



Threshold values of grass pollen (Poaceae) concentrations and increase in emergency department visits, hospital admissions, drug consumption and allergic symptoms in patients with allergic rhinitis: a systematic review

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Abstract Airborne grass (Poaceae) pollen measurements are used in public warning systems to inform people about the risk of allergic symptoms. However, there is no consensus about which exact thresholds of pollen concentrations provoke the allergic symptoms. The aim of this study was to review the relevant scientific information on the relationship between

grass pollen concentrations and the occurrence of emergency department (ED) visits, hospital admissions (HA), drug consumption and allergic symptoms. Literature search was conducted by experts' consultation and snowball strategy. Studies meeting the criteria for inclusion were assessed regarding their risk of bias (RoB). A high RoB resulted in exclusion of the study from data synthesis. Extensive data were extracted and qualitatively compared. The review is registered in PROSPERO. 32 Studies were eligible while 18 showed a low RoB and were qualitatively synthesised. Emergency department visits and hospital admissions were mostly investigated. Threshold values of 10 grains/m³ and 12 grains/m³ were reported

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for ED visits and HA. Evidence exists that an increase of 10 grains/m³ of air leads to a significant increase in adverse health outcomes. Especially at a three-day lag, adverse health effects were shown. Variations in exposure and outcome measurement make the definition of pollen thresholds difficult. As a consequence, no defined pollen threshold values could be identified. Studies with uniform exposure measures and statistical methods are necessary to gain a better understanding of the impact of grass pollen on human health. Determining personal thresholds could be beneficial for affected people.

Keywords Aeroallergens · Allergic rhinitis · Asthma · Emergency medical services · Grass pollen

1 Background

A high prevalence and severity of immunoglobulin E (IgE)-associated allergies are a major and growing health problem in Europe (Bousquet et al., 2011; Thamm et al., 2018). The numbers in the literature on the global prevalence of allergic rhinitis (AR) vary between 1 and 40% in adults and 2% and 25% in children (Brożek et al., 2017).

Seasonal AR and allergic asthma are closely linked, as AR can lead to allergic asthma. Both AR and

allergic asthma can be triggered by airborne pollen (DellaValle et al., 2012; Kiotseridis et al., 2013). In recent decades, a constantly increasing prevalence of AR has been observed (Forkel et al., 2020). Despite a confirmed genetic predisposition for the development of sensitisation to allergens, this rise cannot solely be explained by changes in the genetics of the population (Forkel et al., 2020). Therefore, other factors increasingly shifted into the focus of scientific studies. Environmental factors like climatic variability and change which influence the distribution of aeroallergens and promote the development of allergic reactions have been identified as parameters (Bousquet et al., 2001; Damialis et al., 2019b; Shea et al., 2008). Studies suggest that climate change affects pollen levels in two ways. On the one hand, higher average temperatures lead to an earlier start of flowering for many plants. On the other hand, increased greenhouse gases, such as carbon dioxide, can also lead to an increased pollen production (Beggs, 2015; Reid & Gamble, 2009). A recent review concluded that climate-related developments concerning allergens and allergic diseases might be the most important health impact of climate change (Beggs, 2015). Of all aeroallergens, the grass (Poaceae) pollen family, which consists of over 12,000 species, is regarded as the biggest airborne biological pollutant and the main cause of pollen allergy worldwide (Garcia-Mozo, 2017).

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Asthma and AR severely impair the quality of life. In addition, asthma and AR lead to high direct costs for medical treatment and to high indirect costs for a society due to lost working hours (Global Asthma Network, 2014; Navarro et al., 2009; Reid & Gamble, 2009). These costs amount to more than \$30 billion annually in the USA (Reid & Gamble, 2009). Factors such as reduced work hours, lower productivity, high impact on social life, daily routines and sleep quality can influence these costs (Muzalyova et al., 2019). The use of pollen threshold values could have an influence on the quality of life of patients with pollen allergy.

First attempts to establish pollen threshold values originated in Sweden in the 1970s. These threshold values were based solely on clinical experience and were to be used in public warning systems to inform the population of the likelihood of allergic symptoms occurring. In the study of Kiotseridis et al. (2013), the risk of pollen-induced health symptoms was defined as:

- Low within a range of 0–10 grains/m³,
- Moderate within a range of 10–30 grains/m³,
- High within a range of 30–100 grains/m³ and
- Very high with values of more than 100 grains/m³.

