

Is exposure to pollen a risk factor for moderate and severe asthma exacerbations?

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Abstract

Limited number of studies have focused on the impact of pollen exposure on asthma. As a part of the EAACI Guidelines on Environment Science, this first systematic review on the relationship of pollen exposure to asthma exacerbations aimed to bridge this knowledge gap in view of implementing recommendations of prevention. We searched electronic iPubMed, Embase, and Web of Science databases using a set of MeSH terms and related synonyms and identified 73 eligible studies that were included for systemic review. When possible, meta-analyses were conducted. Overall meta-analysis suggests that outdoor pollen exposure may have an effect on asthma exacerbation, but caution is needed due to the low number of studies and their heterogeneity. The strongest associations were found between asthma attacks, asthma-related ED admissions or hospitalizations, and an increase in grass pollen concentration in the previous 2-day overall in children aged less than 18 years of age. Tree pollen may increase asthma-related ED visits or admissions lagged up to 7-day overall in individuals younger than 18 years. Rare data show that among subjects under 18 years of age, an exposure to grass pollen lagged up to 3 days may lower lung function. Further research considering effect modifiers of pollen sensitization, hay fever, asthma, air pollution, green spaces, and pre-existing medications is urgently warranted to better evaluate the impacts of pollen on asthma exacerbation. Preventive measures in relation to pollen exposure should be integrated in asthma control as pollen increase continues due to climate change.

KEY WORDS

aerobiology, asthma, pollen

1 | INTRODUCTION

Worldwide data provide compelling evidence that the prevalences of asthma and allergic rhinitis have increased in the past decades. It is estimated that, worldwide, up to 20% of all age groups have asthma, and around 20% have allergic rhinitis. In Europe, at least 70 million people suffer from asthma¹ and 100 million from allergic rhinitis,² which are undiagnosed.

Pollen is one of the main risk factors for the development and the aggravation of allergic rhinitis^{1,2} and more recently has been associated also with asthma.³ Pollen rhinitis and asthma are assumed to increase along with their socioeconomic impact⁴ as pollen aeroallergens and allergenicity are influenced by climate, humidity, temperature, and air pollution.⁵⁻⁸

Overall, sparse studies have focused on the links between pollen exposure and asthma events. As a part of the EAACI Guidelines

on Environment Science, this paper aimed to bridge this knowledge gap by providing the first systematic review and metanalyses targeting the question on the relationship between pollen exposure and asthma exacerbation.

2 | STATE OF ART

2.1 | What is known about allergenic pollen?

Less than 100 species of pollen-producing plants cause allergy. Anemophilous plants are wind-pollinated, the airborne pollen being a good indicator of flowering phenology.⁹ The pollen wall, the intine, and the exine contain considerable numbers of proteins with different functions, and some of them are focused on sexual reproduction.^{10,11}

When pollen impact moist surfaces, for example, in the nasal mucosa or in the eyes, some released proteins induce allergic reaction, that is, rhinitis or conjunctivitis, respectively, in persons sensitized to pollen.¹¹ Here, we are referring to allergenic proteins, that is, allergens. These allergens are released upon contact with the mucosa, but they or their by-products (submicronic particles) can also be transported in microaerosols that can penetrate the lower respiratory tract causing asthma. The most relevant is presented in Table 1. Besides, the pollen matrix contains a plethora of low-molecular-weight compounds, such toll-like receptor ligands, lipid mediators, and adenosine, which are co-released with the allergen upon contact with human tissues and act as adjuvants in the allergic sensitization process¹⁷⁻²¹ or aggravate immune responses toward the allergenic proteins.²² Whereas airborne pollen is usually related to flowering phenology in anemophilous plants, aeroallergens are not always related to airborne pollen concentrations. Allergen release from pollen may also occur under specific, isolated events, that is, under high humidity before thunderstorm episodes or in interaction with pollutants, causing an occasional discrepancy between aeroallergen and airborne pollen. Allergens on submicronic particles or free allergens are especially subject to long-distance transport as they remain airborne for longer time periods.^{22,23} Plants under stress processes or extreme situations respond with a decrease in flowering, and therefore with lower pollen concentration, but producing more allergens as a strategy to ensure fertilization, and vice versa. The major pollen allergens are described in Table S1. It has been observed when considering some major allergens from different plants: olive pollen and *Ole e 1*,^{22,24} grass pollen and *Phl p 5*,²⁵ *Urticaceae* pollen, when comparing with *Parietaria major* allergens (*Par j 1* and *Par j*),²⁶ and for *Cupressaceae* pollen and *Cup a 1*.²⁷ Another important consideration is cross-reaction between close lineages, that is, in the *Oleaceae* family, the ash, olive, and privet with *Ole e 1* as major allergen²⁸ or in the *Betulaceae* family, the alder, birch and hornbeam with *Bet v 1* major allergen^{29,30} among others. There is also an interaction with poor air quality, especially air pollutants.³¹ Ozone, nitrogen dioxide (NO_2), and particulate matter (PM) have the biggest influence on the presence of allergens, although with a complex influence during sporadic episodes. Some aeroallergens come from pollen of ornamental trees in the urban spaces, for example, from cypress, ash, birch, olive, and privet. For this reason, a good design on urban green species is very essential. The Index of Urban Green Zone Allergenicity (IUGZA)³² offers information on allergenic risk of species to estimate the allergenic potential of urban green spaces. Some papers have defined the allergenicity index in urban spaces at local level³³ or at regional level, for example, in the Mediterranean basin.³⁴ These studies present recommendations for urban green species design, for example, support the biodiversity, avoiding the massive use of individuals of the same species with significant increase in pollen concentrations in the air; to avoid the use of allergenic allochthonous species; in the case of allergenic dioecious species to avoid planting of male trees; and an adequate management and maintenance of green areas.

2.2 | What is known about occupational pollen exposure?

Few observations exist on occupational pollen exposure and related allergy. Most were conducted in small populations working in heterogeneous settings. They report the existence of allergic sensitization and pollen allergy including asthma. Table S2 shows plants described as causative agents of occupational asthma.

Workers in vegetable plant gardening and crop farming develop occupational allergic respiratory disease due to pollen as reported in epidemiological studies and case reports.³⁵ Allergy to sunflower pollen arises from handling sunflowers, living near plantations during harvesting operations, or working in sunflower processing factories. A study of 102 factory workers showed a high prevalence (23.5%) of sensitization to sunflower (*Helianthus annuus*) and impaired lung function.³⁶ An increased risk of allergic symptoms was associated with employment duration. Similarly, 50 saffron flower-exposed workers revealed that 16% had nasal-, 6% bronchial-, and 8% cutaneous symptoms.³⁷ There were 6% sensitized to saffron pollen and stamen proteins. Furthermore, among 237 general allergic patients, 10 (4%) were sensitized to saffron. A study of 54 workers involved in classical plant breeding of broccoli and cauliflower, 44% reported work-related allergic symptoms and all but one were sensitized to pollen.³⁸ One-third developed symptoms within 2 years of exposure and atopy was identified as a risk factor. Occupational pollinosis has also been reported in commercial gardeners exposed to Solanaceae family pollen from paprika, tomato, eggplant, and potato.³⁹ In addition, occupational asthma in an agricultural worker harvesting asparagus⁴⁰ and sugar beet pollen allergy in a plant breeding laboratory, seed nursery, greenhouse, and processing plant has also been reported.⁴⁰ Pollen allergens of Poaceae family of grasses include many cereal species and are a major cause of pollinosis globally. Although sensitization prevalence patterns in common grass and cereal pollen are comparable due to high cross-reactivity, true cereal sensitization occurs in farmers and field workers or individuals living near cereal fields.⁴¹ Occupational allergy has been reported to wheat, rye, barley, oats, sorghum, rice, and maize (corn) pollen.³⁵ The allergen profilin (*Hel a 2*) from sunflower has a high degree of cross-reactivity with profilins from other Compositae plants.⁴² A significant degree of cross-reactivity also occurs between saffron and *Lolium*, *Salsola*, or *Olea*.³⁷ Cross-reactivity was also observed between paprika and tomato pollen-sensitized workers.⁴³ Two occupational allergens *Beta v 1* and *Beta v 2* in sugar beet pollen (*Beta vulgaris*) showed sequence similarity with other allergens from *Chenopodium*.⁴⁴ Various allergens have been identified in cereal pollens from wheat (*Tri a 12*), rye (*Sec c 1*, *Sec c 5*), barley (*Hor v 16*), sorghum (*Sor h 1*, *Sor h 2*), rice (*Ory s 1*), and maize (*Zea m 1*, *Zea m 12*, and *Zea m 14*).³⁵ Pollen-food syndromes have also been reported in occupationally exposed individuals. Immunoglobulin E (IgE) reactivity to multiple food allergens, birch, and mugwort pollens, as well as a variety of plant profilins has been demonstrated. The cross-reactive allergens include profilins, lipid transfer proteins, and high-molecular-weight allergens and/or glycoallergens.⁴⁵

TABLE 1 Severe asthma exacerbation related to total pollen exposure in the general population (adjusted results).

Study ID	Age	Outcome Definition	Exposure			Effect Estimate		
			Total pollen concentration (pollen or grains/m ³)	Lag	OR	EE	95% CI	
Mazeng (2017) ¹²	3-99 years	Asthma-related ED visits	>0 grains/m ³	0		0.95	0.79	1.16
Hanigan (2007) ¹³	All ages	Asthma-related ED admissions	50%-75% (ref 0%-50%)*	0		-28.12	-54.99	14.78
Darrow (2012)	60+	Asthma-related ED visits	75%-90% (ref 0%-50%)*	1		9.35	-32.21	76.37
Darrow (2012)	>18 years	Asthma-related ED visits	90%-100% (ref 0%-50%)*	3-day moving average	RR	41.42	-20.94	153
Gonzalez-Barcala (2013) ¹⁴	All ages, Mean (SD): 52.1 (24.8)	Asthma-related ED admissions	2nd quartile versus 1st quartile	2	RR male	0.99	0.82	1.20
			Spring		RR female	1.02	0.88	1.18
			Summer	3	RR male	1.01	0.83	1.22
Guilbert (2018)	>60 years	Asthma hospitalization	Interquartile range increase=12 grains/m ³	Cumulative 0-6	RR female	0.98	0.84	1.13
			3rd quartile versus 1st quartile	2	RR male	0.88	0.68	1.14
					RR female	1.16	0.95	1.41
				3	RR male	0.99	0.77	1.26
					RR female	1.08	0.89	1.31
				4th quartile versus 1st quartile	RR male	0.98	0.71	1.35
					RR female	1.11	0.87	1.41
					RR male	1.06	0.78	1.43
					RR female	1.17	0.93	1.48
Chen (2016) ¹⁵	All ages	Asthma-related ED admissions	10-unit increase	Distributed lag	RaR	1.010	1.001	1.019
				Moving average	RR female	1.013	1.004	1.022
Newsom 1998 ¹⁶	All ages	Asthma-related ED admissions	0-501.6 grains/m ³ /day	5-day moving average	RR	6.23	1.29	26.67

Abbreviations: 95% CI, 95% confidence interval; ED, emergency department, *mean (50th centile, 90th centile) grains/m³ of total pollen: 15.4 (13.3, 31.1), †mean (IQR) grains/m³ of total pollen: 52 (13-142), *geometric mean (SD) grains/m³ of total pollen: 4.8 (3.2); OR, odds ratio; RR, relative risk.

