which suggested increased airway inflammation among these asthmatics compared to the healthy controls.[59]

Conclusions

This systematic review and meta-analysis provides new evidence that short-term exposure to pollen grains increases any respiratory symptoms, as well as specifically upper respiratory and ocular symptoms among asthmatic and allergic subjects. It is important that clinicians take into account, when working with allergic and asthma patients that even relatively short-term exposure

to pollen can induce for them symptoms of allergies and asthma. Clinicians should advice allergic and asthmatic subjects to avoid spending much time outdoors during the (main) pollen periods, and to use adequate allergy and asthma medications when such exposures cannot be avoided. Future studies should use personal exposure assessment and it would be important to find out how the variation in pollen exposure affects the health of allergic and asthmatic subjects.

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Contributors

JJ and TH conceived the study; MK, DRY and TH reviewed the articles, NS and MK analyzed the data under supervision of JJ; MK, TH, MJ, and JJ wrote the manuscript, all authors contributed to the intellectual content and approved the final version

Data sharing statement

No additional data available.

Patient consent

Not required

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Competing Interests None declared.

Legends to the figures

Figure 1 Flow diagram showing searches and study selection.

Figure 2 Forest plot for the relation between pollen exposure and any symptom (Weights are from random effects analysis).

Figure 3 A Forest plot for the relation between pollen exposure and lower respiratory symptoms (Weights are from random effects analysis). **B.** Forest plot for the relation between pollen exposure and upper respiratory symptoms (Weights are from random effects analysis). **C.** Forest plot for the relation between pollen exposure and ocular symptoms (Weights are from random effects analysis). **D.** Forest plot for the relation between pollen exposure and symptom score (Weights are from random effects analysis).

Supplementary File, Figure 1 A. Forest plot for the relation between pollen exposure and peak expiratory flow (PEF; Weights are from random effects analysis). **B.** Forest plot for the relation between pollen exposure and forced expiratory volume (FEV; Weights are from fixed effects analysis).

Supplementary File, Figure 2 Funnel plot with pseudo 95% confidence limits for the relation between short-term pollen exposure and any symptom.

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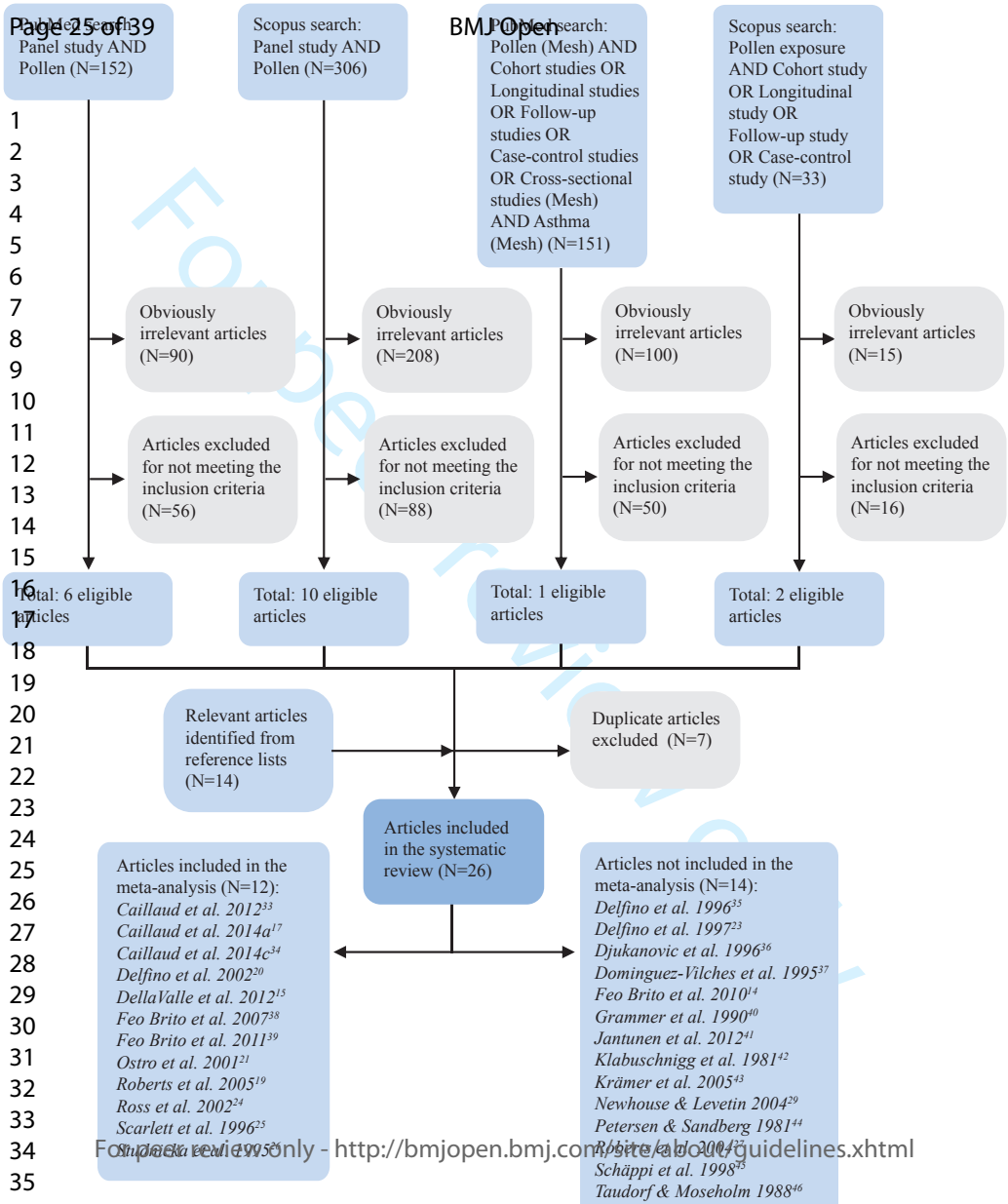
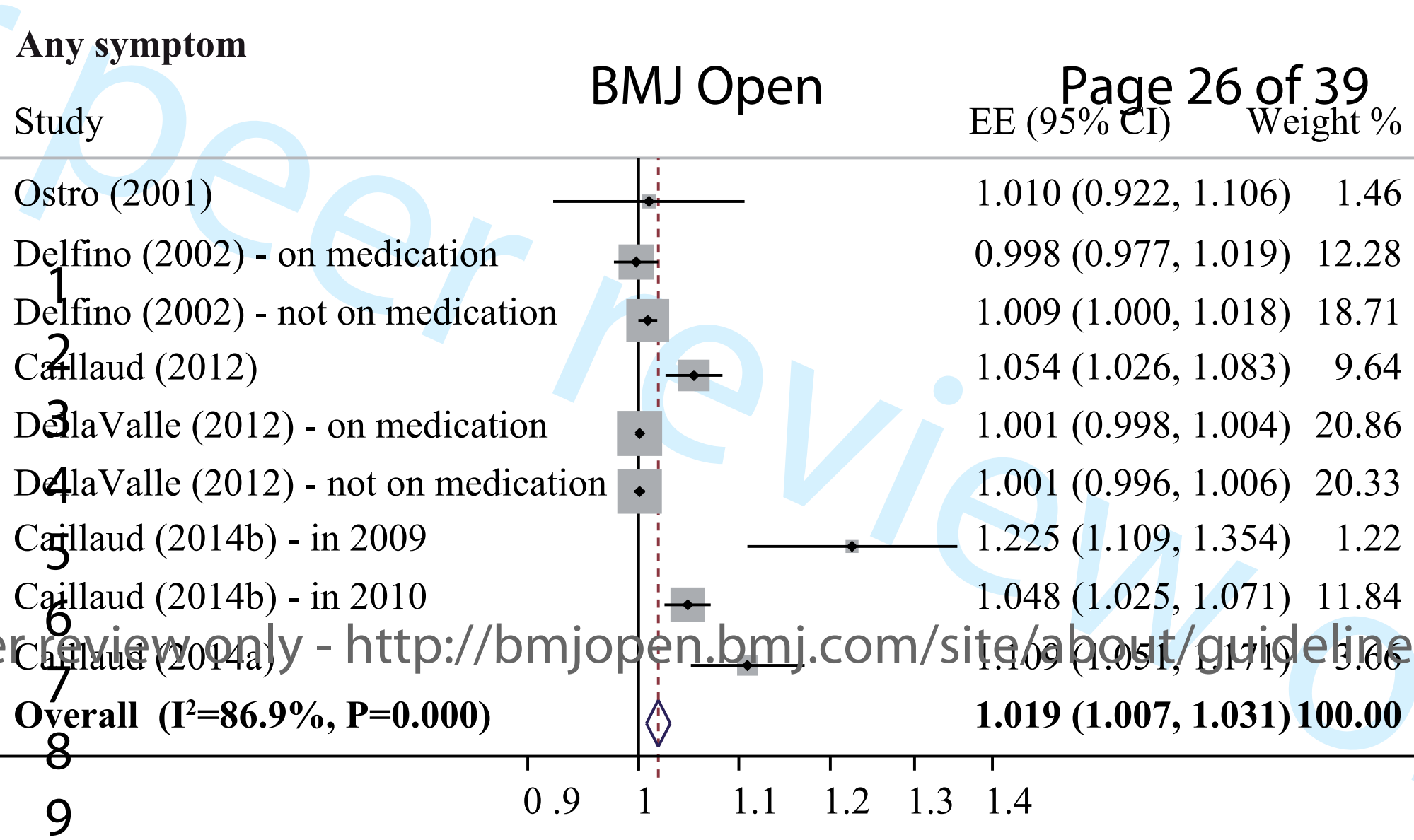
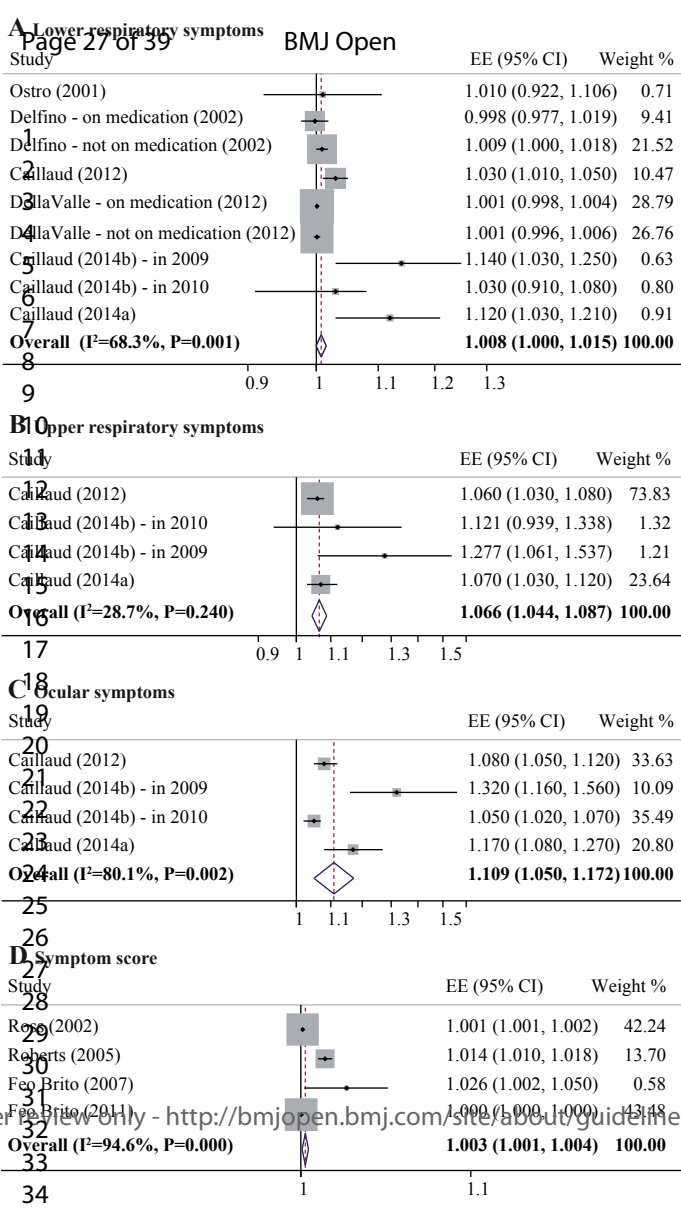


Any symptom





Supplementary Table 1. Risk of bias tables.