In Denmark, the British threshold values have been adopted as follows (Kiotseridis et al., 2013):

- Low within a range of 0–30 grains /m³,
- Moderate within a range of 30–50 grains/m³,
- High within the range of 50–150 grains/m³ and
- Very high with values of more than 150 grains /m³.

The European Academy of Allergy and Clinical Immunology (EAACI) has published a position paper in which a high pollen day was defined as at least 50 grass pollen/m³ (Pfaar et al., 2017). Another study Davies and Smith (1973) suggested that all individuals sensitised to pollen will experience allergic symptoms when grass pollen count exceeds 50 grains/m³. However, these values remain controversial, because there are contradictory threshold values out of other studies (De Weger et al., 2013). Above all, thresholds of pollen must be species specific (De Weger et al., 2013).

The objective of this paper was to systematically review studies on exposure to grass pollen and its association with hospital admissions, emergency

department visits, drug consumption/medication sales, allergic symptoms, as well as asthma and AR. This systematic review aims to provide an overview of health-associated pollen thresholds.

2 Methods

This systematic review was conducted following the PRISMA (Moher et al., 2009) guidelines for reporting systematic reviews and meta-analysis and is registered in PROSPERO (Registration Number: CRD42019112369) since January 24, 2019 (Electronic Supplementary Material 1). The reviewer team was supported by a team of experts who provided advice on the content and methods of this project. The expert team consisted of ten experts from different scientific institutions.

2.1 Search strategy

The aim was to identify publications that investigate the effects of outdoor grass pollen concentrations on health outcomes in pollen-allergic patients. The complex search string was applied in the database PubMed without restriction of publication date. The PubMed database was selected because this review is about medical outcomes. The search term consisted of the following keywords: ‘Pollen’ AND ‘grass’ AND ‘pollen threshold’ AND ‘allergy’ AND ‘association’ NOT ‘animal’ NOT ‘placebo’ (see Electronic Supplementary Material 2). Excluding ‘animal’ and ‘placebo’ proved useful. We searched for literature in English, German, French and Spanish, but only English and German literature was included, as no French or Spanish studies were found. No local restrictions were made. The final search was performed on 14 August 2018. On 3 July 2020, the authors updated the systematic literature search for the period 2018–2020.

Further, a snowball strategy was applied to expand the search beyond peer-reviewed literature listed in PubMed. Other relevant literature such as grey literature, books, reviews and the reference lists of all included studies was screened. To find further relevant literature, the expert team was consulted. The book ‘Allergenic Pollen’ (Sofiev & Bergmann, 2013) must be highlighted at this point. This book provides an overview of the current state of the art in pollen

research. In detail, it addresses pollen production, the distribution of pollen in the atmosphere, the release of allergens from pollen, and the monitoring and prediction of pollen counts. At the time of publication, it was the only book that summarised studies that analysed pollen threshold values. The studies examined in the book ‘Allergenic Pollen’ were not systematically researched.

Two reviewers were independently involved in the screening process. Uncertainties were discussed by both reviewers to reach a consensus on screening decision. The results of the literature search were imported and managed in the literature management program Endnote X8.

2.2 Eligibility criteria

All studies were assessed for eligibility by applying the criteria for inclusion and exclusion listed in Table 1. The criteria for inclusion and exclusion were developed following the PECOS/PICOS criteria (population, exposure, intervention, comparison, outcome and study design). The following technical details regarding the criteria for inclusion and exclusion need to be highlighted:

- a. Including single results of a study was possible (e.g. effects of Poaceae pollen) while excluding others (e.g. effects of weed pollen).
- b. Only individuals sensitised to pollen were of interest for the research question, but information about sensitisation of the study population had not always been included in the publications. Therefore, inclusion criteria were adapted, referring to individuals showing pollen-related allergic symptoms.
- c. The PRISMA flow diagram (Moher et al., 2009) was used to visualise the search results (Fig. 1).