Horticulturists and fruit tree workers can develop occupational respiratory allergic diseases (rhinoconjunctivitis and asthma).³⁵ Teranishi et al⁴⁶ conducted an epidemiological study on pollinosis among Japanese pear orchard workers and found positive skin tests (SPT) in 5.4% of them. Jiang et al⁴⁷ described a case of occupational allergy to peach (*Prunus persica*) pollen in an artificial pollination worker. Victorio-Puche et al⁴⁸ reported occupational rhinitis and/or asthma among 21 peach orchard workers, demonstrating SPT-positive sensitization to this pollen. In addition, sensitization to peach tree pollen is highly prevalent in regions where this tree is widely cultivated, affecting more than 20% of the exposed population,⁴⁸ and can also affect children living in these areas.⁴⁹ The peach tree acts as a source of airborne allergens from pollen or other tree structures (leaves and branches), giving rise to occupational allergy.⁵⁰ *Pru p 9* (PR-1a protein) has been identified as a relevant peach pollen allergen⁵¹ that is involved in the induction of occupational rhinitis and asthma.⁴⁸ In addition, lipid transfer proteins (LTP) like *Pru p 3*, one of the diagnostic markers for Rosaceae-related allergies, and profilin (*Pru p 4*), which have been identified in other peach structures, can also act as aeroallergens.^{52,53} The presence of allergens in pollen from Rosaceae fruit trees has been documented in apple (a protein homologous to *Bet v 1*)⁵⁴ and in pollen from different Rosaceae fruit trees (*Mal d 1*, *Mal d 3*).⁵⁵

Pollens out of all plant-derived allergens most frequently cause hypersensitivity and symptoms.⁵⁶ Bell pepper pollen from plants cultivated in greenhouses are well-documented cause of occupational allergy,⁵⁷ considered as the most important one among subjects with allergic symptoms, significantly impairing QoL.⁵⁸ Work-related respiratory symptoms were found in 53.8% of 472 workers, with IgE-mediated allergy to bell pepper pollen documented in 35.4%.⁵⁸ Follow-up observation of 280 out of these workers revealed cumulative incidences for sensitization to bell pepper pollen, work-related rhinitis, and asthma symptoms to be 9%, 19%, and 8%, respectively, during the 8-year observation.⁵⁹ In the same study, atopy and smoking have been identified as risk factors of work-related symptoms. Moreover, the same research group in an intervention study presented that the interference of bees in bell pepper greenhouses significantly reduced the pollen amount which was associated with less work-related rhinitis symptoms.⁶⁰ It was also demonstrated that allergens of sweet bell pepper pollen have no or limited cross-reactivity with common pollen allergens; thus, this sensitization is not the consequence of primary sensitization to common pollen allergens.⁶¹ Beans, like castor beans, coffee beans, and soybeans as well as locust bean gum have been reported as potential occupational allergens.^{62,63} Green coffee beans display higher allergenic potential than green or roasted beans; however, all of them may cause occupational asthma.⁶³ Dust from raw coffee beans may elicit skin, ocular, and respiratory allergic reactions in up to 50% of exposed workers.⁶⁴ *Cof a 1* (chitinase) (34), *Cof a 2*, and *Cof a 3* (metallothioneins) have been identified as allergens causing work-related allergy due coffee beans.⁶⁵ Investigation of the incidence of allergy to pollen of ornamental plants revealed the incidence among flower growers reaching 52%.⁶⁶

Reports on occupational allergy to flowers usually concern gardeners, greenhouse workers, and florists. The handling, smelling, and managing of flowers may cause rhinoconjunctivitis, asthma, urticaria, and contact dermatitis. Greenhouse flower and or ornamental plant growers are exposed to a wide range of flowers and molds. The cultivation of greenhouse flowers and/or ornamental plants emerged as a significant risk factor for bronchial asthma in the European Farmers' Study.⁶⁷ Positive SPT responses to ornamental plants among flower growers have been found in up to 52% of workers.⁶⁶ The prevalence of work-related asthma-like symptoms was reported in 14.1% of workers,⁶⁷ and occupational asthma in 8%.⁶⁷ The most prominent risk factors reported are work intensity, work duration, workplace size, atopy, and family history of respiratory and allergic problems.⁶⁸ The most common sensitizers described among these workers are Chrysanthemum flowers. However, allergy to Liliaceae, mostly to tulips, hyacinths, lilies, and crocuses, has often been reported. Nevertheless, there are cases of occupational sensitization to flowers of other families, such as rose, spate flowers, primulas, weeping fig, or *Stephanotis floribunda*, the Madagascar jasmine.

2.3 | What is known about pollen allergens?

Many pollen allergens have been described over the last decades. Most of them belong to well-known families of proteins, but others constitute unique allergenic families. In the current clinical practice, the introduction of diagnostics tools able to detect pollen allergens in sensitized allergic individuals has had a relevant impact on improving diagnosis, stratifying allergic patients, and predicting intervention outcomes. The major pollen allergens are described in Table S1.

2.4 | Which are the modifiers of pollen concentrations?

Climate change has a multitude of impacts on allergenic plant productivity and change plant distributions.⁶⁹⁻⁷⁸ Furthermore, increases in air pollution related to climate change can affect plant physiology resulting in more allergenic pollen.⁷⁹ All these factors directly impact the symptoms of allergy sufferers or can lead to increased sensitization rates.^{80,81} Pollen season trend studies have shown that the intensity has increased for tree species while for grasses it has either remained unchanged or even decreased.^{76,82} In addition, the season tends to start, and generally end, earlier for the tree species, while results are less clear for grasses and other summer flowering taxa but there are indications for longer seasons.⁸³⁻⁸⁶ In addition to climate change, the human impact on vegetation cover and composition, for example through increasing urbanization, agricultural practices, or planting of ornamental trees in urban green space, is another important factor influencing the intensity of the pollen season.⁸⁷⁻⁸⁹ Lastly, pollen asthma can be triggered by a particular type of thunderstorm when there are high amounts of bioaerosols in

the air including pollen or molds.^{90,91} Particles containing pollen allergens are released and are so small that they can be breathed into the lungs and trigger asthma.

2.5 | What is known about therapy and prevention for pollen asthma?

Therapy available for pollen allergy and asthma consists of both allergen avoidance and environmental controls together with pharmacologic management and allergen immunotherapy.⁹²

At the level of environmental control, what can be done at a personal level is to be aware of the levels of pollen and avoid going outdoors. However, measures to combat the effects of climate change is an approach that has to be taken at the national and international levels.

The pharmacological approach to allergic pollen rhinitis includes the use of oral antihistamines and intranasal corticosteroids, while for the control of pollen asthma, antileukotrienes and inhaled corticosteroids with or without long-acting β -agonists are recommended. Such treatments can be used in the pollen season but should be started at least 1 month before the season starts. With climate change, the pollen season may be more prolonged needing longer periods of treatment. Biologic therapies such as anti-IgE antibody, omalizumab, are effective against allergen-induced asthma and when used prophylactically before the peak pollen season can reduce autumnal asthma exacerbations caused by viral infections. Other therapies such as anti-IL5/IL5R α receptor or anti-IL4R α antibodies may also be considered with evidence of Type 2 inflammation. Subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) against pollen is strongly recommended for seasonal allergic rhinitis induced by pollen.⁹³ For pollen-induced asthma, SCIT reduces asthma symptoms and asthma medications, with lower evidence for SLIT.⁹⁴ However, it is a key question whether the changes in pollen allergenicity will affect the efficacy of immunotherapy.

3 | METHODS

3.1 | Systematic review (SR) and metanalysis (MA)

The systematic review (SR) was developed following the Cochrane Handbook for Systematic Reviews of Interventions⁹⁵ and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement⁹⁶ to rescue papers from patients or general population studies reporting about the relationship between pollen exposure and asthma exacerbations. We used electronic algorithms with a combination of controlled vocabulary and search terms in the following databases: (i) MEDLINE; (ii) EMBASE; and (iii) Web of Science Core.

The eligible definition of pollen exposure includes availability of mean daily airborne pollen grains per cubic meter of air (pollen grains/m³) of distinct types, including birch, grass, ragweed, mugwort, olive, elm, hazel/alder, cypress, and plane. Asthma

exacerbations were defined either directly in terms of exacerbations (Moderate = temporary change in treatment (rescue or controller), Severe = Emergency Department (ED)/hospitalization with systemic steroid use or systemic steroid for at least 3 days) and asthma symptoms/well days or indirectly through asthma medication, lung function, quality of life, and mortality.