Caillaud et al. 2012		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 71.1%; "43 volunteers were excluded, either because they failed to provide the requested daily health records (n=24) or because they did not fulfill the inclusion criteria (n=19)"
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Caillaud et al. 2014a		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 96.8%; "One participant was excluded because he failed to provide the requested daily health records during the month of August and additionally he experienced hay fever before the pollen season."
Selective reporting (reporting bias)	Low risk	Protocol was not available but it was clear that all pre-specified and expected outcomes of interest were reported
Other bias	Low risk	There was some overlap among the study subjects, so that seven individuals (23% of participants) were included study groups in both years. "Of these 31 patients, 7 participated in the 2 years." Polysensitized patients were involved.

		"It would have been preferable to include patients who were strictly monosensitized to A artemisiifolia in order to obtain more accurate results regarding the relationship between pollen exposure and symptoms [31]. However, due to the rarity of monosensitized patients, the study had to include polysensitized patients."
Caillaud et al. 2014c		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 85.9%; "Ten participants were excluded either because they failed to provide the requested daily health records (n=8) or because they did not qualify for inclusion (N=2)." Partly missing symptom data. "Missing symptom score data occurred on 285 person-days (8.6% of the total expected follow-up of 3,311 person-days) because subjects had left the study area all day…"
Selective reporting (reporting bias)	Low risk	Protocol was not available but it was clear that all pre-specified and expected outcomes of interest were reported
Other bias	Low risk	None were identified

Delfino et al. 2002		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design

Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 88.0%. “A 10-year-old boy and a 10-year-old girl dropped out after the second week of study and are not retained for analysis. One white 10-year-old male was asymptomatic throughout the panel period and therefore contributed no information to the repeated-measures analysis.” Partly missing symptom data. “Missing symptom score data occurred on 51 person-days (3.8% of total expected follow-up of 1,328 person-days) because subjects had left the study area all day, and on 29 person-days because of noncompliance with diary completion (2.2%), …”
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Della Valle et al. 2012		
Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 92.3%; “We restricted the analysis to 430 subjects who completed an exit interview and who lived primarily within the northeastern U.S. throughout follow-up, …”
Selective reporting (reporting bias)	Low risk	Protocol was not available but it was clear that all pre-specified and expected outcomes of interest were reported.
Other bias	Low risk	None were identified

Feo Brito et al. 2007		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 90.1%. "… seven patients withdrew in Puertollano and eight patients in Ciudad Real, leaving a final study population of 137 patients …"
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Feo Brito et al. 2011		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 100%
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Ostro et al. 2001		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design

Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 90.2%; "Five subjects who provided baseline data never provided any daily diary information. In addition, data from 10 subjects (representing 8.3% of the person-days) were excluded from the analysis because of evidence that the intake data or diary data were likely to have been inaccurate, or because the diaries were returned more than 2 weeks late." Partly feasible symptom data. "A total of 10,022 person-days of symptom data were reported, of which we used 9,126 in the analysis after the health data of questionable validity were excluded."
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

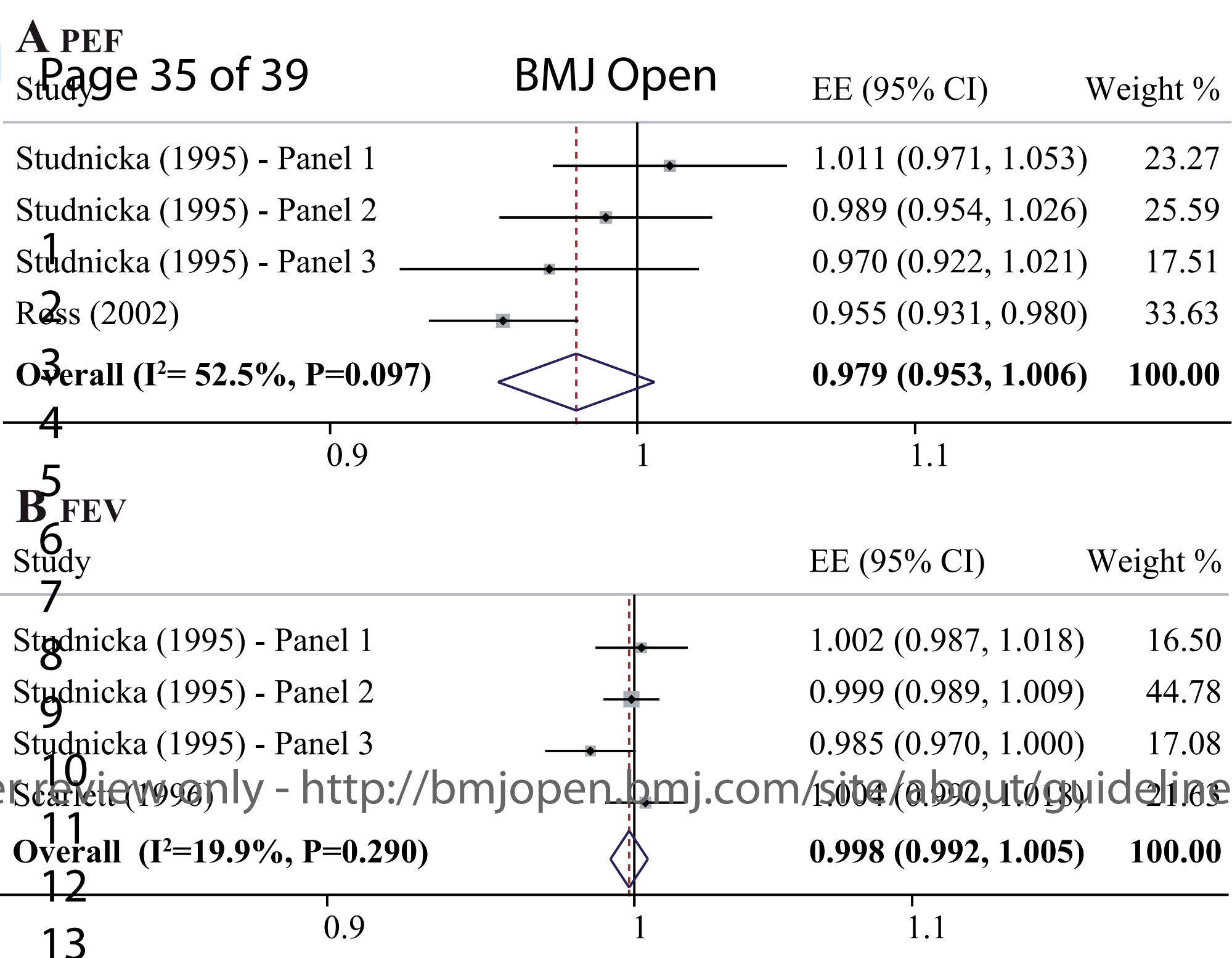
Roberts et al. 2005		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 100%
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

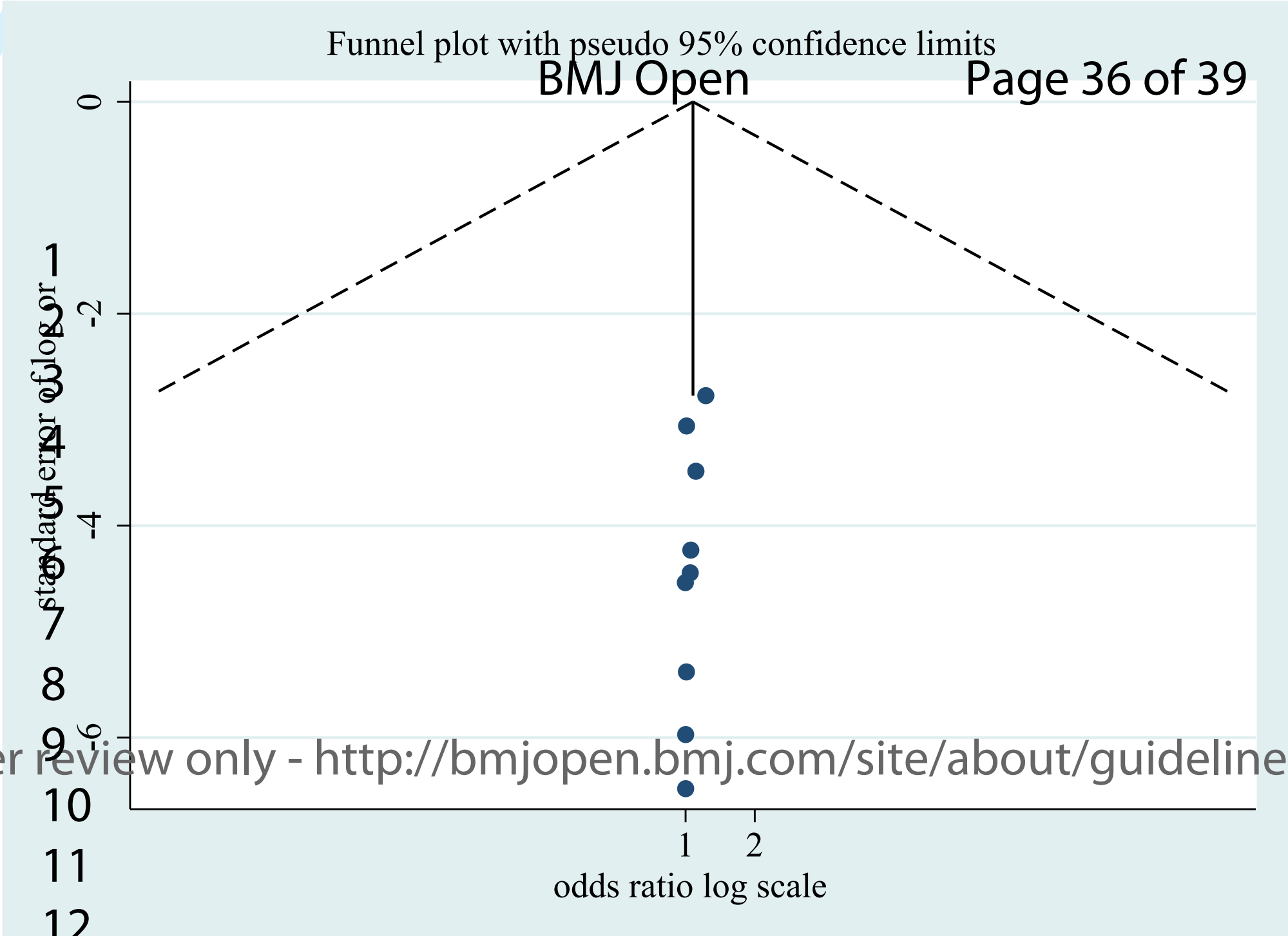
Ross et al. 2002		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 67.8%. "Two families withdrew early in the study period, and a number of participants either withdrew later in the study or failed to provide the requested daily health records … The 2 primary reasons stated for withdrawal from the study were a lack of time or interest in participating, or a move from the study area." Partly missing symptom data. "The last few days of data were excluded because of the small number of remaining participants."
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Scarlett et al. 1996		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk to high risk	Follow-up rate was 100%
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	High risk	Not feasible asthma medication data. "Children on medication for asthma were asked whether they had taken any medication that day. Unfortunately, the quality of these data were

		poor and so they were not used in the analysis. At worst this would bias the regression coefficients towards the null value."