2.3 Data extraction and assessment

Several kinds of study data (e.g. first author and publication year, study design, PECO criteria, findings, etc.) were extracted and arranged in two kinds of tables. Table 2 gives basic information about all included studies and their study characteristics (study design, study location, time period, method of pollen collection, age group, sex and sample size). The most important results, arranged according to included

health outcomes, are presented in Table 3. If given, lag days were extracted. For example, a lag of 0–1 represents the average pollen exposure on the same day and the day before health outcome assessment. Some studies report pollen concentrations using an interquartile range (IQR). The IQR of a pollen concentration describes the concentration in which the middle 50% of the measured values lie during the period from 0 to a maximum of lag days.

We conducted a risk of bias analysis to assess the internal validity of all included studies (Moher et al., 2009). For this, we used the RoB tool of the Office of Health Assessment and Translation (OHAT). This tool had been designed for cohort, case–control and cross-sectional studies and had already been used for time series and case crossover studies. We adapted it to the needs of the review and supplemented it (see below) (Zhao et al., 2018).

Based on the OHAT tool, we applied the following supplements and adaptations: As currently discussed in literature, the criterion ‘Conflict of interest’ (CoI) has been included additionally (Bero, 2013; OHAT, 2015a; Woodruff & Sutton, 2014; Zhao et al., 2018). Selection bias was excluded from the risk of bias analysis because all studies included in the analysis were observational trials. Thus, all included studies in this category would receive a rating of ‘high’ RoB. In this way, all studies would have been excluded from the analysis.

In OHAT, the category of selection bias is described as: ‘Differences in the distribution of risk factors between exposed and non-exposed groups can occur at baseline or during follow-up. In observational studies, selection bias has often been used as a synonym for confounding, but recent efforts encourage consideration of selection bias and confounding as distinct’. The authors followed this definition. Based on this definition, the authors investigated confounding instead of selection bias.

In agreement with the involved expert team, precise rules for the RoB assessment were formulated based on the available instructions for ratings of the OHAT criteria (OHAT, 2015a, 2015b) (Table 4). The OHAT criteria for the RoB assessment are: confounding bias, detection bias for exposure and outcome, attrition bias, selective reporting bias and conflict of interest. The following options were used: ‘definitely low RoB (+ +)’, ‘probably low RoB (+)’, ‘probably high RoB (-)’, ‘definitely high RoB (- -)’ and ‘not applicable

Table 1 Criteria for inclusion and exclusion

Criteria	Inclusion	Exclusion
<i>PECO/PICOS</i>		
Population	General human population showing pollen-related allergic symptoms, any gender, age and nationality	Population showing never pollen-related allergic symptoms
Exposure		
Pollen type	Grass (Poaceae)	Other pollen, e.g. grass-like (Cyperaceae); a mixture of the included pollen
Pathway	Airborne	Any other than airborne
Origin	Natural exposure	Allergen challenge, pollen chamber
Unit	Pollen concentrations (grains/m ³)	Exposure estimate without pollen concentration measurement
Time reference	Exposure was assessed in any time period (e.g. daily, weekly)	No exclusion
Interventions	No interventions	Any interventions
Comparison	Different humans exposed to different concentrations of pollen or equal humans exposed to different concentrations of pollen at various points in time	Other comparisons than the included
Outcome		
Main outcomes	Pollen-related allergic symptoms, bronchial (e.g. allergic asthma), nasal (e.g. seasonal allergic rhinitis, SAR) and ocular (e.g. rhinoconjunctivitis)	Not pollen-related allergic symptoms, e.g. perennial allergic rhinitis (PAR), other related health outcomes like Eosinophilic esophagitis (EOE), mortality, health indicators like quality of life scores, lung/pulmonary function, medical interventions, testes of sensitisation (e.g. IgE value or Skin Prick Test);
Additional outcome	Pollen-related hospital admissions, emergency department visits, physician visits, drug consumption, reimbursement of anti-allergenic drugs	
Measurement	Diagnosed, self-reported, reported by someone else (e.g. mother), measured by symptoms scores indicating the start of (a) symptom(s) or indicating in which range of pollen counts (a) symptom(s) occur	Health outcomes not measured, measured by symptoms scores indicating a change of the score
Time reference	Daily (including averaged values and lag days)	Summarised values per month, year etc
Study design*		
Design	Epidemiological observational studies, control groups of intervention studies	Epidemiological experimental studies, basic research studies, clinical research studies, study protocols, case studies, case series, reviews, meta-analysis, intervention groups of intervention studies
Association	Association between pollen concentration and occurrence of the health outcomes	Pollen concentration and frequency of the health outcomes were described separately; the association was not analysed. Pollen concentration in relation to health symptoms was not quantified
Effect measures	Relative risk, odds ratio, threshold values, percent change, results are presented numerically and not only graphically	Correlation coefficient, results are presented graphically and not numerically
<i>Others</i>		
Language	English, German, French, Spanish	All other languages
Publication year	All publication years	No exclusion
Reference place	All places/countries	No exclusion
Study sample	Every study sample was included once, even if more than one paper was published. The paper was included that covered the longest observation periods or the largest sample size	Paper with overlapping study samples. Excluded were the paper with the shortest observation period or the smallest sample size