Estimates of effect sizes included odds ratio, relative risk, mean change in risk, scaled beta coefficient (linear regression), and correlation coefficient and were presented if possible for an increase per grains/m³ of pollen. Analyses were stratified according to age (<12, 12–18, \geq 18 years) and asthma severity (mild, moderate, and severe) and other relevant asthma exacerbation outcomes for which adjusted estimates were available. When possible, we conducted a formal quantitative synthesis (meta-analysis) using linear and day lag using mixed effects models that assume the presence of a random effect, by the DerSimonian–Laird estimator method to calculate the variance parameter.⁹⁷

We judged the magnitude of heterogeneity using the Higgins' I^2 statistic (0%–40%: low, 30%–60%: moderate, 50%–90%: substantial, and 75%–100%: considerable). Additionally, we visually inspected the meta-analysis' forest plots for consistency, given that I^2 statistics might be artificially inflated when effect estimates from primary studies are very precise. The risk of bias in non-randomized studies of exposure (ROBINS-E) tool was used. This tool was developed by building upon tools for risk of bias assessment of randomized trials, diagnostic test accuracy studies, and observational studies of interventions. The seven items included in ROBINS-E are as follows: (1) Bias due to confounding, (2) Bias in selection of participants, (3) Bias in classification of exposures, (4) Bias due to departures from intended exposures, (5) Bias due to missing data, (6) Bias in measurement of outcomes, and (7) Bias in selection of reported results. Judgments for each risk of bias (RoB) item can be: "Low RoB," "Moderate RoB," "Serious RoB," or "Critical RoB".⁹⁸ For meta-analyses with at least 10 included studies, we assessed publication bias by visual inspection of Begg's funnel plot, and statistically, using Egger's test for small study effects (funnel plot asymmetry). We reported a summary of the main findings using tabulated summaries (evidence profiles), and forest plots graphs. We rated the certainty of evidence across each outcome as high, moderate, low, or very low, taking into consideration risk of bias, imprecision, inconsistency, indirectness, and publication bias for each outcome with the GRADE approach.⁹⁹

4 | RESULTS

4.1 | Systematic review and meta-analyses

We identified 3244 individual records through our search conditions and assessed 270 full texts respecting eligibility criteria and finally included 73 studies relating objective assessments of pollen and severe asthma exacerbation (Figure 1).

The obtained studies were heterogeneous in terms of study designs, selected populations, age locations, and lags between pollen

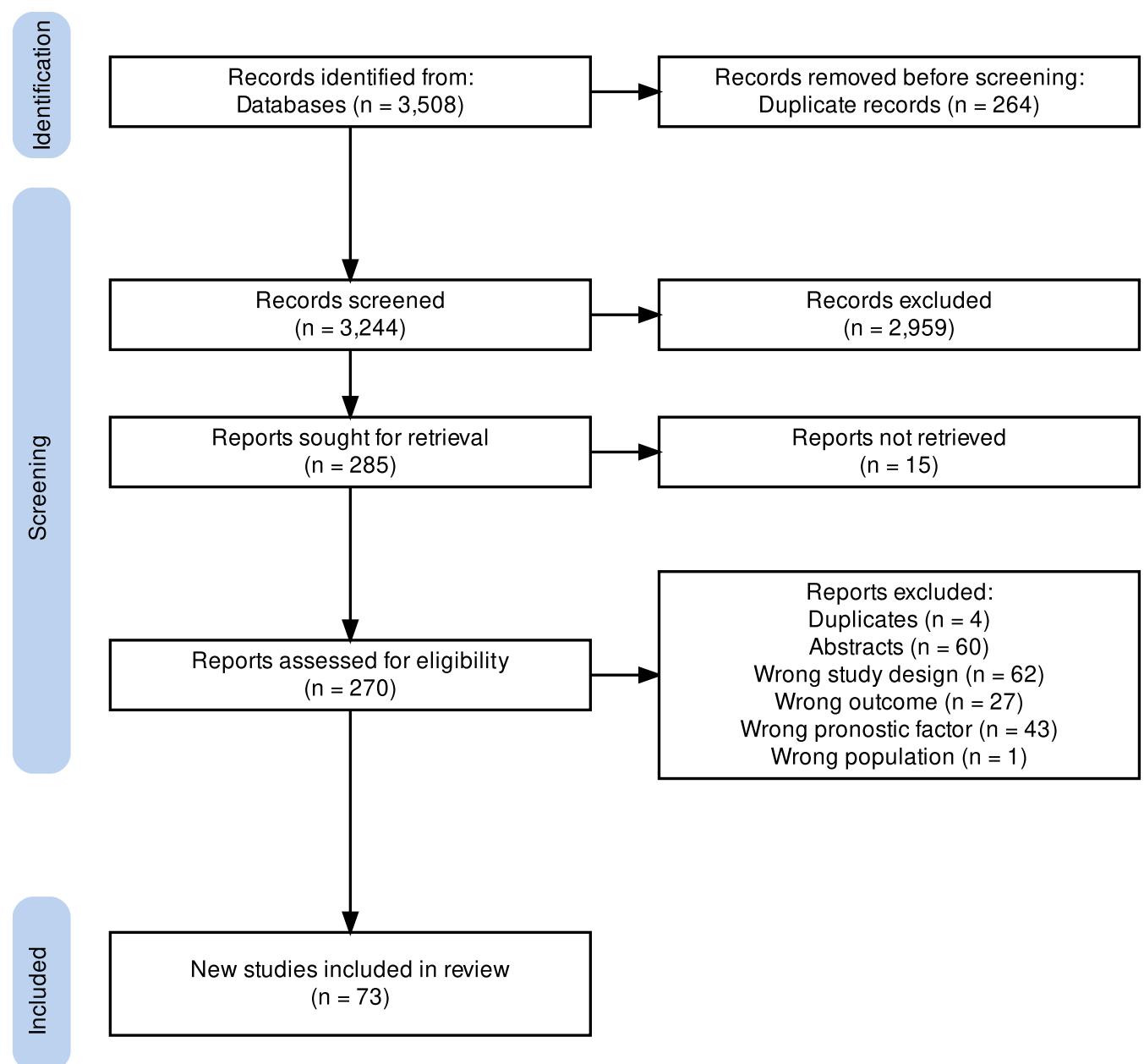


FIGURE 1 Identification of studies allowing to assess the relationship between objective assessments of pollen and severe asthma exacerbation indicators.

assessment and asthma exacerbation. Most studies did not account for potential confounders in their results.

Selected studies were distributed as follows:

- 26 studies (longitudinal (n=18), time series (n=5), case-crossover (n=1), case-control (n=1), and cross-sectional (n=1)) on the impact of total pollen concentrations
- 30 studies (time series (n=9), longitudinal (n=12), case-crossover (n=5), case-control (n=2), and cross-sectional (n=2)) on grass pollen.

- 19 studies (time series (n=6), longitudinal (n=6), case-crossover (n=5), and cross-sectional (n=1)) on tree pollen concentrations.
- One time series study on alder pollen and one time series study on hazel pollen.
- Six studies (time series (n=4), case-crossover (n=1), and longitudinal (n=1)) on birch pollen concentrations.
- Seven studies (time series (n=3), case-crossover (n=3), and case-control study (n=1)) on cypress pollen concentrations.
- Three studies (time series (n=2) and case-crossover (n=1)) on elm pollen.

- Two time series analysis on mugwort pollen.
- Three studies (time series ($n=2$) and longitudinal study ($n=1$) on olive pollen.
- Nine studies (longitudinal ($n=5$), case-crossover ($n=3$), and time series ($n=1$) on ragweed pollen.
- Twelve studies (longitudinal ($n=6$), time series ($n=5$), and case-control ($n=1$)) assessed the impact of pollen during thunderstorms on severe asthma exacerbations, three examined total pollen concentrations, eight only grass pollen, and one examined grass and birch pollen.

We present here in detail the results of the systematic review for severe asthma exacerbation, moderate asthma exacerbation, asthma control and well days, quality of life, lung function, severe asthma symptoms, and mortality in the case of total pollen, grass pollen, weed pollen, and tree pollen.

Although many studies reported estimated effects, conducting meta-analysis for all outcomes was not possible due to substantial heterogeneity related to the pollen species, participant's age, method of analysis used to estimate the effect size, and the differences in lagged day effects considered for the analysis. Effect estimates were not standardized because a dose-response relationship in which increasing levels of exposure are associated with either an increasing or a decreasing risk of the outcome was not observed. However, we conducted a meta-analysis for severe asthma exacerbations associated with an increase in grass pollen, tree pollen, cypress, and ragweed exposure.

4.2 | Severe asthma exacerbation

Overall, the relationship of pollen concentrations to severe asthma exacerbation was the most dealt with in the literature. Results are contrasting but support the hypothesis of an impact of pollen concentrations on severe asthma exacerbations.

4.2.1 | Total pollen

The majority of studies reported a significant positive association (asthma events increase with pollen increase, i.e., odds ratio or relative risk higher than 1) between asthma-related hospitalizations and total pollen concentrations at different lags (Table 1). However, some relationships were imprecise and six studies did not account for potential confounders.

4.2.2 | Grass pollen

Eight studies in individuals under 18 years of age reported the association between asthma attacks or asthma-related ED admissions, visits or hospitalizations, and the concentrations of grass pollen on the same day (lag 0) (Table 2). Five of these reported a positive, and three a negative association. Seven studies (four

case-crossover, one time series analysis, and two longitudinal studies) reported the association between asthma exacerbations or asthma-related ED visits or hospitalizations with concentrations of pollen lagged up to 6 days. All but four studies showed a positive, though imprecise association with a quantified increase in grass pollen (Table 2). A quantitative synthesis—meta-analysis—of three studies that measured this outcome^{104,110,111} showed an inverse association for an increase of 0–50 grains/m³ of grass pollen for studies that measured this outcome on the same day (lag 0) in patients under 18 years of age (OR = 0.99, 95% CI: 0.95, 1.03) (Figure 2).

A positive association (OR = 1.0032, 95% CI: 0.9960, 1.0105) between severe asthma exacerbation and an increase in grass pollen concentrations from >0 to 50 pollen grains/m³ was found at lag 0 to 2 for patients under 18 years of age in a metanalysis of five studies^{101,102,104,105,107} (Figure 3).

The existence of a positive although imprecise association was confirmed among patients over 18 years of age for various lags (Table 3) as well as among patients drawn from the general population level (Table 4). A meta-analysis for studies that measured this outcome between lag 2 and 4 (Figure 4) found a positive association between increase in grass pollen concentrations from >0 to 50 grains/m³ and severe asthma exacerbation at the general population level (OR = 1.02, 95% CI: 1.01, 1.03).

In two studies without specified age, an association between grass pollen concentrations and asthma-related ED visits or admissions on the same day (lag 0) was observed.^{120,121} A longitudinal study¹²² showed two seasonal peaks that could be correlated with outdoor grass/weed pollen in Kolkata. Similarly, through a retrospective chart review, an increased risk of asthma-related ED visits or admissions was observed for a rise of 1 grain/m³ of grass pollen in the concentration range of 10 to 28 grains/m³. For the other two ranges (0–10 and 58–53 grains/m³), there was a negative but imprecise association. Both studies had considered also air pollution.