Studnicka et al. 1995		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 88.7%; "For three, five, and seven children, respectively, permission was denied (for the 1st, 2nd, and 3rd panel). For Panel 3, two children were not able to perform reproducible spirometry."
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified





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.	2
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
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.	4
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	9, FIG1
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.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	study protocol
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.	14
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
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.	9

PRISMA 2009 Checklist

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).	14
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.	10
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.	Table 1
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).	Table 1
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.	FIG2-FIG3, Suppl Fig1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	FIG2-FIG3, Suppl Fig1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
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).	14
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).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
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.	18

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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Short-term exposure to pollen and the risk of allergic and asthmatic manifestations: A systematic review and meta-analysis

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Short-term exposure to pollen and the risk of allergic and asthmatic manifestations: A systematic review and meta-analysis

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ABSTRACT

Background Several studies have assessed effects of short-term exposure to pollen on allergic and asthmatic manifestations. The evidence is inconclusive, and no meta-analysis has been published.

Objective To synthesize the evidence on the relations between short-term pollen exposure and the risk of allergic and asthmatic manifestations.

Methods We performed a systematic literature search of PubMed and Scopus databases up to the end of August 2018. In addition, we reviewed the reference lists of relevant articles. Two authors independently evaluated the eligible articles and extracted relevant information in a structured form. We calculated summary effect estimates (EE) based on the study-specific odds ratios and regression coefficients (β) by applying both fixed- and random-effects models.

Results 26 studies met the *a priori* eligibility criteria, and 12 of them provided sufficient information for the meta-analysis. The summary EE related to 10 grains per m^3 increase in pollen exposure showed an 1% increase (EE=1.01 95% CI 1.00 to 1.02) in the risk of lower respiratory symptoms and a 2% increase (EE=1.02 95% CI 1.01 to 1.03) in the risk of any allergic or asthmatic symptom. Correspondingly, the risk of upper respiratory symptoms and ocular symptoms increased 7% (EE=1.07 95% CI 1.04 to 1.09) and 11% (EE= 1.11 95% CI 1.05 to 1.17), respectively, in relation to such pollen exposure. Short-term exposure to pollen did not show any significant effect on daily lung function levels.

Conclusion: Our results provide new evidence that short-term pollen exposure significantly increases the risks of allergic and asthmatic symptoms.

Strengths and limitations of this study

- Identification of individual studies based on a clearly defined and extensive search strategy based on a priori set inclusion and exclusion criteria.
- In addition, secondary references were included
- The study-specific effect estimates were converted into comparable effect estimates for exposure corresponding to 10 pollen grains increase per cubic meter**.**
- Publication bias was assessed by visual inspection of the funnel plots and by applying Begg's and Egger's tests.
- The number of studies available for the sub-analyses investigating effects on various outcomes was quite low.

Keywords

Allergy; asthma; panel study; pollen exposure; systematic review; meta-analysis

INTRODUCTION

Allergy and asthma are common diseases and consequently, of public health importance globally. Approximately 500 million people suffer from allergic rhinitis worldwide and more than 300 million people have asthma.[1-3] The prevalence of rhinitis and/or rhinoconjunctivitis varies globally between 1% and 45%[4] and that of asthma between 1% and 21%.[5] In Western Europe, the prevalence of allergic rhinitis and/or rhinoconjunctivitis ranges from 17% to 29%[6] and the prevalence of asthma from 6% to 18%.[7] Respectively, the prevalence of rhinitis and/or rhinoconjunctivitis and asthma are 12–30%[8] and 5-10% in the U.S.[9]

The prevalence of physician-diagnosed pollen-induced allergic rhinitis was 18.5% among people living in northern China.[10] The majority of individuals suffering from allergic rhinitis experience seasonal symptoms when exposed to pollen.[11] Correspondingly, exposure to pollen grains increases the risk of asthma exacerbations among asthmatic persons.[12] There are no universally accepted, clinically meaningful threshold levels for pollen exposure. In previous studies, threshold levels have varied between 30 and 60 pollen grains per cubic meter of air.[13,14] However, exposures to relatively low levels of pollen (6-9 grains/m^3) have been associated with asthma symptoms among those who already have this disease.[15] Pollen allergy has been found in 80–90% of children suffering from asthma and in 40–50% of adult-onset asthmatics.[16]

Several panel studies have suggested an association between short-term exposure to pollen and allergic/asthmatic manifestations, although the magnitude and statistical significance of such estimated relations have varied.[17-21] Lung function levels have not been found to clearly associate with pollen exposure.[22-26] However, the amount of exhaled nitric oxide (NO)[22,27] and allergy and/or asthma medication use[18,24] seem to increase during pollen season. Caillaud et al.[28] reviewed qualitatively three panel studies that provided some evidence on a relation between daily counts of atmospheric pollen and occurrence of health outcomes.

The panel studies on pollen exposure and manifestations of asthma or allergy have provided somewhat conflicting results.[23,29] To our knowledge there are no previous systematic reviews with meta-analysis that have assessed the effects of short-term pollen exposure on the risk of allergic and asthmatic symptoms and lung function. Therefore, we conducted a systematic review and meta-analysis to summarize the existing evidence on the relations between short-term exposure to pollen and the occurrence of various allergic and asthmatic symptoms and/or lung function manifestations.

METHODS

This systematic review and meta-analysis is based on a review protocol accessible online (http://www.oulu.fi/cerh/node/50459).

Search strategy and eligibility criteria

We performed a systematic literature search of PubMed and Scopus databases up to the end of August 2018, as shown in figure 1. In the first phase, we used the search terms “panel study” and “pollen”. In order to have a more extensive data search, we included the terms “pollen exposure”, “asthma”, “cohort study”, “longitudinal study”, “follow-up study”, “case-control study” and “cross-sectional study” in the second search (Supplementary Table 1). All languages were included in the search.

Studies that met the following *a priori* eligibility criteria were included in this systematic review: the study (1) was an original study; (2) was a panel study where a group of people were followed longitudinally over a certain time period; (3) included allergic or asthmatic symptoms or measurements of lung function as the outcome; (4) included a study population of children or adults or both; and (5) reported on relations between daily mean airborne pollen exposure and manifestations of allergies and/or asthma.

Articles that were obviously irrelevant were excluded applying title screening. Articles that did not meet our *a priori* inclusion criteria were excluded by reading the abstract or full text.

Outcome and exposure definitions

The outcome of interest was occurrence of allergy and/or asthma manifestations. The definitions of allergy and asthma manifestations included self- or parent-reported symptoms (lower and upper respiratory tract symptoms, ocular symptoms, skin symptoms and/or symptom scores), lung function measurements (Peak expiratory flow, PEF, Forced expiratory volume, FEV, Forced vital capacity, FVC, Exhaled nitric oxide, NO), and use of allergy and/or asthma medications. The exposure of interest was exposure to pollen, expressed as the amount of pollen grains per cubic meter of air sampled (grains/m^3). The eligible definition of exposure included exposure to mean daily total airborne pollen or exposure to mean daily airborne pollen of distinct types (including birch, grass, ragweed, mugwort, olive, elm and/or hazel/alder pollen). All the available studies assessed the associations between pollen concentrations and symptoms during the same day, i.e. the duration of short-term exposure was here one day.

Data extraction and quality assessment

Eligible studies were examined and their relevant characteristics recorded in a standardized data extraction form independently by two authors (M.A.K. and D.R.Y.). Any disagreements were discussed together with additional two authors at the end of the data extraction process (T.T.H. and J.J.K.J.) until a consensus was achieved. Table 1 displays the main characteristics of the eligible studies. The study quality was assessed applying the Newcastle-Ottawa Scale (NOS) with the maximum score of 9.

In one study, the occurrence of allergic and asthmatic symptoms in relation to pollen exposure was investigated by recruiting a group of study subjects in two consecutive years.[17] There was some overlap among the study subjects, so that seven individuals (23% of participants) were included in both of these study groups. These two groups provided independent effect estimates (EE) for our meta-analysis. In another study, subjects were recruited in three distinct but successive periods of time within the pollen season.[26] These three groups also provided three independent effect estimates for the meta-analyses. The protocol was conducted according to PRISMA guidelines.[30]

Statistical methods

In the meta-analysis, we calculated summary effect estimates (EEs) from the study-specific odds ratios (OR) or regression coefficients (β) by using fixed- and random-effects models. When available, we preferred the adjusted EEs to the crude estimates. The summary EE from the fixed-effects model is presented when the study-specific EEs were homogenous, whereas the summary EE from the random-effects model is presented when moderate or substantial heterogeneity was observed between the study-specific estimates. Heterogeneity was evaluated using the Q- and I^2-statistics. I^2-statistic >50% indicates high, 25-50% moderate and <25% low heterogeneity. Publication bias was assessed by visual inspection of the funnel plots and application of Begg's and Egger's tests.[31,32] Individual studies included in the meta-analysis assessed their EEs in relation to different levels of pollen exposure. Because of this, individual EEs were converted into a common pollen concentration, i.e. as 10 pollen grains increase per cubic meter of air, before estimating the summary effect.

Because of only a small number of studies or inadequacy of data in the existing studies, we were not able to analyze potential relations between pollen exposure and skin symptoms, forced vital

capacity (FVC), exhaled NO or allergy and/or asthma medications. The panel studies with allergic and/or asthmatic populations examined usually allergy- and asthma-related symptoms as outcomes. In panel studies including general populations, the outcomes were lung function measurements. We used the "metan" command of the Stata 11 statistical program to analyze the fixed and random effects (StataCorp, College Station, Tex).