*See Röhrig et al. (2009) for the applied categorisation of study designs

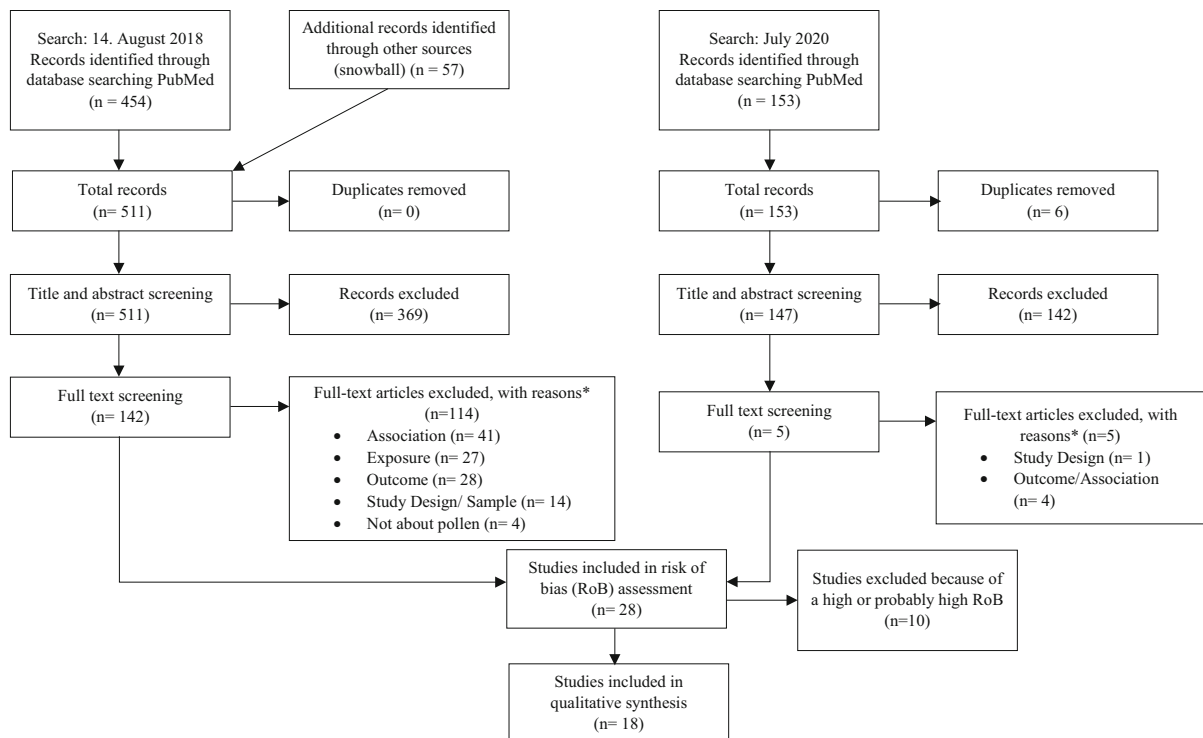


Fig. 1 PRISMA flow chart (adapted from (Moher et al., 2009)). *The first obvious reason was listed while multiple reasons are possible. The reasons listed correspond to the criteria for inclusion (Table 1)

(NA)'. The last option (NA) was only accepted for attrition bias and the assessment of the other criteria was considered mandatory (Table 4).