4.2.3 | Weed pollen

In the case of mugwort pollen, Guilbert 2018 reported the association between asthma-related hospitalizations and an increase of 1 grain/m³ of mugwort pollen with a 0- to 6-day cumulative lag.¹⁰⁸ Results were stratified by age, with a positive though imprecise association for participants aged 0–59, and a negative though imprecise association for participants over 60 years of age. Tobias (2003) examined the association between asthma-related hospitalizations and 2.1 grains/m³ of mugwort pollen lagged 1 day in the general population and reported a positive though imprecise association.¹¹⁵ In the case of ragweed, one time series analysis¹²² examined the association between asthma-related ED visits and a 10-grain increase in ragweed pollen concentrations in lags 0 to 6 under 18 years of age. No trend was observed, with a positive though imprecise association in lags 0 and 1, and a negative though imprecise association in lags 3, 5, and 6. One case-crossover

TABLE 2 Severe asthma exacerbation related to grass pollen exposure in patients under 18 years of age (adjusted results).

Study ID	Age	Outcome definition	Exposure			Effect estimate (EE)		
			Grass pollen concentration (pollen or grains/m ³)	Lag	EE	95% CI		
Mazenq (2017) ¹²	3–18 years	Asthma-related ED visits	Not specified	0	OR	0.99	0.99	0.01
Newsom (1997) ¹⁰⁰	<14 years	Asthma-related ED admissions	>50 grains/m ³	0	RR	1.16	1.04	1.31
Batra (2021) ¹⁰¹	2–17 years	Asthma attacks	34 grains/m ³	0	OR	0.999	0.96	1.011
Shrestha (2017) ¹⁰²	2–18 years	Asthma hospitalization	75th to 90th percentile increase (geometric mean (SD) 4.8 (3.2))	2	OR	1.017	0.999	1.035
Khot (1998) ¹⁰³	18 mo–16 years	Asthma-related ED admissions	112–133 grains/m ³	Cumulative lag	1.037	1.005	1.070	
Lee (2019) ¹⁰⁴	0–2 years	Asthma-related ED visits	Increment 1 grain/m ³	1	Contribution to the regression analysis	1.005	0.995	1.015
Mazenq (2017)	2–5 years	Asthma-related ED visits	Not specified	2	OR	5.4	d.f. 1	
De Roos (2020) ¹⁰⁵	6–17 years	Asthma exacerbation	>0 to 8.5 grains/m ³	Cumulative 0–2	OR	1.001	0.995	1.006
	0–2 years		>8.5 to 23.2 grains/m ³	Cumulative 0–2		1.013	0.997	1.030
	2–5 years		>23.2 to 33.8 grains/m ³	Cumulative 0–2		1.04	0.99	1.10
	6–17 years		>33.8 to 51.8 grains/m ³	Cumulative 0–2		0.96	0.90	0.01
Newsom (1997)	<14 years	Asthma-related ED admissions	>51.8 grains/m ³	Cumulative 0–2	RR	1.04	0.88	0.01
Witonksy (2018) ¹⁰⁶	Pediatric	Asthma-related ED admissions	Full year	3-day moving average	Beta linear regression model	0.064	p=0.008	—
Khot (1998)	18 mo–16 years	Asthma-related ED admissions	Spring	1	Contribution to the regression analysis	-0.042	p=4.59	—
Gleason (2014) ¹⁰⁷	3–17 years	Asthma-related ED visits	10-unit increase	3-day average	OR	0.214	p=.000	—
Guilbert (2018) ¹⁰⁸	0–14 years	Asthma hospitalization	12 grains/m ³ (IQR)	Cumulative 0–6	Percentage change	5.2	-0.9	11.5
Erbas (2012) ¹⁰⁹	<15 years	Asthma-related ED visits						

Abbreviations: 95% CI, confidence interval at 95%; ED, emergency department; IQR, interquartile range increase; OR, odds ratio.

^aAsthma ED visits in children¹⁰

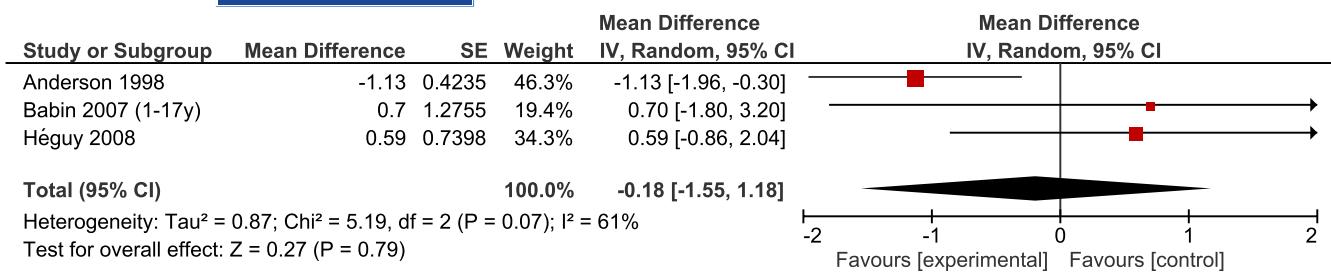


FIGURE 2 Severe asthma exacerbations associated with an increase of 0 to 50 pollen grains/m³ of grass pollen at lag 0 in patients under 18 years of age.

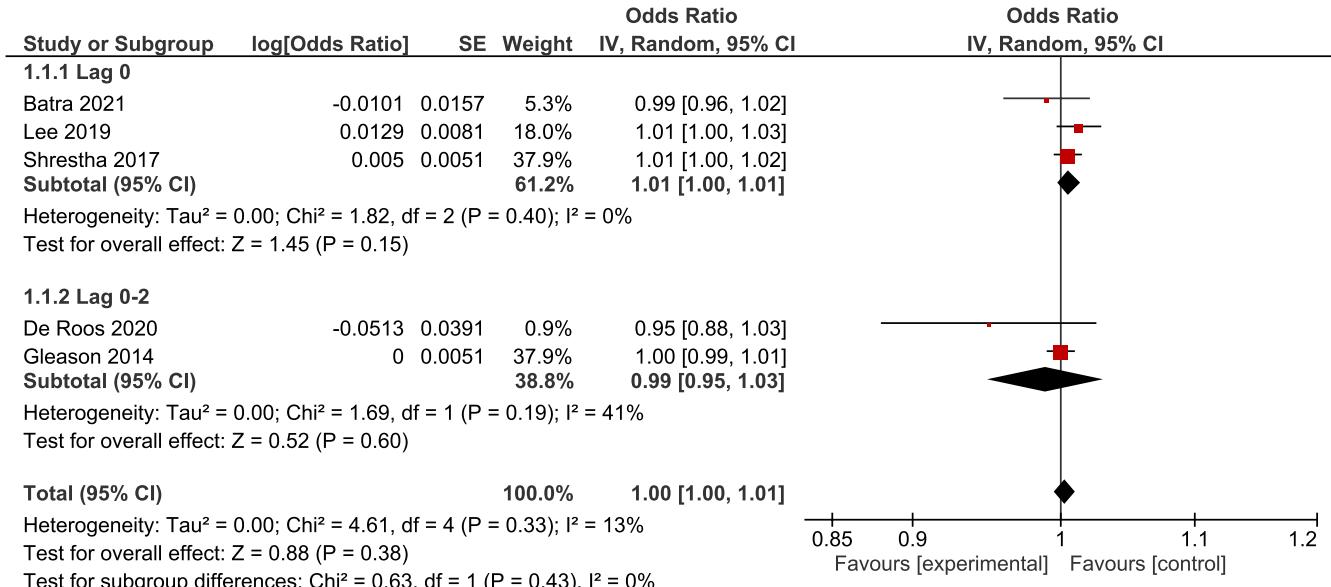


FIGURE 3 Severe asthma exacerbations associated with an increase of 0–50 pollen grains/m³ of grass pollen (lag 0–2) in patients under 18 years of age.

study¹⁰⁵ examined the association between asthma exacerbations and ragweed pollen concentrations in 0- to 2-day cumulative lag. A trend was observed to lower odds of asthma exacerbation with higher ragweed pollen concentrations. Similarly, another case-crossover study¹⁰⁷ reported a negative association with a 10-grain increase. The meta-analysis for studies that measured this outcome between lag 0 to 2 (Figure 5) showed no association between increase in ragweed pollen concentrations from >0 to 50 grains/m³ and severe asthma exacerbation in patients under 18 years (OR=0.97, 95% CI: 0.94, 1.01). Reversely, one longitudinal study¹²³ reported an association between asthma attacks and non-specified ragweed pollen concentrations lagged 2 days, which was positive only among male adults but no quantitative estimation was shown.

4.2.4 | Tree pollen

Four studies assessed the association between asthma exacerbations, ED visits or hospitalizations, and tree pollen concentrations on the same day (lag 0) in individuals under 18 years of age. Three

reported a positive association, while one reported a negative one (Table 5).

Two studies reported the association with asthma-related ED visits and tree pollen lagged 1 day. When lagged 2 days, Babin et al¹²⁴ reported a positive though imprecise association with a 100 grains/m³ increase, but a case-crossover study reported no association with higher concentrations (614–747 grains/m³)¹⁰¹ (Table 5). At lags 3 and 4, the two studies^{104,124} reported a positive but imprecise association (Table 5). Three case-crossover studies examined the association of asthma exacerbations, hospitalizations, or ED visits with tree pollen concentrations with either cumulative lags (0–2) or the 3-day average. Shrestha et al¹⁰² found a positive though not significant association with a non-specified concentration, while De Roos et al and Gleason et al^{105,107} found positive associations with concentrations from >0 to 537 grains/m³, and with a 10-unit increase, respectively. A longitudinal study which also assessed the 3-day average found a positive association during the full year and spring, though not during the summer.¹⁰⁶

No meta-analysis was conducted in the case of only two studies that measured this severe asthma exacerbation for tree pollen concentrations from >0 to 50 grains/m³ between lag 0 and 2 showing

TABLE 3 Severe asthma exacerbation related to grass pollen exposure in patients over 18 years of age (adjusted results).