Patient and public Involvement

Due to nature of systematic review and meta-analysis, there was no patient and public involvement in this study.

RESULTS

Literature search

Reference lists of the articles that fulfilled the eligibility criteria were also reviewed and additional 14 articles fulfilling the criteria were included. Seven duplicate studies were excluded. A step-by-step approach of the literature search is presented in figure 1. Twenty-six studies met the *a priori* inclusion criteria and were included in the systematic review, while 12 studies of them were included in the quantitative meta-analysis. Table 1 displays the characteristics of the 26 eligible studies.[14,15,17,19-21,23-27,29,33-46]

Ten of the 26 studies specifically investigated the relation between total pollen exposure and allergic and/or asthmatic manifestations. Thirteen reported on grass (*Poaceae*), 5 on birch (*Betula*), 5 on ragweed (*Ambrosia*), 3 on hazel/alder (*Corylus/Alnus*), 3 on olive (*Olea*), 2 on elm (*Ulmus*), and 1 on mugwort (*Artemisia*) exposure and allergy and/or asthma manifestations.

186 **Table 1** Characteristics of the eligible studies included in the systematic review and meta-analysis (n = 26).

Reference (Region, country)	Study population	Study size (number of participants)	Follow-up (length and rate, %)	Outcomes	Method for pollen exposure assessment and the range of exposure expressed as mean daily pollen concentrations (pollen grains/m³ of air)	NOS quality score [a]
Caillaud et al., 2012[33] (France and Switzerland)	Adults with hay fever sensitized to grass pollen	106	17 weeks; 71.1%	Self-reported ocular, nasal and lower respiratory symptoms	Regional monitoring by a volumetric pollen trap; range 0-130	4/9
Caillaud et al., 2014a[17] (France and Switzerland)	Adults with seasonal rhinitis sensitized to ragweed pollen	16 in 2009, 22 in 2010, a total of 30	11 weeks; 96.8%	Self-reported daily SAR symptoms: ocular (itching and/or tear flow and/or conjunctival redness), nasal (sneezing and/or runny nose and/or blocked nose) and respiratory (cough and/or wheezing and/or asthma) symptoms, use of medication	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level; range 0-543	6/9
Caillaud et al., 2014c[34] (France and Switzerland)	Adults with seasonal rhinitis sensitized to birch pollen	61	8 weeks; 85.9%	Self-reported daily SAR symptoms: ocular (itching and/or tear flow and/or conjunctival redness), nasal (sneezing and/or runny nose and/or blocked nose) and respiratory (cough and/or wheezing and/or asthma) symptoms	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level; range 0-400-	5/9
Delfino et al., 1996[35] (US)	9-18 years old subjects with physician-diagnosed asthma	12	6 weeks; 80.0%	Asthma symptoms (wheeze, cough, sputum production, shortness of breath, chest tightness) and use of as-needed beta-agonist inhalers	Regional monitoring by a volumetric pollen trap located 10 meters above the ground level; range 4-115	4/9
Delfino et al., 1997[23] (US)	9-46 years old subjects with physician-diagnosed asthma sensitized to tree, grass or weed pollen	22	8 weeks; 91.7%	Self-reported daily asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness), each evening and morning three PEF blows and daily asthma medication use (i.e. beta-agonist inhaler)	Regional monitoring by a volumetric pollen trap located 4 meters above the ground level; range 11-611	5/9

Delfino et al., 2002[20] (US)	9-19 years old subjects with physician-diagnosed asthma	22	8 weeks; 88.0%	Self-reported daily asthma symptoms (cough, wheeze, sputum production, shortness of breath, and chest tightness)	Regional monitoring by a volumetric pollen trap located 4 meters above the ground level; range 12-1257	5/9
DellaValle et al., 2012[15] (US)	4-12 years old children with physician-diagnosed asthma	430	24-26 weeks during the years 2000-2004; 92.3%	Self-reported daily asthma symptoms (wheeze, night symptoms, shortness of breath, chest tightness, and persistent cough), use of asthma medication	Personal pollen exposure assessment based on modeling; range 0-4187	5/9
Djukanović et al., 1996[36] (United Kingdom)	20-49 years old adults with atopic asthma	17	15 weeks; 94.1%	Self-reported asthma symptoms (nocturnal wheeze, nocturnal cough, morning chest tightness, day-time wheeze, subjective worsening of asthma due to exercise, cold air or fumes), self-reported morning and evening PEF values, FEV1	Not specified; range 0-318 (based on weekly pollen counts)	1/9
Dominguez-Vilches et al., 1995[37] (Spain)	Patients with pollen induced allergic rhinitis	70 in 1991 and 23 in 1992	12 weeks in 1991 and 12 weeks in 1992; 70.0% in 1991 and 46.0% in 1992	Daily conjunctival, nasal and respiratory symptoms	Regional monitoring by a volumetric pollen trap placed on the roof of a university building; ranges of pollen concentrations are not clearly stated	2/9
Feo Brito et al., 2007[38] (Spain)	Subjects with mild to moderate seasonal asthma sensitized to grass and/or olive pollen	137	6 weeks; 90.1%	Self-reported symptoms of asthma, self-reported morning and evening PEF values	Regional monitoring by a volumetric pollen trap; ranges 1-559 (grasses) and 0-596 (olives)	4/9
Feo Brito et al., 2010[14] (Spain)	10-51 years old patients with seasonal rhinitis and/or asthma, mono-sensitized to grass pollen	27	52 weeks; 100%	Self-reported symptoms / symptom and medication scores (including nasal obstruction, runny nose, sneezing/congestion, itching of the eyes, asthma attacks, use of medication)	Regional monitoring by a volumetric pollen trap located 5 meters above the ground level; range 0-585	2/9
Feo Brito et al., 2011[39] (Spain)	10-51 years old patients with seasonal rhinitis or asthma mono-sensitized to olive pollen	20	52 weeks; 100%	Self-reported symptoms (including conjunctival, nasal and respiratory symptoms)	Regional monitoring by a volumetric pollen trap located 15 meters above the ground level; range 0-443	3/9

Grammer et al., 1990[40] (US)	Patients with history of ragweed rhinitis	29	10 weeks; 100%	Self-reported daily symptoms / symptom medication scores (nasal congestion, nasal discharge, sneezing, ocular pruritus, cough, use of medication)	Not specified; A rotating arm impactor and weekly pollen data were used; range 0-2100	2/9
Jantunen et al., 2012[41] (Finland)	8-70 years old persons with physician-diagnosed birch pollen allergy (rhinoconjunctivitis)	28 in 2009 and 33 in 2010	8 weeks; 95.3%	Self-reported symptoms (conjunctival symptoms [itchy, swollen, watery, or sore eyes], nasal symptoms [sneezing, runny, itchy, or blocked nose], other allergy symptoms), use of medication	Regional pollen monitoring by a volumetric pollen trap located 14 meters above the ground level; ranges 0-1970 (alders) and 0-6890 (birches)	3/9
Klabuschnigg et al., 1981[42] (Austria)	7-14 years old children with clinically-diagnosed asthma	40	6 weeks; 92.5%	Self-reported asthma symptoms, lung function (PEF, FEV1, FVC) measured every second day, use of medication	Regional pollen monitoring by a volumetric pollen trap located 12 meters above the ground level; ranges of pollen concentrations are not clearly stated	2/9
Krämer et al., 2005[43] (Germany)	9 years old children with diagnosed allergic eczema	39	26 weeks; 69.6%	Self-reported daily eczema symptoms: itching and the extent of skin lesions	Regional pollen monitoring by a volumetric pollen trap located 12 meters above the ground level; ranges 0-215 (hazel/alder), 0-1673 (birches), 0-184 (grasses) and 0-10 (mugworts)	5/9
Newhouse & Levetin, 2004[29] (US)	9-64 years old patients with physician-diagnosed asthma	24	8 weeks; 63.2%	Self-reported asthma symptoms, morning and evening PEF values	Regional pollen monitoring by a volumetric pollen trap located on the roof of a university building; ranges 1-498 (ragweeds), 0-167 (elms), 0-132 (grasses)	3/9
Ostro et al., 2001[21] (US)	8-13 years old children with physician-diagnosed asthma	138	13 weeks; 90.2%	Self-reported daily asthma symptoms (shortness of breath, cough, and wheeze)	Pollen monitoring by a Rotorod device (taking a sample for 30 seconds every 10 minutes); range 1-75	5/9
Petersen & Sandberg, 1981[44] (Denmark)	Patients suffering from diagnosed pollen allergy	78	36 weeks; 83.2%	Daily scoring of symptoms and use of medication; before, during and after pollen season	Regional pollen data; range 0-1600 (based on weekly pollen counts)	3/9

Roberts et al., 2004[27] (United Kingdom)	7-16 years old children with mild to moderate seasonal allergic asthma and rhinoconjunctivitis sensitized to grass pollen	44	10 weeks; 100%	Exhaled NO –measurements and FEV1	Regional pollen monitoring by a volumetric pollen trap; range 0-178	4/9
Roberts et al., 2005[19] (United Kingdom)	6-17 years old children with seasonal allergic rhinoconjunctivitis, asthma and/or eczema sensitized to grass pollen	84	12 weeks; 100%	Self-reported weekly pediatric allergic disease quality based on life questionnaire, symptoms (chest, nasal, ocular, cutaneous and other symptoms) and emotional problems	Regional pollen monitoring by a volumetric pollen trap; ranges of pollen concentrations are not clearly stated	3/9
Ross et al., 2002[24] (US)	5-49 years old subjects with asthma	40	26 weeks; 67.8%	Self-reported morning and evening PEF, symptom score, occurrence of asthma attacks and frequencies of asthma medication use	Local pollen monitoring by Rotorod devices located 2 meters above the ground level; range 0-1492	4/9
Scarlett et al., 1996[25] (United Kingdom)	7-11 years old children with and without asthma	154	6 weeks; 100%	Daily lung function measurements (FEV0.75, FVC, FEV0.75/FVC)	Regional pollen monitoring, pollen counts were derived from the local monitoring site; range 2-183	6/9
Schäppi et al., 1998[45] (Australia)	17-50 years old volunteers with moderate to severe hay fever sensitized to grass pollen	21	3 weeks; 75.0%	Nasal (blockage, discharge or itching) and eye symptom scores (itching, swelling or running)	Regional pollen monitoring by a volumetric pollen trap located 14 meters above the ground level; range 0-400	3/9
Studnicka et al., 1995[26] (Austria)	7 years old and older children with and without asthma	47 in panel 1, 45 in panel 2, 41 in panel 3	3 weeks; 88.7%	Daily lung function measurements (FEV1, FVC, PEF)	Regional pollen monitoring by a volumetric pollen trap located 10 meters above the ground level; ranges of pollen concentrations are not clearly stated	7/9
Taudorf & Moseholm, 1988[46] (Denmark)	16-47 years old pollinotic (hay fever) patients sensitized to birch pollen	15	16 weeks in 1983 and 16 weeks in 1984; 75.0%	Nose and eye symptom scores, use of medication	Regional pollen monitoring by a volumetric pollen trap; ranges of pollen concentrations are not clearly stated	3/9

SAR, Seasonal allergic rhinitis. PEF, Peak expiratory flow. FEV1, Forced expiratory volume in the first second. FVC, Forced vital capacity. NO, Nitric oxide. FEV0.75, Forced expiratory volume at 3/4 of a second. [a] For panel studies, the maximum score is 7/9.