The assessment criteria for a 'low RoB' as defined by the author team are described in Table 5 (OHAT, 2015a, 2015b). All studies with a 'probably low' or 'low RoB' in all categories were included in the analysis (Table 6). All studies with a 'probably high' or 'high RoB' in at least one category were excluded. All studies excluded from the analysis due to a 'probably high' or 'high RoB' in at least one category can be found in the electronic supplementary material 3. However, an exception to the described criteria for RoB assessment was made for the category 'conflict of interest'. If no conflict of interest information was available, the study was rated as 'probably high RoB' in the 'conflict of interest' category. If a study had a low or probably low RoB in all categories except the 'conflict of interest' category, the overall RoB of the study was assessed as low and this study was included in the analysis.

Additional quality assessments (e.g. application of the Newcastle Ottawa Scale (Wells et al., 2018)) were omitted because of the following reasons:

- The Assessment of the study quality focuses on aspects not related to the internal validity. Therefore, the Cochrane Collaboration recommends prioritising the RoB Assessments.
- We aimed to avoid repeating criteria already included in the selected RoB tools.
- The comparability of the quality assessment tool was restricted due to the diversity of study designs, because there is not one tool for all possible study designs, and thus, the tools per design were not comparable.

Data synthesis was performed in a qualitative way, arranged according to different health outcomes (Tables 2 and 3). This was carried out by the reviewer team and an additional third reviewer. The reported increases in pollen always assume a baseline of 0 grains/m³. All of the following pollen threshold values are based on daily averages.

Table 2 Characteristics of included studies

Study Author	Pollen sampler		Population							
	Design	Location	Time period [day,month,year]	Method of pollen collection	High	Number of pollen samplers	Location	Age Group	Sex	Sample size (analysed)
Annesi-Maesano et al. (2012)	Semi-individual approach	Metropolitan France	03.05.04–29.08.04	Hirst type (without specification)	n.a	52	52 cities in metropolitan France	> 6 years	Male 46.83% Female 53.17%	17,567
Babin et al. (2007)	Time series	Washington, DC, USA	10.2001–09.2004	Not stated	n.a	n.a	n.a	1–17 years	Not stated	Not stated
Caillaud et al. (2012)	Time series	Clermont-Ferrand area, France	01.01.03–31.12.12	Hirst type (without specification)	30 m	1	In Clermont-Ferrand	> 5 years	Male: 44.45% Female: 55.55%	97,611
Cirera et al. (2012)	Time series	Cartagena, Spain	01.01.95–31.12.98	Hirst type (without specification)	10 m	1	Central railway station of Cartagena	All ages	Not stated	1617
Dales et al. (2004)	Time series	Saint John, Halifax, Ottawa, Toronto, London, Windsor, Winnipeg, Calgary, Edmonton, Vancouver, Canada	01.04.93–31.03.00	Rotary Impact Sampler	n.a	10	One in each city	All ages	Not stated	60,066
Darrow et al. (2012)	Time series, case-crossover design	Atlanta metropolitan area, USA	1993–2004 (March–June)	Rotorod Sampler	Roof top height	2	Away from vegetation, air conditioners and building vents	All ages	Not stated	400,819
DellaValle et al. (2012)	Prospective cohort design	Connecticut, south central Massachusetts, New York State, USA	03.2000–10.2004	Mixed-effects model	n.a	n.a	n.a	4–12 years	Male 63.02% Female 36.98%	172 (Subsample: 30)