Study ID	Age	Outcome definition	Lag	Exposure		Effect estimate (EE)	95% CI
				Grass pollen concentration (pollen or grains/m ³)	10-unit increase		
Anderson (1998) ¹¹⁰	>65 years	Asthma-related ED admissions	Increment 1 grain/m ³	0		-0.63	-2.69
Lee (2019) ¹⁰⁴	18–59 years	Asthma-related ED visits	NR	0		1.008	0.996
Darrow (2012) ¹¹¹	60+	Asthma-related ED visits	NR	1	RR	1.005	0.998
Witonsky (2018) ¹⁰⁶	>18 years	Asthma-related ED admissions	Full year	3-day moving average	RR	1.030	1.017
			Spring	3-day moving average	Beta linear regression model	0.163	p=.000
			Summer	Cumulative 0–6		0.043	p=.432
				Percentage Change		0.277	p=.000
Guilbert (2018) ¹⁰⁸	>60 years	Asthma hospitalization	12 grains/m ³ (IQR)			4.1	-2.1
							10.7

Abbreviations: 95% CI, confidence interval at 95%; ED, emergency department; IQR, interquartile range increase; RR, relative risk.

a positive significant association with in patients under 18 years (OR=1.19, 95% CI: 1.17, 1.21¹⁰⁷ and OR=1.02, 95% CI: 0.99, 1.04,¹⁰² respectively). When tree pollen concentrations increased >50 grains/m³, no association of a risk of severe asthma exacerbation was observed in the meta-analysis (OR=1.00, 95% CI: 0.99, 1.02) (Figure 5).

Only three studies examined the association between asthma-related ED visits or admissions and tree pollen concentrations in different lags in individuals aged >18 years. For an increment in 100 grains/m³ on the same day (lag 0), a time series analysis¹⁰⁴ reported a positive association. When assessing the 3-day moving average, a longitudinal study¹⁰⁶ reported a positive association during the full year and spring, though a negative association during the summer analysis.

Several studies reported the association between asthma-related ED visits or admissions with tree pollen concentrations in samples drawn from the general population. Results are contrasting and depend on the lag (Table 6). No meta-analysis was conducted for the two studies that measured between lag 0 and 3 in the general population the association between severe asthma exacerbation and any increase in tree pollen concentrations from >0 to 50 grains/m³. in the general population (OR=1.00, 95% CI: 0.99, 1.02¹¹¹ and OR=1.00, 95% CI: 0.97, 1.12¹¹⁷).

In the case of specific tree pollens, mostly positive associations were also found.

Only one time series analysis assessed the impact of alder pollen concentrations on asthma hospitalizations¹⁰⁸ for an increase of 9 grains/m³ of alder pollen with a 0- to 6-day cumulative lag. The association was positive though imprecise only for participants over 60 years of age. All the studies conducted in individuals under 18 years reported a positive association. Anderson et al¹¹⁰ reported a positive association between asthma-related ED admissions with a 10-unit increase in birch pollen lagged 2 days (Table 7). One case-crossover study¹⁰⁵ reported a positive association on 0- to 1-day cumulative lag with concentrations up to 175.7 grains/m³ with a peak between 23.8 and 45.5 grains/m³. One time series analysis¹⁰⁸ reported a positive association between asthma hospitalization and a 40 grains/m³ increase of birch pollen on 0- to 6-day cumulative lag. In individuals aged over 18 years, only one study out of the three that were conducted reported a positive association. A time series analysis¹⁰⁸ reported a positive association between a 40 grains/m³ increase and asthma hospitalizations with a 0- to 6-day cumulative lag (Table 7). On the contrary, one longitudinal study¹¹⁰ reported a negative though imprecise association between a 10-unit increase in birch pollen and same day (lag 0) asthma-related ED admissions (Table 7) and one study taking into account air pollution showed that the most significant risk for asthma hospitalization is associated with hornbeam pollen levels in the city of Zagreb.¹²⁶ At the general population level, three studies reported the association between asthma exacerbations and birch pollen concentrations in the general population. One time series analysis¹¹⁴ assessed the association between asthma-related ED admissions and birch pollen concentrations on the same day (lag 0), and observed a trend with an increased risk of

TABLE 4 Severe asthma exacerbation related to grass pollen exposure in the general population (adjusted results).

Study ID	Age	Outcome definition	Exposure			Effect estimate (EE)		
			Grass pollen concentration (pollen or grains/m ³)	Lag	Smooth term df (chi-square)	EE	95% CI	
Erbas (2007) ¹⁰⁹	All ages	Asthma hospitalization	Not specified	0		5.1	—	—
Newson (1997) ¹⁰⁰	>15 years	Asthma-related ED admissions	>50 grains/m ³	0	RR	1.47	1.32	1.64
Dales (2004)	All ages	Asthma-related ED visits	14 grains/m ³ increase	Cumulative 0–5	Percentage change	1.31	1.21	1.42
Lewis (2000) ¹¹²	>14 years	Asthma-related ED visits	50 grains/m ³	0	OR	2.1	1.4	3.3
Hanigan (2007) ¹³	All ages	Asthma-related ED admissions	IQR change in pollen load for linear responses	0	Percentage change in relative risk	0.77	-16.75	21.97
Anderson (1998) ¹¹⁰	All ages/ mean 35.1	Asthma-related ED admissions	10 unit increase	0	Percentage change	-1.16	-1.82	-0.5
	15–64 years			1		-0.073	-1.71	0.26
Celenza (1996) ¹¹³	>16 years	Asthma-related ED visits	1–28 grains/L	0	Percentage change	0.29	0.09	0.98
			29–74 grains/L	3		0.26	0.12	0.56
			>74 grains/L	4		0.18	0.07	0.49
			>10 grains/L increase	2		2.15	1.21	3.84
			>30 grains/L increase	0		0.83	0.42	1.67
			>10 grains/L fall	2		1.89	1.24	2.89
			>30 grains/L fall	0		2.50	1.36	4.59
Osborne (2017) ¹¹⁴	16–64 years	Asthma-related ED admissions	Increase from 0 to 104 grains/m ³	0	Percentage change	-6.18	-14.69	2.33
				1		-6.69	-16.19	2.82
				2		6.2	-3.28	15.69
				3		1.24	-7.67	10.15
				4		17.23	8.93	25.54
Darrow (2012)	All ages (0 to +18)	Asthma-related ED visits	10 grains/m ³	5	RR	14.11	6.22	22.01
Lee (2019)	All ages (0 to +60)	Asthma-related ED visits	Increment 1 grain/m ³	6	RR	5.95	-2.04	13.94
	>15 years			7		3.31	-4.21	10.83
	all ages		Medium ≥30 grains/m ³ & ≤49 grains/m ³	0	RaR	0.95	0.85	1.06
Sun (2016)	All ages (mean (SD)=32 (22))	Asthma-related ED visits	10 grains/m ³	3	RR	1.02	0.90	1.14
Lewis (2000)	>14 years	Asthma-related ED visits	High ≥50 grains/m ³ & ≤149 grains/m ³	0	OR	0.98	0.88	1.09

Study ID	Age	Outcome definition	Exposure			Effect estimate (EE)		
			Grass pollen concentration (pollen or grains/m ³)	Lag	Percentage change in pollen load for linear responses	EE	95% CI	
Hanigan (2007)	All ages	Asthma-related ED admissions	Interquartile range (IQR) change in pollen load for linear responses	3	Percentage change in relative risk	1.14	1.01	1.28
Lee (2019) ¹⁰⁴	All ages	Asthma-related ED visits	Very High ≥ 150 grains/m ³	0		0.72	0.59	0.87
Tobias (2003) ¹¹⁵	All ages	Asthma-related ED admissions	Increment 1 grain/m ³	3	RR	1.46	1.20	1.78
Tobias (2004) ¹¹⁶	All ages less than 14 more than 14	Asthma-related ED admissions	Variation of 98.4 grains/m ³	3	Percentage change in risk	17.1	3.2	32.8
Darrow (2012) ¹¹¹	All ages 0 to 18+	Asthma-related ED visits	p50-p75	3	Percentage change in risk	10.6	0.0	22.4
Witonksy (2018) ¹⁰⁶	All ages	Asthma-related ED admissions	p75-p90			19.4	5.6	35.1
Erbas (2007)	All ages	Asthma hospitalization Asthma-related ED visits	p90-p95			38.1	14.3	66.9
Sun (2016) ¹¹⁷	All ages mean (SD)= 32 (22)	Asthma-related ED visits	p95-p99			32.2	6.9	63.6
Dales (2004) ¹¹⁸	All ages younger and older than 13	Asthma hospitalization	p99-max	2	RR	78.7	34.6	137.2
Guilbert (2018) ¹⁰⁸	All ages 0 to +60	Asthma hospitalization	10 grains/m ³	3	3-day moving average	1.019	1.008	1.029
Silver (2018) ¹¹⁹	0-64 years		10 grains/m ³ (IQR)	2-4	RR	0.030	<i>p</i> =.602	
			12 grains/m ³ (IQR)	0-5	Smooth term df (chi-square)	0.054	<i>p</i> =.255	
			12 grains/m ³ (IQR)	0-6	0.129	<i>p</i> =.000		
					-0.002	<i>p</i> =.969		
					0.314	<i>p</i> =.000		

Abbreviations: 95% CI, confidence interval at 95%; ED, emergency department; OR, odds ratio; QRI, interquartile range increase; RR, relative risk.

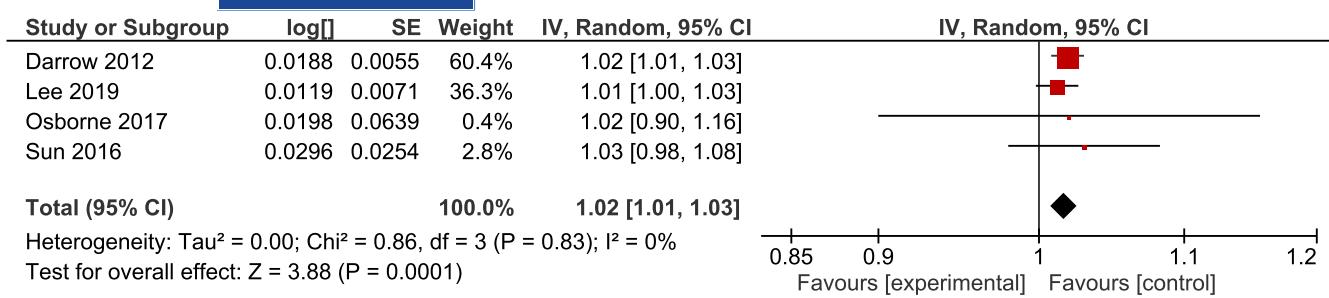


FIGURE 4 Severe asthma exacerbations associated with an increase of 0–50 grains/m³ of grass pollen (lag >2) in patients in the general population.