Characteristics of included studies

Characteristics of the 26 eligible studies are shown in table 1. In 13 studies subjects were asthmatics, in 11 studies subjects were sensitized to pollen (i.e. positive Skin prick test, SPT or Allergen-Specific Immunoglobulin E Test, IgE test) and in 8 studies subjects had hay fever (i.e. allergic rhinitis, pollen allergy, pollinosis). One study investigated subjects with eczema. In 2 studies, subjects with and without asthma were analyzed together without taking into account the prior disease status. Ten studies investigated children, four adults, and 9 both children and adults. In 3 studies, authors did not specify the age of the subjects. Six studies applied logistic regression, 9 studies linear regression, 2 studies Poisson regression, and 2 studies time series regression for the analyses. The NOS scores varied between studies from one to seven of total nine.

The studies defined the allergic and/or asthmatic manifestations in different ways. Sensitization based on SPT or IgE analysis was the most common criterion used for the definition of allergy. Current presence of asthma, previous history of asthmatic symptoms, and/or physician (i.e. clinical) diagnosis were frequently applied as inclusion criteria in the reviewed studies. We systematically categorized outcomes into any symptom, lower respiratory tract symptoms, upper respiratory tract symptoms, ocular symptoms, skin symptoms, symptom scores, lung function measurements (PEF, FEV, FVC and exhaled NO), and use of allergy and/or asthma medications.

Pollen monitoring used for exposure assessment was based on regional sampling in 21 studies, on local sampling in 2 studies, and on personal exposure modelling in one study. In 2 studies, authors did not specify the type of pollen sampling. The height of the pollen sampler varied between 2-15 meters above the ground level. Thirteen of the studies did not give the height information for pollen sampler. Twenty-five studies expressed the mean pollen concentration as pollen grains per cubic meter of air per 24 h. In 3 studies, daily pollen counts were converted into weekly pollen sums, and consequently, the relations between weekly pollen counts and weekly symptoms were presented. In 2 studies, hourly/bihourly pollen counts were presented in addition to daily counts. Main outcomes for the studies that were not included into the meta-analysis are presented in table 2.

Risk of bias across the studies

In the majority of studies, exposure assessment was based on single stationary regional sampler located on the roof level (Table 1). Although it has been suggested that different types of pollen sampling can be used to get a rough estimate of pollen exposure,[47] many of the approaches may

not have captured the daily individual exposures at the breathing level in satisfactory detail. In 2013, we monitored grass pollen concentrations at 16 sites in the cities of Helsinki and Espoo during the peak pollen season by using rotorod-type samplers at the breathing height.[48] We identified substantial variation in exposure concentrations at breathing height according to urbanity of the site and time of the day within areas covered by our roof level monitoring stations. Most valid estimates of pollen exposure could be obtained by using personal pollen sampling. There were also other potential sources of heterogeneity in the exposure measured by these studies linked to variation in weather/climatic conditions, type and period of monitoring, nature of pollen season, daily activities/time spent outdoors by the study subjects, variation in the height of monitoring and pollen types monitored. This heterogeneity in exposure can generate a substantial variation in occurrence and severity of symptoms among exposed subjects. Therefore, we converted individual effect estimates into a common (comparable) pollen concentration, i.e. as 10 pollen grains increase per cubic meter of air.

In all studies, selection of study subjects was based on predefined and justified eligibility criteria. Due to the study design that included inference based on within-individual variation of health outcome, the risk of selection bias is rather small (Supplementary table 2). Also the relatively high follow-up rates (varying from 46.0 to 100%) across studies reduce the risk of selection bias. However, there was substantial diversity in the type and measurement of outcomes, which resulted in difficulties in forming the major outcome groups for the meta-analyses. Status of allergic and/or asthmatic diseases varied from mild to moderate or from moderate to severe.

The studies could be divided roughly into two major groups on the basis of what kind of adjustment was applied for confounding. The first group of studies provided only descriptive results without any or only with very basic statistical analyses. The second group performed extensive statistical analyses, including controlling for a few or several confounders. Due to study design where individuals act as their own controls on days with no (major) exposure, individual characteristics were not potential confounders. In contrast, environmental factors, such as temperature and air pollution can be potential confounders. A significant number of the studies adjusted for temperature (13) and other meteorological parameters (12), as well as for air pollution (4). Other potential sources of heterogeneity include variation in the studied time lags between the exposure and the outcome (varying from 0 to 14 days), potential differences in allergen content of pollen of interest, and different characteristics and size of the study populations (varying from 12 to 430 subjects). In 24 studies, the study focused on asthmatics

and/or subjects with allergies, whereas two studies included both healthy and non-healthy subjects.[25,26]

256 **Table 2** The main findings in articles not included into the meta-analysis (n = 14)

Reference	Main findings
Delfino et al. 1996[35]	Pollen exposure was not associated with either asthma symptom scores or as-needed beta-agonist inhaler use.
Delfino et al. 1997[23]	Pollen exposure was not associated with asthma symptom severity, morning or evening peak expiratory flow rate (PEFR), or β-agonist inhaler use.
Djukanovic et al. 1996[36]	The peak pollen season was associated with a significant increase in asthma symptoms (P<0.05).
Dominguez-Vilches et al. 1995[37]	A greater seasonal pollen intensity was associated with a higher occurrence of daily symptoms.
Feo Brito et al. 2010[14]	A significant positive association was found between the presence of symptoms and pollen grains (r=0.62; P<0.001).
Grammer et al. 1990[40]	The peak pollen periods were associated with a twofold increase in symptom-medication scores among a subset of patients.
Jantunen et al. 2012[41]	The number of subjects with allergy symptoms increased significantly with the daily pollen concentrations (r= 0.35-0.36, P<0.01).
Klabuschnigg et al. 1981[42]	Two hourly pollen counts or daily pollen counts were not associated with the frequency of asthma attacks. In contrast, consecutive 10-day mean symptom scores (assessing asthma attacks) associated with the total pollen counts. No associations were found between pollen exposure and lung function measurements (including PEF, FEV1 and FVC).
Krämer et al. 2005[43]	Pollen exposure had no significant effect on skin symptom severity among children with winter type eczema (relative change in grass pollen exposure 0.98-1.00; 95% confidence limits 0.81-1.18). In contrast, grass-pollen exposure showed a significant effect on the severity of skin symptoms among children with summer type eczema (relative change in grass pollen exposure 1.16-1.19; 95% confidence limits 1.02-1.39).
Newhouse & Levetin 2004[29]	*Ambrosia* pollen concentrations were significantly correlated with composite asthma scores (r=0.263, P<0.05), rhinitis scores (r=0.513, P<0.001) and several individual symptoms. *Chenopodiaceae/Amaranthaceae* pollen concentrations showed significant associations with composite asthma scores (r=0.256, P<0.05). *Ulmus* (r=0.367, P<0.01), *Chenopodiaceae/Amaranthaceae* (r=0.458, P<0.001) and *Poaceae* (r=0.326, P<0.05) pollen concentrations showed significant correlations with composite rhinitis scores. Pollen concentrations significantly influenced morning (but not evening) PEF values measured in the following day (r=-0.261–-0.364, P<0.05-0.01).
Petersen & Sandberg 1981[44]	There was a positive association between the appearance of pollen grains in the air and the symptom-medication score.
Roberts et al. 2004[27]	Fractional exhaled nitric oxide (FENO) levels increased significantly during the grass pollen season (median change 2.9 ppb, 95% confidence interval 1.5-5.4). There were no apparent associations between pollen counts and other lung function measurements.
Schäppi et al. 1998[45]	The grass pollen counts associated significantly with the average nasal (r=0.637, P<0.001) and eye symptom (r=0.586, P<0.005) scores.
Taudorf & Moseholm 1988[46]	Occurrence of symptoms and daily medication increased during the season with a constant pollen load.

PEFR, Peak expiratory flow rate = PEF, Peak expiratory flow. FEV1, Forced expiratory volume in the first second. FVC, Forced vital capacity. FENO, Fractional exhaled nitric oxide.

Relations between pollen exposure and allergy- and asthma-related symptoms among allergic / asthmatic subjects

A total of 12 studies were included in the meta-analyses. In 8 studies [15,17,20,21,33,34,38,39] the effect estimate was based on odds ratio and in 4 studies [19, 24-26] on a regression coefficient which was or was converted to a change per 10 grains per m3 of air. The summary EE for the relation between pollen exposure and any symptoms was statistically significantly increased at 1.02 (95% confidence interval (CI): 1.01-1.03) from the random effects model (figures 2, 3 and Supplementary File, figure 1). The study-specific estimates showed high heterogeneity. This estimate was based on 6 studies (providing 9 EEs). The funnel plot and the results from the Begg's (z= -1.25; P value= 0.211) and Egger's tests (Bias coefficient .0457453; 95% CI -.0048418-.0963324; P value= 0.070) on short-term pollen exposure and any symptoms provided no indication of publication bias (Supplementary File, figure 2).

A total of 6 studies (9 EEs) provided study-specific EEs for pollen exposure and lower respiratory symptoms. The summary EE from the random effects model was 1.01 (95% CI: 1.00-1.02). The study-specific estimates showed high heterogeneity.

The summary EE for pollen exposure and upper respiratory symptoms, based on 3 studies (4 EEs), was significantly increased at 1.07 (95% CI: 1.04-1.09) from the random effects model. There was moderate heterogeneity between the study-specific estimates.

The relation between pollen exposure and ocular symptoms was reported in 3 studies (4 EEs). The summary EE from the random-effects model was 1.11 (95% CI: 1.05-1.17). The study-specific estimates showed high heterogeneity.

The relation between pollen exposure and symptom scores was based on 4 studies applying linear regression modelling (giving regression coefficients). The summary EE was significantly elevated (1.003; 95% CI: 1.001-1.004). The study-specific estimates showed high heterogeneity.

Relations between pollen exposure and lung function among general population

The relation between pollen exposure and peak expiratory flow (PEF) was assessed in 2 studies (giving 4 EEs), resulting in a summary EE of 0.98 for 10 pollen grains increase per cubic meter of air (95% CI: 0.95-1.01) in the random effects model based on linear regression modelling. The study-specific estimates showed large heterogeneity.

Two studies estimated the relation between pollen exposure and forced expiratory volume (FEV). One study used forced expiratory volume in the first second, FEV1 as the outcome and the

other forced expiratory volume at 3/4 of a second, FEV0.75. Different FEV estimates were combined in the analysis. Meta-analysis gave the summary EE of 1.00 for 10 pollen grains increase per cubic meter of air (95% CI: 0.99-1.01) in the fixed effects model based on linear regression modelling. There was little heterogeneity between the studies.