Table 2 continued

Study Author	Pollen sampler		Population						Sample size (analysed)	
	Design	Location	Time period [day.month.year]	Method of pollen collection	High	Number of pollen samplers	Location	Age Group		Sex
Feo Brito et al. (2007)	Time series/ Cohort study	Puertollano, Ciudad Real, Spain	2000–2001 (pollen season)	Burkard	n.a	1	In Ciudad Real	> 5 years		66 Puertollano 71 Ciudad Real
Fuhrman et al. (2007)	Time Series	Clermont-Ferrand area, France	01.01.2000–1.12.2001 and 01.01.2003–31.12.2004	Burkard	30 m	1	Town centre	> 5 years	Male: 44.45% Female: 55.55%	Yearly average of 6780
Gleason et al. (2014)	Time-stratified case crossover	New Jersey, USA	2004–2007 (April–September)	Hirst type (without specification)	n.a	2	Springfield in New Jersey	3–17 years	Male: 60.55% Female: 39.45%	21,854
Guilbert et al. (2016)	Time series	Brussels, Belgium	2005–2011 (pollen season)	Burkard	Roof top height	1	Centre of the study area	All ages		1,370,535 reimbursable allergy medication purchases
Guilbert et al. (2018)	Time series	Brussels, Belgium	01.01.08–31.12.13 (April–September)	Hirst type (without specification)	16 m	1	Centre of the study area	All ages	Not stated	5,094
Heguy et al. (2008)	Time series	Montreal, Canada	01.04.–31.10 1994–2004	Rotary impact sampler	2.45 m	1	In Montreal, situated 1 km from the Saint-Lawrence River	< 9 years	Male: 64.88% Female: 35.12%	43,780
Motreff et al. (2014)	Time series	2 urban areas centred around Nîmes and Montpellier	01.01.04–31.12.07	Hirst type (without specification)	20 m	2	Each one located in the outskirts of town Centres of Nîmes and Montpellier	> 5 years	Not stated	118,723 Montpellier 78,072 Nîmes
Osborne et al. (2017)	Time series	London, England	01.04.–31.08 2005–2011	Burkard	n.a	1	Central London	16–64 years	Not stated	11,984

Table 2 continued

Study Author	Pollen sampler		Population							
	Design	Location	Time period [day.month.year]	Method of pollen collection	High	Number of pollen samplers	Location	Age Group	Sex	Sample size (analysed)
Silver et al. (2018)	Time series	Metropolitan Melbourne, Australia	01.10.–31.12 1991–2015	Burkard	13 m and 20 m	4	at the University of Melbourne (1.7 km north of central Melbourne)	All ages	Not stated	170,344
Sun et al. (2016)	Time series	Wake County, North Caroline, USA	01.03.–31.10 2006–2012	Rotorod Sampler	n.a	1	n.a	All ages	Male: 38.55% Female: 61.45%	82,825
Tobias et al. (2003)	Time series	Madrid, Spain	1995–1998	Not stated	n.a	10	n.a	All ages	Not stated	4827

3 Results

There were 454 articles found during the PubMed literature search. In addition, 57 papers were identified through snowball searching of additional literature. There were 28 articles that met the inclusion criteria (Fig. 1). Out of these 28 articles, ten articles were excluded from the data analysis due to a probably high or high RoB assessment (Table 6 and Electronic Supplementary Material 3 and 4). Subsequently, 18 studies were included in the qualitative data synthesis.

When the literature search was updated, 153 articles were found. None of the 153 articles met the inclusion criteria, so all articles were excluded from data analysis (Table 1, Fig. 1).

Of 18 included studies, eleven studies analysed hospital admissions (HA) and/or emergency department (ED) visits in relation to pollen season. Four studies documented the association of medication sales and pollen concentration. Three studies examined the occurrence of symptoms in relation to pollen concentration (Fig. 2). The studies were conducted in seven countries on three continents: Europe ($n = 10$), North America ($n = 7$) and Australia ($n = 1$) (Table 7). The time period for data collection started for the oldest study in 1991 and ended for the most recent study in 2015. The following subgroups were analysed: individuals without restrictions regarding age ($n = 8$), individuals except children under five or six years of age ($n = 5$), children only ($n = 4$) and adults only ($n = 1$, see Table 2). All studies included both sexes. The sample size varied considerably between studies, ranging from $n = 30$ up to $n = 400,819$ (Table 2).

A summary of the key aspects of each study is presented in Table 2. Detailed information for all 18 studies is given in Table 3.