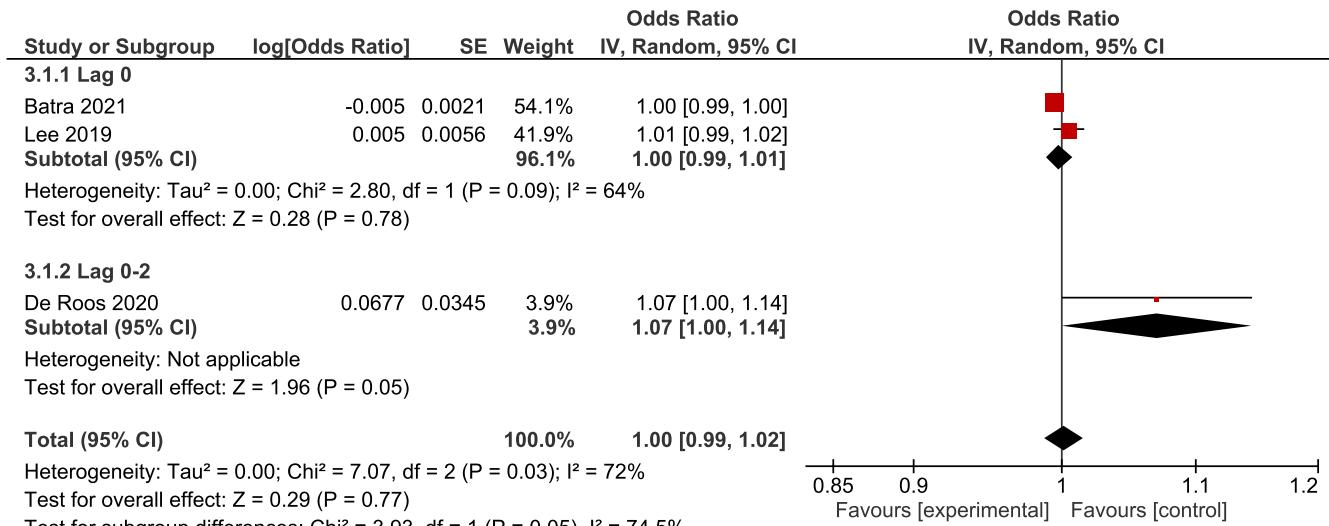


FIGURE 5 Severe asthma exacerbations associated with an increase of >50 grains/m³ of tree pollen (lag 0–2) in patients under 18 years.

admissions with higher birch pollen concentrations (Table 7). When assessing lagged associations up to 7 days, no trend was observed on the same study, with mostly positive though imprecise associations. Additionally, a longitudinal study¹¹⁰ reported a positive association with a 10-unit increase on birch pollen lagged 1 and 2 days (Table 7). One time series analysis¹⁰⁸ reported positive associations between asthma hospitalizations and a 40 grains/m³ increase in birch pollen in 0- to 6-day cumulative lag (Table 7). In the case of cypress pollen, two studies reported in individuals aged <18 years the association between asthma-related ED visits or hospitalizations and cypress pollen concentrations on the same day (lag 0). One case-control study¹² reported a negative though imprecise association with a non-specified pollen concentration, while a case-crossover study¹⁰² reported a positive though imprecise association with an increase between the 75th and 90th percentile of cypress pollen concentrations. Three studies reported the association between asthma exacerbation or hospitalization and cypress pollen with cumulative lags up to 6 days. Shrestha et al¹⁰² reported a positive though imprecise association with an increase between the 75th and 90th percentile, and another case-crossover study¹⁰⁵ reported a positive association with concentrations up to 23.3 grains/m³. However, for concentrations above 23.3 grains/m³, this same case-crossover study¹⁰⁵ and a

time series analysis¹⁰⁸ reported a negative though imprecise association. Meta-analysis for studies that measured this outcome was not conducted.

Only one time series analysis¹⁰⁸ reported a negative though imprecise association between asthma hospitalizations and an increase in 49 pollen cypress grains/m³ for 0 to 6 days cumulative lag in individuals aged >18 years. At the general population level, three time series analyses and one case-crossover study examined the association between cypress pollen and asthma exacerbations in the general population. Three reported negative and one positive associations. Hanigan et al¹³ reported a negative though imprecise association between asthma-related ED admissions and a non-specified pollen concentration on the same day (lag 0) (Table 8). Darrow et al¹¹¹ reported a negative association between asthma-related ED visits with a 3-day moving average concentration of 25 grains/m³ of cypress pollen (Table 8). Guilbert et al¹⁰⁸ reported a negative though imprecise association between asthma hospitalizations and a 49 grains/m³ increase in pollen concentrations in a 0- to 6-day cumulative lag (Table 8). Tobias et al¹¹⁵ reported a positive though imprecise association between asthma-related ED admissions and 194.6 grains/m³ of cypress pollen lagged 3 days (Table 8).

TABLE 5 Severe asthma exacerbation related to tree pollen exposure in patients under 18 years of age (adjusted results).

Study ID	Age	Outcome definition	Exposure		Effect estimate (EE)		
			Tree pollen concentration	Lag	EE	95% CI	
Batra (2021) ¹⁰¹	2-17 years	Asthma exacerbations	60-216 grains/m ³	0	OR	0.995	0.991 0.998
Lowe (2012)	0-1 years	Asthma hospitalization	614-747 grains/m ³	2	OR	1.000	1.000 1.001
Lee (2019) ¹⁰⁴	0-2 years	Asthma-related ED visits	Increase in 100 grains/m ³	1	RR	1.005	0.999 1.011
Darrow (2012)	2-5 years	Asthma-related ED visits	NR	0	RR	1.005	0.994 1.016
	6-17 years			4		1.014	1.004 1.024
Babin (2007) ¹²⁴	1-17 years	Asthma-related ED visits	Increase in 100 grains/m ³	0	Percentage change	0.5	0 1.1
Lierl (2003)	Pediatrics	Asthma-related ED visits	Not specified	1	RR	0.4	-0.2 1
				2		0.5	-0.1 1.1
				3		0.2	-0.4 0.8
				4		0.2	-0.4 0.9
		Asthma-related ED visits			Not Specified	1.5	-0.3 3.3
Shrestha (2017) ¹⁰²	2-18 years	Asthma hospitalization	75th to 90th percentile increase*	0	OR	1.015	0.988 1.042
					Cumulative lag	1.002	0.993 1.010
De Roos (2020) ¹⁰⁵	<18 years	Asthma exacerbations	>0 to 157.7 grains/m ³	Cumulative 0-2	OR	1.10	1.06 1.14
			>157.7 to 531 grains/m ³			1.07	1.00 1.15
			>531 to 911 grains/m ³			1.16	1.07 1.25
			>911 to 1514 grains/m ³			1.13	1.03 1.24
			>157.7 to 537 grains/m ³			1.35	1.18 1.54
Gleason (2014) ¹⁰⁷	3-17 years	Asthma-related ED visits	10-unit increase	3-day average	OR	1.19	1.17 1.20
Witonsky (2018) ¹⁰⁶	Pediatrics	Asthma-related ED admissions	Full year Spring Summer	3-day moving average	Beta linear regression model	0.287 0.269 0.037	p=.000

Abbreviations: 95% CI: confidence interval at 95%; ED, emergency department, *geometric mean (SD) grains/m³ of total pollen: 4.8 (3.2); OR, odds ratio; RR, relative risk.

Less studies were found for other trees such as elm, hazel, olive trees, and others. In the case of elm pollen, in individuals aged under 18 years of age, one case-crossover study¹⁰⁵ examined the association between asthma exacerbations and elm pollen concentrations in 0- to 5-day cumulative lag a reported a positive association for concentrations up to 4.1 grains/m³, though a negative and imprecise association for concentrations over 4.1 grains/m³. At the population level, one time series analysis¹²⁵ reported a positive association between asthma hospitalizations and an increase of 14.03 grains/m³ of elm pollen on the same day (lag 0). However, one study did not

account for potential confounders in their results.¹²⁷ Guilbert et al¹⁰⁸ reported the association between asthma-related hospitalizations and an increase of 4 grains/m³ of hazel pollen with a 0- to 6-day cumulative lag. They reported results stratified by age, with a negative though imprecise association for children from 0 to 14 years of age, no association for participants from 15 to 59 years, and positive though imprecise association for participants over 60 years of age. One time series analysis¹¹⁶ examined the association between asthma-related ED admissions and olive pollen concentrations on the same day (lag 0) and reported a negative though imprecise

TABLE 6 Severe asthma exacerbation related to tree pollen exposure in the general population (adjusted results).

Study ID	Age	Outcome definition	Exposure		Effect estimate (EE)		95% CI
			Tree pollen concentration	Lag	RR	EE	
Lee (2019) ¹⁰⁴	All ages	Asthma-related ED visits	Increment 100 grains/m ³	0	RR	1.009	1.002 1.017
Osborne (2017) ¹¹⁴	16-64 years 0-2 years	Asthma-related ED admissions	0 to 95th percentile increase in pollen exposure	0 1	Percentage Change	-4.01 -8.65	-17.95 -24.08 9.93 6.78
Darrow (2012)	2-5 years 6-17 years	Asthma-related ED visits	NR	2	RR	2.06 -10.82	-13.6 -26.86 17.74 5.21
Lierl (2003)	Pediatrics	Asthma-related ED visits	Not specified	3 4	RR	4.59 -10.66	-9.45 -24.66 5.75 -14.32 16.17
Sun (2016) ¹¹⁷	All ages	Asthma-related ED visits	10 grains/m ³	0-3	RR	2.67 -11.66	2.67 -11.66 16.99
Darrow (2012) ¹¹¹	All ages	Asthma-related ED visits	37 grains/m ³ 3500 grains/m ³	1 2	RR	1.04 2.10	0.97 1.21 1.11 3.65
Witonksky (2018) ¹⁰⁶	All ages	Asthma-related ED admissions	20 grains/m ³	3-day moving average	RR	1.004	0.993 1.016
Gleason (2014)	3-17 years	Asthma-related ED visits	Full Year Spring Summer	3-day moving average	Beta Linear Regression Model	0.311 0.268 -0.062	p=.000
Dales (2004) ¹¹⁸	All ages	Asthma-related ED visits	Full Year Spring	3-day average	OR	0.042 -0.002	0.042 -0.002
Dales (2008) ¹²⁵	All ages	Asthma hospitalization	Increase from 25th to 75th percentiles*	cumulative 0-5	Percentage Change	2.87 1.45	0.87 0.07 4.97 2.83

Abbreviations: 95% CI: confidence interval at 95%; ED, emergency department; *mean grains/m³ tree pollen concentration: 32.3; OR, odds ratio; relative risk.