Relations between pollen exposure and use of allergy and/or asthma medication

In 2 studies, the use of allergy and/or asthma medication was combined with information on allergy and/or asthma symptoms (in forming symptom-medication score). In 5 studies that investigated the relation between pollen exposure and the use of medication, pollen exposure increased the use of medication. In contrast, 3 studies did not show any association between pollen exposure and use of allergy/asthma medication.

DISCUSSION

Main findings

This systematic review and meta-analysis provides new evidence that short-term pollen exposure significantly increases the risk of allergic and asthmatic symptoms. The summary EE for a 10 grains /m³ increase in pollen exposure showed on average a 2% increase in the risk of any allergic or asthmatic symptom. The corresponding increases in the risk of upper respiratory symptoms and ocular symptoms were 7% and 11%, respectively. All summary EEs were statistically significant. This meta-analysis did not show any statistically significant relations between pollen exposure and lung function measurements. The summary EE for 10 grains /m³ increase in pollen exposure indicated a 2% decrease in PEF values, while no change was detected in relation to FEV values.

Validity of results

The strengths of our study include identification of individual studies based on a clearly defined search strategy. In addition to the primary PubMed and Scopus database searches, we also used secondary references that were cited by the articles and reviews identified in the primary search to achieve as complete set of studies as possible. Two reviewers checked independently the eligibility of the studies according to *a priori* set inclusion and exclusion criteria and identified the most appropriate effect estimate.

The present systematic review and meta-analysis focused on panel studies mainly with relatively brief follow-up periods. The follow-up periods in the studies varied from 3 weeks to 52 weeks.

However, pollen related allergic and asthmatic symptoms are usually induced after only a few hours or days of exposure.[49,50] Thus, variable and/or relatively short follow-up periods are probably not problematic when assessing the relationship between pollen exposure and outcomes of interest in this study.

Our statistical analyses included 12 studies, because only 12 studies out of a total of 26 presented the exact mean or interquartile range (IQR) values of pollen grains per cubic meter. Information on the mean and IQR values were needed to convert the study-specific effect estimates into common effect estimates for exposure corresponding to 10 pollen grains increase per cubic meter. The aim of this transformation was to make studies containing different pollen concentration values comparable. Although the total number of panel studies was reasonable, the numbers of studies available for the sub-analyses investigating various outcomes were quite low. Therefore, the conclusions based on results of the sub-analyses should be interpreted with caution. NOS scoring gave varying values, indicating partly the low quality of included studies. Although it can reduce the confidence of the results, we did not see any major difference between the effect estimates of the lower and higher scored studies.

"Any exposure" was applied in the analyses due to the heterogeneity of exposure assessment. Total daily mean pollen concentration values were preferred, but when such were not available, information on the mean daily airborne concentration of distinct pollen types (birch, grass, ragweed, mugwort, olive, elm and/or hazel/alder) was used as the measure of exposure in the analyses. This should not cause any problem, because the pollen seasons of different pollen types commonly overlap, so individuals can react to exposure to several pollen types. Consequently, the reaction to pollen exposure is likely to be a combined reaction to a sum of various pollen types.[51] It is not always possible to define exactly which specific pollen type caused the symptoms. Therefore, the exact separation of distinct pollen types in health effect studies is somewhat artificial and thus, unnecessary.

Synthesis with previous knowledge

Our results indicated that short-term pollen exposure increases the risk of any respiratory or other allergic symptom, lower and upper respiratory symptoms and ocular symptoms among allergic and/or asthmatic subjects. Depending on the plant species, concentrations of pollen grains in the breathing air can vary between zero and thousands. Eventually, increases in pollen exposure can have a considerable effect on the well-being of allergic/asthmatic people. In a recent systematic

review and meta-analysis of 14 studies,[52] the mean number of emergency department attendance among children and adolescents with asthma increased 1.88% (95% CI = 0.94%-2.82%) in relation to a 10 grass pollen grain increase per cubic meter. These results are in line with a recent ecologic study from Japan, where a positive association was observed between cedar and cypress pollen counts and the prevalence of symptoms of allergic rhinoconjunctivitis and asthma in school children.[53] Similarly, our results are also in line with the register-based time-series analysis among Belgian population, where a positive association was observed between pollen exposure and allergy medication sales.[54] A time-stratified case-crossover study showed a positive association between tree and weed pollen exposure and emergency department visits due to asthma exacerbations among 13-17 year- old U.S. asthmatics.[55]

According to our results, the effect of pollen exposure was stronger in upper respiratory tract than in lower respiratory tract. This could be explained by the large size of the pollen grain. Generally, the size of pollen varies between 20 and 100 micrometers in diameter.[56] Therefore, particles of pollen grain size do not penetrate well into the lower respiratory tract.[57] Pollen grains are likely to adhere and release their allergenic content already in the upper respiratory tract. As a consequence of this, the majority of the direct allergic inflammatory effects caused by pollen may be experienced in the region of the upper respiratory tract.

Our systematic review did not detect any major effect of pollen exposure on lung function. The results may be explained by the fact that the study population for lung function effects included healthy people in addition to allergic and asthmatic subjects. If these studies would only include allergic and/or asthmatic persons, more pronounced effects might be detected. In the Swedish cohort-based study, exposure to grass pollen during the preceding day was associated with a reduced forced expiratory volume in relation to an increase in three pollen counts (/m^3) among the 8-year-old children.[58] This association was more pronounced among children who were sensitized to pollen allergens. In line with those results, another study of Swedish adults showed that pollen exposure resulted in significantly increased concentration of nitric oxide in exhaled air, which suggested increased airway inflammation among these asthmatics compared to the healthy controls.[59]

Conclusions

This systematic review and meta-analysis provides new evidence that short-term exposure to pollen grains increases any respiratory symptoms, as well as specifically upper respiratory and

ocular symptoms among allergic and asthmatic subjects. It is important that clinicians take into account, when working with allergic and asthmatic patients that even relatively short-term exposure to pollen can induce for them symptoms of allergies and asthma. Clinicians should advice allergic and asthmatic subjects to avoid spending much time outdoors during the (main) pollen periods, and to use adequate allergy and asthma medications when such exposures cannot be avoided. Future studies should use personal exposure assessment and it would be important to find out how the variation in pollen exposure affects the health of allergic and asthmatic subjects.

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Contributors

JJ and TH conceived the study; MK, DRY and TH reviewed the articles, NS and MK analyzed the data under supervision of JJ; MK, TH, MJ, and JJ wrote the manuscript, all authors contributed to the intellectual content and approved the final version

Data sharing statement

Data are available upon reasonable request.

Patient consent

Not required

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Competing Interests None declared.

Legends to the figures

Figure 1 Flow diagram showing searches and study selection.

Figure 2 Forest plot for the relation between pollen exposure and any symptom (Weights are from random effects analysis).

Figure 3 A Forest plot for the relation between pollen exposure and lower respiratory symptoms (Weights are from random effects analysis). **B.** Forest plot for the relation between pollen exposure and upper respiratory symptoms (Weights are from random effects analysis). **C.** Forest plot for the relation between pollen exposure and ocular symptoms (Weights are from random effects analysis). **D.** Forest plot for the relation between pollen exposure and symptom score (Weights are from random effects analysis).

Supplementary File, Figure 1 A. Forest plot for the relation between pollen exposure and peak expiratory flow (PEF; Weights are from random effects analysis). **B.** Forest plot for the relation between pollen exposure and forced expiratory volume (FEV; Weights are from fixed effects analysis).

Supplementary File, Figure 2 Funnel plot with pseudo 95% confidence limits for the relation between short-term pollen exposure and any symptom.