3.1 Outcome

3.1.1 Emergency department visits and hospital admissions

We found eleven studies, which investigated grass pollen concentrations and numbers of HA or ED visits (Babin et al., 2007; Cirera et al., 2012; Dales et al., 2004; Darrow et al., 2012; Gleason et al., 2014; Guilbert et al., 2018; Heguy et al., 2008; Osborne et al., 2017; Silver et al., 2018; Sun et al., 2016; Tobias

Table 3 Results of the included studies by health outcome

Symptoms	Study	Population	Outcome	Concentration category	Grains/m ³	Lag (days)	Measure of effect	Effect (lower CI; upper CI)	Covariates
Symptoms	Amnesi-Maesano et al. (2012)	Individuals consulting a physician	Patients with a SGS in the upper third quartile = suffering from severe SAR	Concentration increase	60	Lag 0	Odds ratio	1.08 (1.04–1.11)	Model 1: age, date of visit, previous asthma
						Lag 0	Odds ratio	1.08 (1.01–1.14)	Model 2: age, date of visit, previous asthma, NO ₂ (Lag 1), SO ₂ (Lag 1), O ₃ (Lag 1), PM ₁₀ (Lag 2)
	DellaValle et al. (2012)	Non-users of Asthma Maintenance Medication sensitised to grass pollen	Asthma symptoms (wheeze, night symptoms, shortness of breath, chest tightness, persistent cough, rescue medication use)	Concentration category vs. concentration category	3–4 vs. 0–2	Lag 0	Odds ratio	1.80 (1.31–2.47)	Temperature, O ₃ , PM _{2.5} , season, antibiotic use
					5–8 vs. 0–2	Lag 0	Odds ratio	2.09 (1.31–3.33)	
					9–15 vs. 0–2	Lag 0	Odds Ratio	2.58 (1.60–4.18)	
Antihistamine Consume	Feo Brito et al. (2007)	Mild–moderate seasonal asthmatics allergic to grass and/or olive pollen	Number of symptoms	IQR increase	> 15 vs. 0–2	Lag 0	Odds ratio	2.64 (1.55–4.49)	Correction for over dispersion, linear and quadratic tendency terms
					99	Lag 0	Percentage change	0.8 (– 2.6 to 4.2)	
	Motreff et al. (2014)	Individuals with prescriptions for oral antihistamine or local anti-allergic treatment	ARC = oral antihistamine drug and local (nasal or ocular) anti-allergic drug on the same prescription)	IQR increase Montepellier	31	Lag 2	Percentage change	0.4 (– 4 to 3.4)	
						Avg. Lag 0 and 1	Relative Risk	1.13 (1.1–1.17)	O ₃ , NO ₂ , PM ₁₀ , day of the week, public holidays and vacation, temperature, humidity/precipitations
						Cum. Lag 0–6	Relative Risk	1.11 (1.08–1.14)	(No sig. effect, therefore not included in the final model: O ₃ , NO ₂ , PM ₁₀ , precipitation)
Antihistamine Consume	Caillaud et al. (2015)	Individuals with prescriptions for oral antihistamine or local anti-allergic treatment	ARC = oral antihistamine drug and local (nasal or ocular) anti-allergic drug on the same prescription)	IQR increase Nîmes	14	Avg. Lag 0 and 1	Relative Risk	1.12 (1.08–1.15)	
						Cum. Lag 0–6	Relative Risk	1.11 (1.07–1.14)	
						Lag 0	Relative Risk	1.04 (1.038–1.05)	Air pollution, weather, day of the week, long-term trend, season, public holidays, school holidays