TABLE 7 Severe asthma exacerbation in the general population exposed to birch pollen (adjusted results).

Study ID	Age	Outcome definition	Birch pollen concentration (pollen or grains/m ³)	Lag	Effect estimate (EE)			
					Exposure	Percentage change	EE	95% CI
Osborne (2017) ¹¹⁴	16–64 years	Asthma-related ED admissions	Increase from 0 to 195 grains/m ³	0			1.44	-7.22
				1		1.33	-7.59	10.1
				2		2.77	-6	10.26
				3		0.06	-8.59	11.52
				4		3.1	-5.56	8.7
				5		-5.77	-14.29	11.78
				6		1.76	-6.36	2.75
				7		-1.78	-9.3	9.89
			Medium: ≥40 grains/m ³ & ≤79 grains/m ³	0	RaR	0.97	0.78	5.73
				3		1.08	0.88	1.21
			High: ≥80 grains/m ³ & ≤199 grains/m ³	0		1.02	0.81	1.33
				3		1.03	0.83	1.29
			Very high: ≥200 grains/m ³	0		1.07	0.85	1.28
				3		1.02	0.81	1.36
Anderson (1998) ¹¹⁰	15–64 years	Asthma-related ED admissions	10-unit increase	1	Percentage change	1.11	0.11	1.28
	All ages			2		0.78	0.15	2.12
Guilbert (2018) ¹⁰⁸	15–59 years	Asthma hospitalization	40 grains/m ³ IQR ₁	Cumulative 0–6	Percentage change	3.3	1.1	1.42
	All ages					3.2	1.1	5.6
							5.3	5.3

Abbreviations: 95% CI, 95% confidence interval; ED, emergency department; IQR₁, interquartile range increase; RaR, incidence risk ratio.

TABLE 8 Severe asthma exacerbation in the general population in relation to cypress pollen exposure.

Study ID	Age	Outcome definition	Exposure		Effect estimate (EE)		
			Cypress pollen concentration (pollen or grains/m ³)	Lag	EE	95% CI	
Hanigan (2007) ¹³	All ages	Asthma-related ED admissions	IQR change in pollen load for linear responses	0	Percentage change	-3.26	-9.74 3.68
Tobias (2003)	All ages	Asthma-related ED admissions	p95-p99: 194.6 grains/m ³	3	Percentage change	6.0	-3.4 16.5
Darrow (2012)	All ages	Asthma-related ED visits	25 grains/m ³	3-day moving average	RR	0.988	0.978 0.998
Guilbert (2018)	15-59	Asthma hospitalizations	49 grains/m ³ IQRI	Cumulative 0-6	Percentage change	-3.0	-7.9 2.2
	All ages		>23.3 to 62.5 grains/m ³			-2.5	-6.9 2.1

Note: Results are adjusted.

Abbreviations: 95% CI, 95% confidence interval; ED, emergency department, IQRI, interquartile range increase, RR, risk ratio.

association for concentrations between the percentiles 50 to 75 and over the 90th percentile. The other time series analysis¹¹⁵ reported a positive though imprecise association between asthma hospitalizations and a variation of 106 grains/m³ of olive pollen lagged 1 day.

4.3 | Moderate asthma exacerbation

Moderate asthma exacerbation was considered only in two studies that examined the use of extra medication (i.e., medication above each person's defined baseline) due to asthma exacerbation in relation with total pollen concentration at different lags in individuals aged under¹²⁸ or over¹²⁹ 18 years of age. They found no association with non-specified total pollen concentration. No study of specific pollen was conducted.

4.4 | Asthma control and well days

Only one longitudinal study examined the association of asthma control status with the preceding week's total pollen severity index and found that pollen severity was significantly associated with poorer asthma control after adjusting for the season effect and participant's socio-demographics.¹³⁰ No study of specific pollen was conducted.

4.5 | Lung function

Results on the association between lung function and total pollen concentrations are reported in four studies. Two found that the median of both forced expiratory volume in 1 second (FEV₁) and forced expiratory flow at the 25% and 75% of pulmonary volume (FEF25-75) of participants were significantly lower during the pollen season than in the rest of the year. Two longitudinal studies

reported the association between lung function and grass pollen concentrations in individuals aged under 18 years of age. Lambert et al¹³¹ reported positive though imprecise association between an interquartile range increase of 7 grains/m³ for lags 0 to 3 and forced expiratory volume during the first second (FEV₁) and forced vital capacity (FVC), although for this last parameter the association was negative and imprecise for the 8-years-old participants (Table 9). Klabuschinnig et al¹³¹ reported that no correlation was established between FEV and FVC and their changes according to nonspecified grass pollen concentrations (Table 9). However, in individuals aged more than 18 years, only a cross-sectional study reported that exposure to higher levels of grass pollen (increase in 29 grains/m³) at lag 0, 1, 2, and cumulative lag 3 were associated with an increase in absolute bronchodilator response (BDR) and fractional exhaled nitric oxide (FeNO) in subjects with current asthma³ (Table 9). Kralimarkova et al¹³² did not find any difference between the mean FEV₁ before the pollen season and during the season, defined as when high atmospheric grass pollen concentrations (Table 9). Only one cohort study of high-risk children reported a positive association between an interquartile range increase of 22 grains/m³ of cypress pollen for lags 0 to 3 and the odds of <80% predicted forced expiratory volume during the first second (FEV₁) and forced vital capacity (FVC).¹³¹

4.6 | Asthma symptoms/well days

The association of pollen and asthma symptoms was estimated only at the general population level. No studies could find a statistical association between total pollen concentration and asthma symptoms. Kralimarkova et al¹³² reported the overall discomfort from symptoms with a 100mm VAS (Visual Analogic Scale) ranging from worst symptoms ever (100) to no symptoms (0) relevant for the time of the visit and the 72 h before. The mean (SD) VAS score was 93.2

TABLE 9 Lung function in participants under 18 years of age and general population (adjusted results).

Study ID	Age	Outcome definition	Exposure			Effect estimate (EE)		
			Grass pollen concentration (pollen or grains/m ³)	Lag	OR	EE	95% CI	
Lambert (2020) ³¹	8 years	FEV1 (<80% predicted)	Interquartile range increase of 7 gr/m ³	0-3	OR	0.68	0.13	3.74
		FVC (<80% predicted)		1.32		0.46	3.83	
		FEV1		0.72		-6.98	5.54	
	14 years	FVC	% predicted value (95% CI)	-0.30	% predicted value (95% CI)	-0.30	-7.2	6.6
		FEV1		0.73		0.73	2.9	
		FVC		0.32		-1.4	2.9	
Klabuschigg (1981) ³²	7-14 years	"No correlations between FEV and FVC and their changes according to pollen and spore counts and general and local weather situation could be established over the 6 weeks investigated."						
Idrose (2020) ³	18 years	FENO (ppb)	Increase in 29 grains/m ³	0-3	coef (95% CI)	13	1.3	24
		Absolute BDR		0-3		2.0	-0.4	4.6
Kralimarkova (2014) ³³	7-55 years	FEV1 (% predicted)	Before season During season	Not applicable	mean (SEM)	104.8	3.4	Difference <i>p</i> = .71.
		FEV1 (% predicted)				103.6	3.6	

Abbreviations: 95% CI, confidence interval at 95%; ED, emergency department; FeNO = fractional exhaled nitric oxide; BDR = bronchodilator response; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; OR: odds ratio; RR = relative risk.

TABLE 10 Severe asthma exacerbations in individuals exposed to total pollen concentrations during thunderstorms.

Study ID	Age	Outcome Definition	Exposure		Effect estimate (EE)			
			Total pollen concentration (pollen or grains/m ³)	Lag	EE	95% CI		
Newson (1998) ¹⁶	All ages (general population)	Asthma-related ED admissions	0–501.6 grains/m ³ /day high sferic density days	5-day moving average	RR	6.23	1.29	26.67
			0–501.6 grains/m ³ /day low sferic density	5-day moving average		2.39	0.69	8.61
			Grass pollen concentration (pollen or grains/m ³)	Lag	EE		95% CI	
Newson (1997) ¹⁶	<14 years	Asthma-related ED admissions	High pollen counts: >50 grains/m ³ with sferics ^a	0	RR	1.16	1.04	1.31
			High pollen counts: >50 grains/m ³ without sferics ^a			1.00	0.94	1.07
Hajat ¹³⁵	Children	Asthma-related visits	258 grains/m ³	3	RR	1.21	1.03	1.41
Erbas (2018) ¹³⁶	<15 years	Asthma-related ED visits	"The smoothed plot shows that as ambient grass pollen increased to about 19 grains/m ³ same day risk of childhood ED visits also increased linearly (from about 6 grains/m ³), then declined before further increasing as grass pollen levels reached about 53 grains/m ³ ($p < .001$ from the nonlinear term for grass pollen). Grass pollen was also associated with an increased risk in asthma ED visits the following day (lag 1, $p < .001$). Two days after, exposure to grass pollen was no longer significantly associated with asthma ED visits in children"					

Abbreviations: 95% CI, 95% confidence interval; ED, emergency department; OR, odds ratio; RR, risk ratio; RR, relative risk.

^aCompared with 0–50 grains/m³.

(2.2) before the pollen season and 69.9 (4.8) during the pollen season (defined as when high atmospheric grass pollen concentrations triggered symptoms in the sensitized population) with a difference that was statistically significant ($p = .001$). This outcome was not reported for the other selected age groups.