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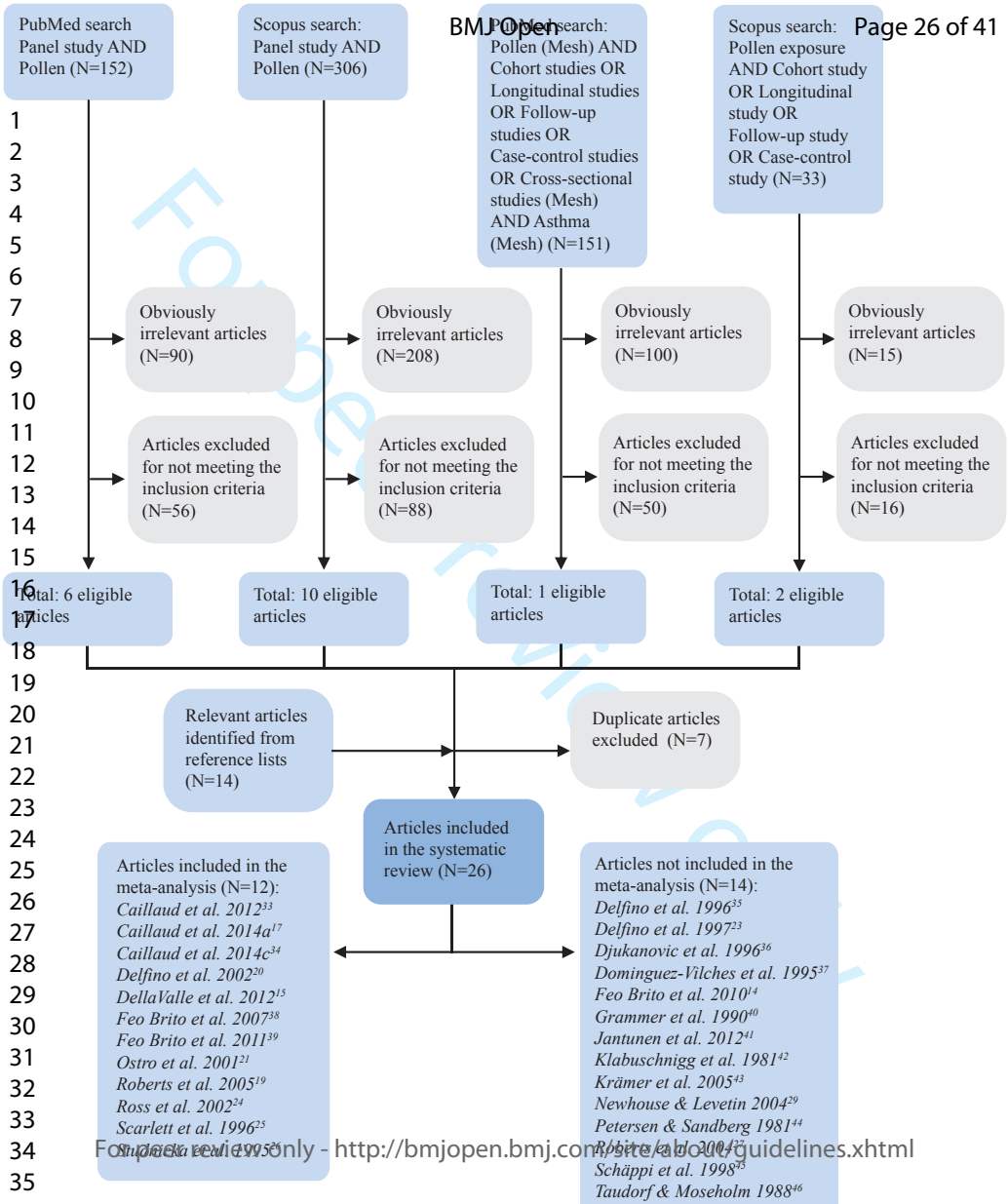
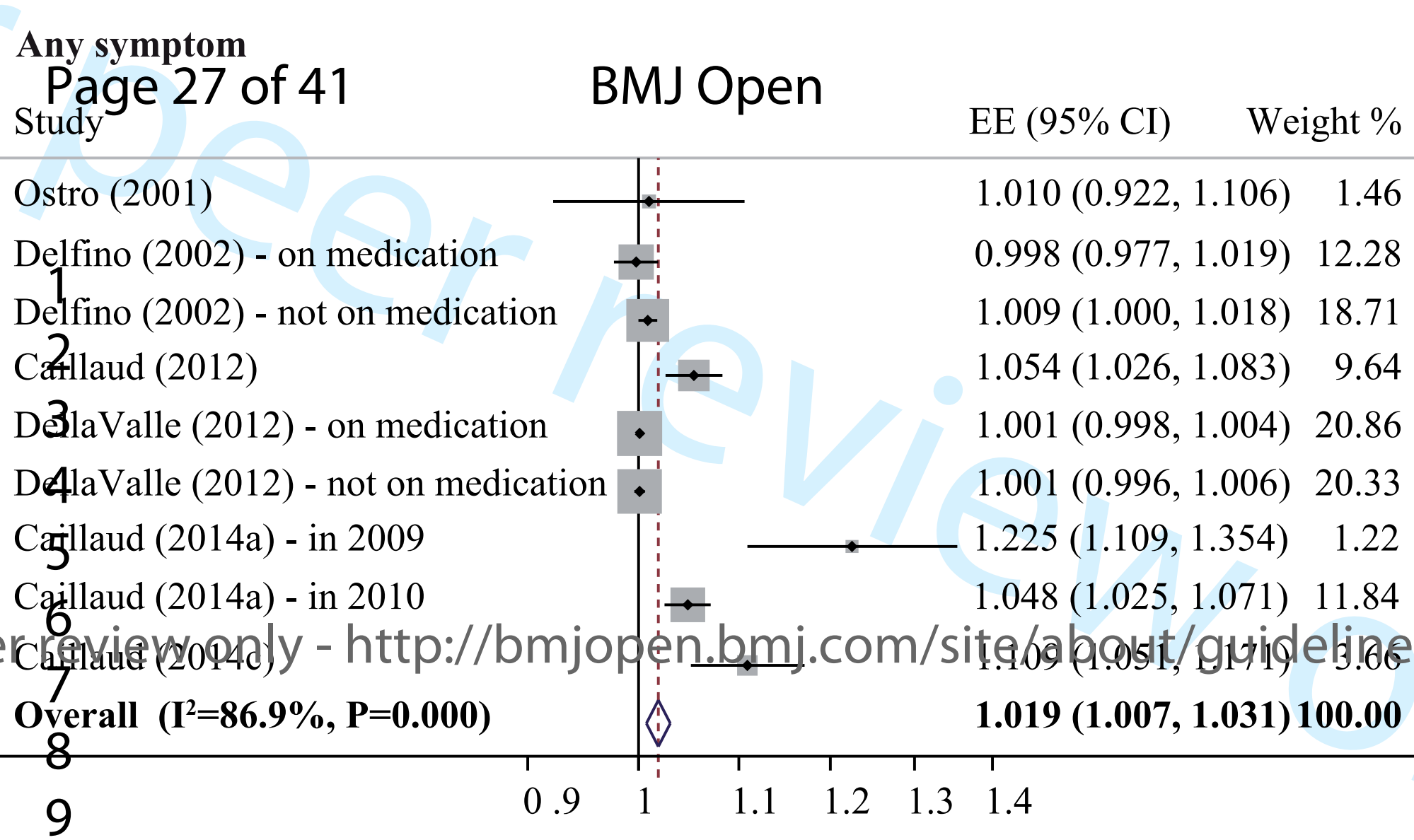
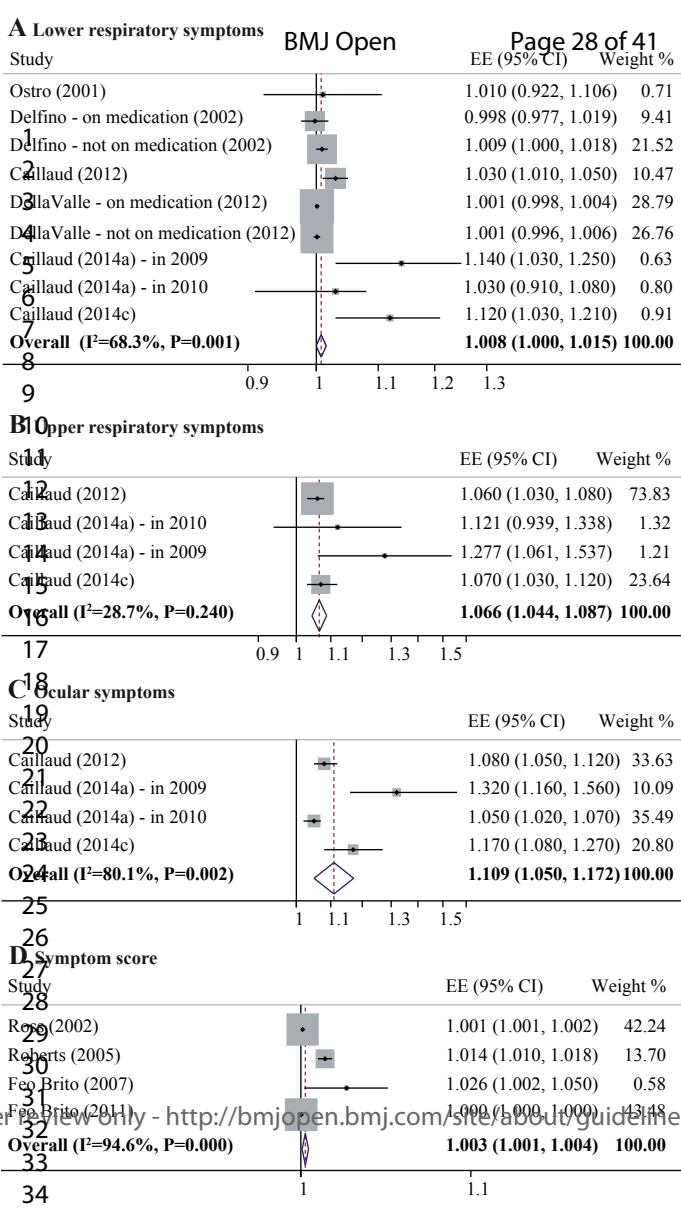


Any symptom





Supplementary File, Table 1. List of search terms and related combinations used in PubMed database search.

First phase	Second phase
Panel study AND Pollen	Pollen (Mesh) AND Cohort studies (Mesh)
	Pollen (Mesh) AND Longitudinal studies (Mesh)
	Pollen (Mesh) AND Follow-up studies (Mesh)
	Pollen (Mesh) AND Case-control studies (Mesh)
	Pollen (Mesh) AND Cross-sectional studies (Mesh)
	Pollen (Mesh) AND Cohort studies (Mesh) AND Asthma (Mesh)
	Pollen (Mesh) AND Longitudinal studies (Mesh) AND Asthma (Mesh)
	Pollen (Mesh) AND Follow-up studies (Mesh) AND Asthma (Mesh)
	Pollen (Mesh) AND Case-control studies (Mesh) AND Asthma (Mesh)
	Pollen (Mesh) AND Cross-sectional studies (Mesh) AND Asthma (Mesh)

Supplementary Table 2. Risk of bias tables.

Caillaud et al. 2012		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 71.1%; "43 volunteers were excluded, either because they failed to provide the requested daily health records (n=24) or because they did not fulfill the inclusion criteria (n=19)"
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Caillaud et al. 2014a		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 96.8%; "One participant was excluded because he failed to provide the requested daily health records during the month of August and additionally he experienced hay fever before the pollen season."
Selective reporting (reporting bias)	Low risk	Protocol was not available but it was clear that all pre-specified and expected outcomes of interest were reported
Other bias	Low risk	There was some overlap among the study subjects, so that seven individuals (23% of participants) were included study groups in both years. "Of these 31 patients, 7 participated in the 2 years." Polysensitized patients were involved.

		"It would have been preferable to include patients who were strictly monosensitized to A artemisiifolia in order to obtain more accurate results regarding the relationship between pollen exposure and symptoms [31]. However, due to the rarity of monosensitized patients, the study had to include polysensitized patients."
Caillaud et al. 2014c		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 85.9%; "Ten participants were excluded either because they failed to provide the requested daily health records (n=8) or because they did not qualify for inclusion (N=2)." Partly missing symptom data. "Missing symptom score data occurred on 285 person-days (8.6% of the total expected follow-up of 3,311 person-days) because subjects had left the study area all day…"
Selective reporting (reporting bias)	Low risk	Protocol was not available but it was clear that all pre-specified and expected outcomes of interest were reported
Other bias	Low risk	None were identified

Delfino et al. 2002		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design

Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 88.0%. "A 10-year-old boy and a 10-year-old girl dropped out after the second week of study and are not retained for analysis. One white 10-year-old male was asymptomatic throughout the panel period and therefore contributed no information to the repeated-measures analysis." Partly missing symptom data. "Missing symptom score data occurred on 51 person-days (3.8% of total expected follow-up of 1,328 person-days) because subjects had left the study area all day, and on 29 person-days because of noncompliance with diary completion (2.2%), …"
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Della Valle et al. 2012		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 92.3%; "We restricted the analysis to 430 subjects who completed an exit interview and who lived primarily within the northeastern U.S. throughout follow-up, …"
Selective reporting (reporting bias)	Low risk	Protocol was not available but it was clear that all pre-specified and expected outcomes of interest were reported.
Other bias	Low risk	None were identified

Feo Brito et al. 2007		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 90.1%. "… seven patients withdrew in Puertollano and eight patients in Ciudad Real, leaving a final study population of 137 patients …"
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Feo Brito et al. 2011		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 100%
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

Ostro et al. 2001		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design

Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 90.2%; "Five subjects who provided baseline data never provided any daily diary information. In addition, data from 10 subjects (representing 8.3% of the person-days) were excluded from the analysis because of evidence that the intake data or diary data were likely to have been inaccurate, or because the diaries were returned more than 2 weeks late." Partly feasible symptom data. "A total of 10,022 person-days of symptom data were reported, of which we used 9,126 in the analysis after the health data of questionable validity were excluded."
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

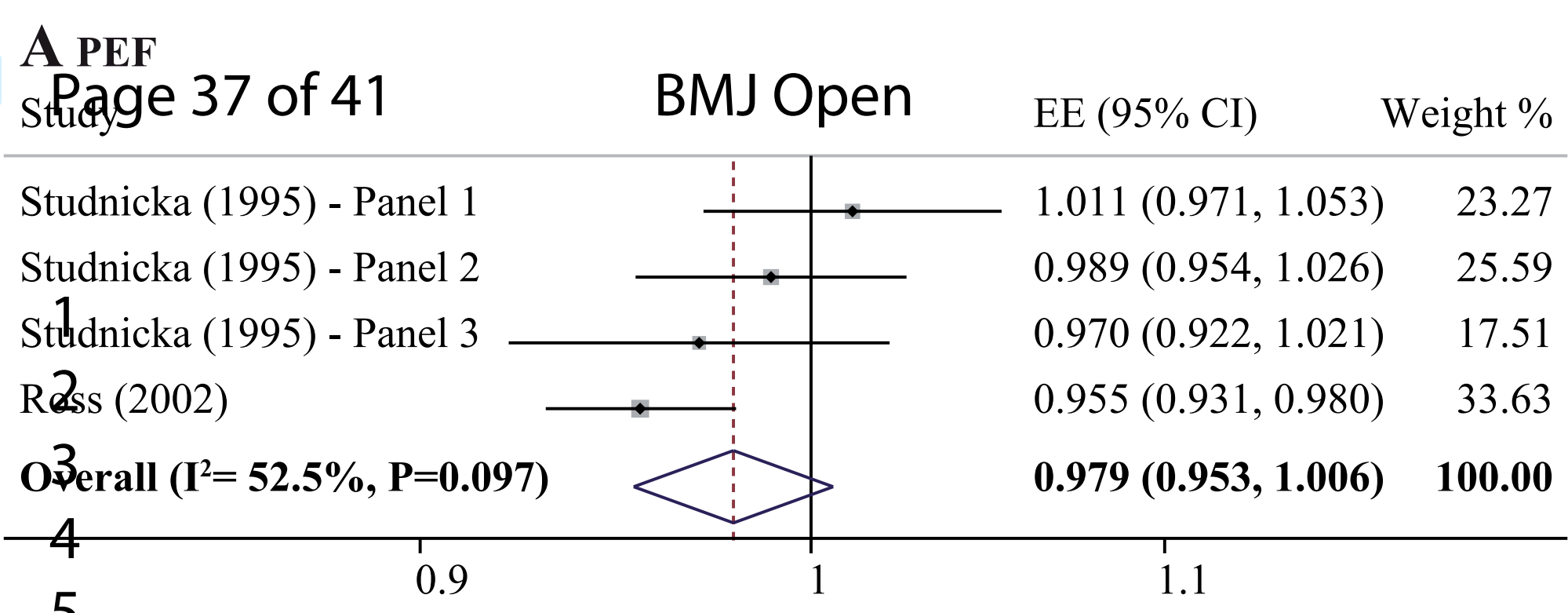
Roberts et al. 2005		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 100%
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

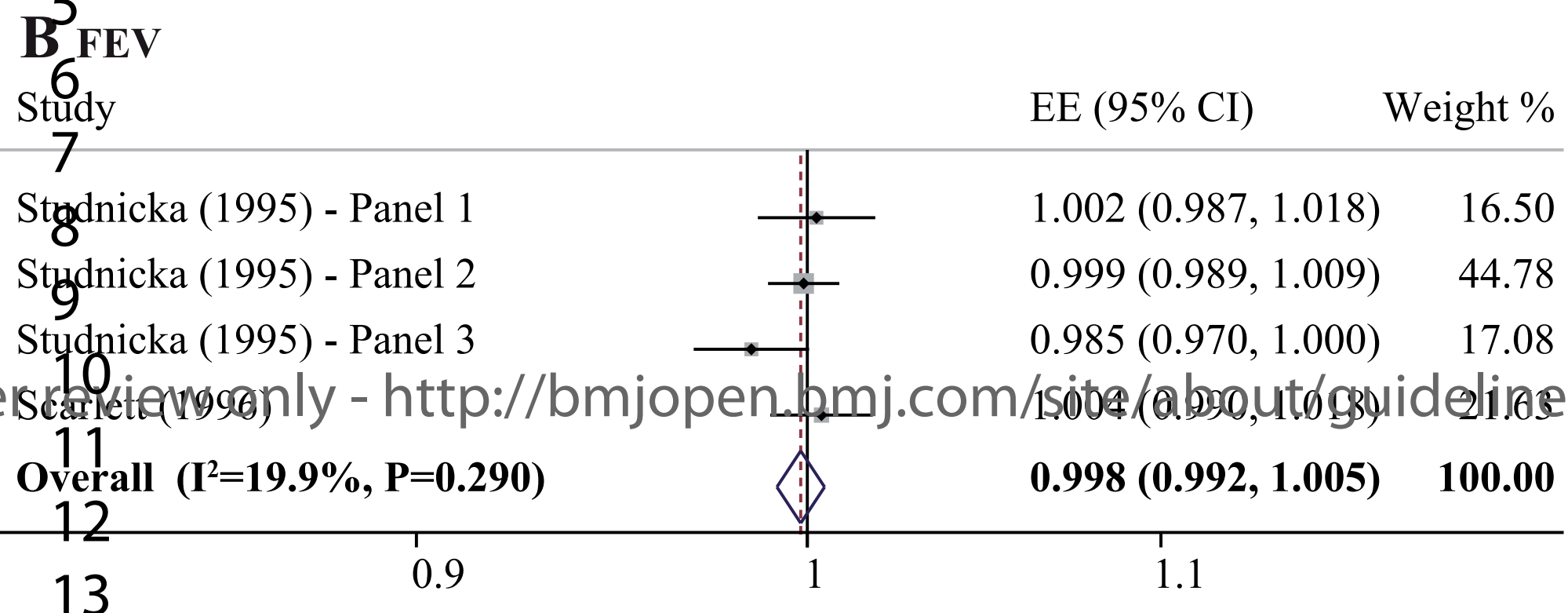
Ross et al. 2002		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 67.8%. "Two families withdrew early in the study period, and a number of participants either withdrew later in the study or failed to provide the requested daily health records … The 2 primary reasons stated for withdrawal from the study were a lack of time or interest in participating, or a move from the study area." Partly missing symptom data. "The last few days of data were excluded because of the small number of remaining participants."
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified

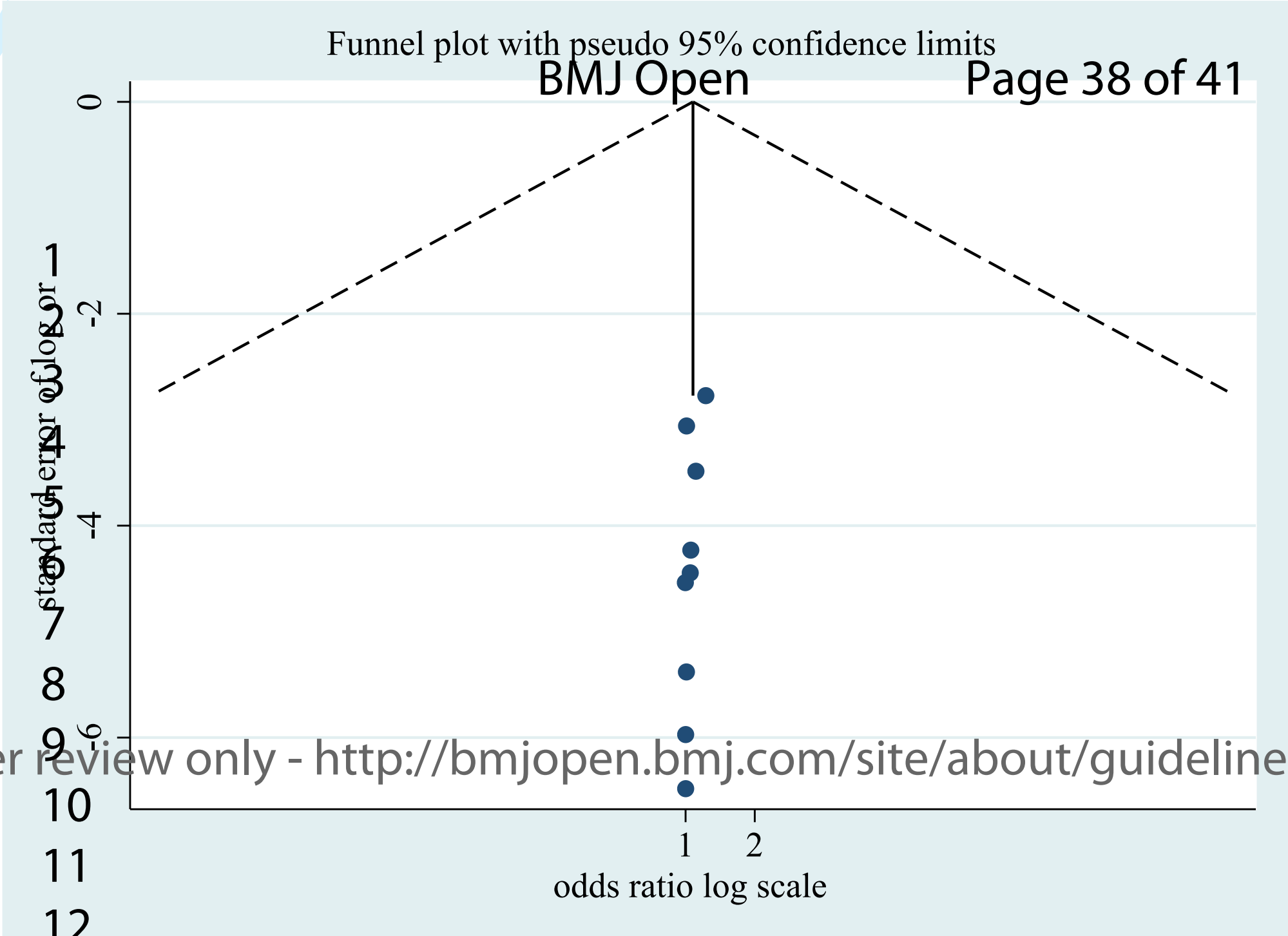
Scarlett et al. 1996		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk to high risk	Follow-up rate was 100%
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	High risk	Not feasible asthma medication data. "Children on medication for asthma were asked whether they had taken any medication that day. Unfortunately, the quality of these data were

		poor and so they were not used in the analysis. At worst this would bias the regression coefficients towards the null value."

Studnicka et al. 1995		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Not applicable	Epidemiologic study design
Allocation concealment (selection bias)	Not applicable	Epidemiologic study design
Blinding (performance bias and detection bias)	Not applicable	Epidemiologic study design
Incomplete outcome data (attrition bias)	Low risk	Follow-up rate was 88.7%; "For three, five, and seven children, respectively, permission was denied (for the 1st, 2nd, and 3rd panel). For Panel 3, two children were not able to perform reproducible spirometry."
Selective reporting (reporting bias)	Unclear	Not enough information to make a clear judgement
Other bias	Low risk	None were identified







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.	2
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
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.	4
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	9, FIG1
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.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	study protocol
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.	14
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
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.	9

PRISMA 2009 Checklist

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).	14
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.	10
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.	Table 1
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).	Table 1
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.	FIG2-FIG3, Suppl Fig1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	FIG2-FIG3, Suppl Fig1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
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).	14
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).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
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.	18

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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