4.7 | Mortality

No association between mortality and the total pollen concentrations and asthma mortality was found. Similarly, two longitudinal (retrospective) studies that assessed the relation between asthma-related mortality and grass pollen concentrations did not find a relationship. Targonsky et al reported that grass and ragweed pollen concentrations were not significantly different between days on which asthma-related deaths occurred and days on which such deaths did not occur,¹³³ and Mackay et al¹³⁴ reported no association between the peak in mortality and the peak in grass pollen concentrations. However, one Finnish study¹⁶ found that daily pollen counts of alder pollen significantly increased the risk of deaths from respiratory diseases including asthma. The authors speculated that alders as the first sources of allergen load could prime the immunologic system

of allergic people. Therefore, exposure to similar kind of allergens as alder may provoke immunologic system, elicit first adverse reactions producing an "immunologic shock" and therefore, and harvest susceptible individuals already before the birch flowering takes place.

4.8 | Quality of life

Although quality of life is an important outcome measure for asthma, no study investigated quality of life in relation with pollen exposure in asthmatics.

4.9 | Pollen-related thunderstorm asthma

ED asthma admissions in relation to thunderstorm were considered as informative. A time series analysis¹³⁵ examined the effects of total pollen during thunderstorms and reported that with high sferics (lightning flashes) and an increase up to 501.6 pollen grains/m³ there was a positive association, while with low sferics this association was imprecise (Table 10). This time series analysis examined the effects of grass pollen on the same day (lag 0) of thunderstorms

TABLE 11 Severe asthma exacerbations in the general population exposed to grass pollen during thunderstorms.

Study ID	Age	Outcome definition	Exposure		Effect estimate		
			Grass pollen concentration	Lag	EE	95% CI	
Newson (1997) ¹⁶	>15 years	Asthma-related ED admissions	Pollen count >50 grains/m ³ with sferics ^a	0	RR	1.47	1.32 1.64
			Pollen count >50 grains/m ³ without sferics ^a			1.06	0.99 1.13
	All ages		Pollen count >50 grains/m ³ with sferics ^a			1.31	1.21 1.42
			Pollen count >50 grains/m ³ without sferics ^a			1.03	0.98 1.08
Lewis (2000) ¹¹²	>14 years	Asthma-related ED visits	>50 grains/m ³	0	OR	2.1	1.4 3.3
Celenza (1996) ¹¹³	>16 years	Asthma-related ED visits	>30 grains/L increase	9 h before	Relative change	0.83	0.42 1.67
			>30 grains/L fall			2.50	1.36 4.59
			>10 grains/L increase	2		2.15	1.21 3.84
			>10 grains/L fall			1.89	1.24 2.89
Hajat (1997) ¹³⁵	All ages	Asthma-related visits	258 grains/m ³	3	RR	1.17	1.06 1.29
Silver (2018) ¹¹⁹	0-64 years	"High levels of grass pollen over the 3 days preceding the thunderstorm were associated with increased admissions (roughly three to five additional admissions). When average grass pollen concentration of the previous 3 days exceeded 70 grains/m ³ , the exacerbation became significant, plateauing at around four additional admissions per day for mean concentrations of 100 grains/m ³ or more."					

Abbreviations: 95% CI, 95% confidence interval; ED, emergency department; OR, odds ratio; RR, risk ratio.

^aCompared with 0-50 grains/m³.

in individuals under 18 years of age and reported that with sferics and concentrations over 50 pollen grains/m³, there was also a positive association, while without sferics there was no association (Table 11). A longitudinal study¹³⁶ reported a positive association with asthma-related visits to general practitioners with high pollen concentrations (258 pollen grains/m³) lagged 3 days (Table 11). Similarly, another time series analysis¹³⁶ reported that as ambient grass pollen rose from 6 to about 19 pollen grains/m³, risk of asthma-related visits increased linearly, and then declined, before rising again at 53 pollen grains/m³ (Table 10). A longitudinal study¹³⁵ examined the association between asthma-related visits to general practitioners and high pollen concentrations (258 grains/m³) lagged 3 days in people over 18 years and found a positive association for adults, and a negative though imprecise association for the elderly. In the general population, two time series analysis examined the effects of grass pollen concentrations over 50 pollen grains/m³ on the same day (lag 0) of thunderstorms. Newson et al¹⁶ reported that with sferics, there was a positive association, while without sferics, this association was imprecise. Lewis et al¹¹² reported that there was a significant interaction between the effects of grass pollen and weather conditions, such that ED visits were not related to grass pollen on dry days, but increased on wet or stormy days, most markedly on days of light rainfall (Table 11). One longitudinal study¹¹³

reported that the asthma thunderstorm epidemic was associated with changes in grass pollen concentrations. There was a peak in pollen concentration about 9 h before the peak in asthma ED visits. Additionally, the change in grass pollen concentration was also associated with asthma ED visits lagged 2 days (Table 11). Another longitudinal study¹³⁵ examined the association between asthma-related visits to general practitioners and high pollen concentrations (258 pollen grains/m³) lagged 3 days and found a positive association. Additionally, a time series analysis¹¹⁹ reported that high levels (over 70 pollen grains/m³) of grass pollen over the 3 days preceding a thunderstorm were associated with increased admissions due to asthma (three to five additional admissions) (Table 11). One time series analysis¹¹² reported that the effect of non-specified birch pollen concentrations on asthma-related ED admissions during a thunderstorm was only apparent on wet days ($p=.1$), but no estimate was presented by these authors.

4.10 | Risk of bias

Using the ROBINS-E tool, we judged only six (8.33%) studies as having a low risk of bias on all domains. We judged 42 (58.33%) studies as having an overall high risk of bias and 24 (33.33%) as having an

overall moderate risk of bias. The domain with the most assessments as low risk of bias across studies was risk of bias arising from measurement of the outcome, with 45 studies (62.5%). We judged only two studies (2.77%) as having a high risk of bias. The domain with most high risk of bias assessments across studies was risk of bias due to confounding, which evaluates the validity and reliability of the method of measurements, and the appropriate accounting for confounders, with 24 studies (33.33%). Additionally, we judged 21 studies (29.16%) as having a moderate risk of bias for the same domain. In two domains, most studies were judged as having a moderate risk of bias: 44 (61.11%) for the risk of bias in selection of participants into the study (or into the analysis) mainly due to a lack of reporting of key characteristics of the population and 46 (63.88%) of the studies for the risk of bias arising from the measurement of the exposure, mostly due to a lack of reporting of the method of measurement. Lastly, risk of bias in selection of the reported results was judged as high risk of bias for 12 studies (16.66%), as moderate for 33 studies (45.83%), and as low for 27 studies (37.5%). Risk of bias due to missing data was judged as not applicable for most studies (68, 94.44%) given their design, and risk of bias due to post-exposure interventions was considered as low for all studies due to the assessment of acute or short-term exposure.

5 | DISCUSSION

To our best knowledge, this is the first systematic review and meta-analysis to comprehensively summarize the relationships between pollen exposure and asthma exacerbation, as assessed through various respiratory outcomes with strict methodological concerns. The existing literature collected in a recent review of the respiratory health burden attributable to short-term exposure to pollen had already suggested evidence of an association between outdoor pollen concentrations and most of the asthma outcomes we considered, especially in people with pre-existing respiratory diseases.³⁻¹³⁹ Our overall meta-analysis, subgroup analysis, and publication bias assessment confirm that a relationship between pollen exposure and asthma exacerbation exists but this requires additional research due to its heterogeneity. Total pollen concentrations were associated with an increased risk of severe asthma exacerbation as assessed by asthma-related ED visit, but this result is uncertain because potential confounders were not considered. The strongest associations were found in children under 18 years of age between asthma attacks or asthma-related ED admissions or hospitalizations and an increase in grass pollen concentration in the previous 2 days. The existence of a significant association between severe asthma exacerbation and grass pollen concentration was also confirmed in patients older than 18 years of age although data are less accurate. Severe asthma attacks were related to weed pollen increase in individuals younger than 60 years of age. Similarly, tree pollen may increase asthma-related ED visits or admissions lagged up to 7 days overall in individuals younger than 18 years. Results for other pollens and for thunderstorm asthma

were uncertain and inconsistent. Hence, these associations should be viewed with caution and require more research. Little evidence was observed for lung function changes. Rare data show that among subjects under 18 years of age, an exposure to grass pollen lagged up to 3 days may lower lung function, which confirms a previous meta-analysis.¹³⁹

Such significant associations are supported by experimental studies showing that pollen exposure can induce both early and delayed responses in the airways.¹⁴⁰ Only two epidemiological studies considered the impact of acute pollen exposure on lower airways.^{141,142}

People of all ages may be affected by pollen exposure, except elderly. However, pollen impact is greater in some groups. Both children and individuals with pre-existing hay fever or asthma are at higher risk. For instance, stronger associations between outdoor pollen concentrations and lung function were found in asthmatics, allergic rhinitis patients, and/or pollen-sensitized patients.¹³⁹ Similarly, the risk of thunderstorm asthma is higher in patients suffering from allergic rhinitis or in those who had poor adherence to treatment.¹⁴³ Finally, people with low socio-economic status may be at higher risk of pollen-induced asthma because of reduced health access and poor air quality at their residence.⁸⁸ Air pollution may also impact the association between pollen exposure and asthma attacks as observed at the general population level.¹⁴⁴

Data on other effect modifiers of the relationship like ethnicity, gender, air pollution, green spaces and location, and type of residency are still scarce and need further investigations following the exposome approach.^{145,146}

6 | CONCLUSION

Current evidence suggesting an impact of pollen on asthma exacerbation incite to propose recommendations and preventative measures to protect individuals during pollen seasons. However, further research is urgently warranted to evaluate whether they are effective. If proven, future adaptation measures should be integrated in asthma control and prevention programs as pollen increase continues due to climate change.¹⁴⁶

AUTHOR CONTRIBUTIONS

This paper was designed, directed, and coordinated by Isabella Annesi-Maesano, Lorenzo Cecchi, Ioana Agache, Carlos Canelo-Aybar, and Marek Jutel. Isabella Annesi-Maesano and Lorenzo Cecchi as the principal contributor provided conceptual and technical guidance for all the aspects of the paper. Pablo Alonso-Coello, Carlos Canelo-Aybar, Yahveth Cantero-Fortiz, David Rigau, Josefina Salazar, and Francisca Verdugo-Paiva conducted the statistical analysis of the data. All authors contributed to the text and read and approved the final manuscripts.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare inside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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