Table 3 continued

Study	Population	Outcome	Concentration category	Grains/ m ³	Lag (days)	Measure of effect	Effect (lower CI; upper CI)	Covariates
41	Fuhrman et al. (2007)	Individuals with prescriptions for oral antihistamine or local anti-allergic treatment	ARC = oral antihistamine drug and local (nasal or ocular) anti-allergic drug on the same prescription)	IQR increase	41	Avg. Lag 0 and 1 Percentage change	4.8 (3.7–6.0)	Day of the week, public holiday, temperature, relative humidity, O ₃
	Guilbert et al. (2016)	Individuals purchasing reimbursable allergy medication	Reimbursable antihistamines for systemic use sales	IQR increase	20	Cum. Lag 0–6 Relative Risk	8.7 (6.9–10.5)	Air pollution (PM10, NO ₂ , SO ₂ , O ₃), meteorological conditions (daily minimal temperature, avg. relative humidity) flu, seasonal component, day of the week
	Babin et al. (2007)	Paediatric emergency department visits in several hospitals	Asthma (ICD-9; 493.XX) (in one of the first 3 of 9 possible diagnosis fields)	Concentration increase	10	Lag 0 Mean percentage change	0.7 (– 1.8 to 1.3)	Long-term seasonal trends
					Lag 1	1.9 (– 0.4 to 4.3)	Interactions among O ₃ , PM _{2.5} and different types of pollen were analysed (no sig. interactions found)	
Emergency department visit					Lag 2	2.3 (– 0.1 to 4.7)		
					Lag 3	2.6 (0.3–5.0)		
					Lag 4	– 0.4 (– 2.9 to 2.3)		
					Lag 0	– 3.7 (– 7.7 to .6)		Long-term trends, seasonality, temperature, relative humidity, barometric pressure, influenza cases notification, seasonality, multipollutant model (TSP, NO ₂ , O ₃ , SO ₂)
Cirera et al. (2012)	Emergency department visits in two hospitals	Asthma cases identified by nurses from registries	Concentration increase	0–10 10–28 28–53	Lag 0 Lag 0	Relative risk	7.2 (3.2–1.4) – 4.2 (– 10.7 to 2.7)	
Darrow et al. (2012)	Emergency department visits in Atlanta in 41 hospitals	Asthma (ICD-9; 493.XX) or Wheeze (ICD-9; 786.07/09)	Concentration increase	10	3-day moving avg	Relative risk	1.02 (1.01–1.03)	Month, year, temperature, URI, hospital, day of the week, holidays
Gleason et al. (2014)	ED visits in New Jersey obtained by New Jersey Health Department	Asthma (ICD-9; 493.XX)	Concentration increase	10	Lag 0 Lag 1 Lag 2 3-day avg 5-day avg	Adjusted odds ratio	0.99 (0.98–1.00) 0.99 (0.98–1.00) 1.01 (1.00–1.01) 0.99 (0.98–1.00) 1.02 (1.01–1.03)	Holiday, school-in-session, temperature, humidity

Table 3 continued

Study	Population	Outcome	Concentration category	Grains/ m ³	Lag (days)	Measure of effect	Effect (lower CI; upper CI)	Covariates
Héguy et al. (2008)	Visits to emergency departments for asthma of residents of Montreal in all Montreal hospitals	Asthma (ICD-9; 493.XX)	Concentration increase	10	Lag 0	Mean	0.31 (− 0.48 to 1.15)	Minimum temperature, change in barometric pressure over the previous 24 h, maximum O ₃ , maximum NO ₂
					Lag 1	Percentage Change	0.05 (− 1.41 to 1.54)	
					Lag 2		0.05 (− 1.42 to 1.55)	
					Lag 3		1.67 (0.18–3.19)	
					Lag 4		0.87 (− 0.64 to 2.39)	
					Lag 5		1.29 (− 0.2 to 2.81)	
					Lag 6		0.83 (− 0.67 to 2.34)	
				10	Lag 0	Mean	0.31 (− 1.16 to 1.79)	Maximum temperature, maximum barometric pressure, maximum O ₃ , maximum NO ₂
					Lag 1	Percentage Change	0.26 (− 1.2 to 1.74)	
					Lag 2		0.18 (− 1.29 to 1.67)	
					Lag 3		1.73 (0.24–3.25)	
Sun et al. (2016)	Visits in all (8) civilian hospital- affiliated emergency departments in Wake County, North Carolina	Asthma (ICD-9; 493.XX)	Selected Level	10	Lag 4		0.95 (− 0.55 to 2.48)	Air pollutant (ozone), meteorological data, temporal factors, PM10, PM2.5 and precipitation were not correlated with pollen (thus, not included in the multivariable analysis)
					Lag 5		1.43 (− 0.06 to 2.95)	
					Lag 6		0.82 (− 0.67 to 2.33)	
					Lag 2–4	Adjusted Risk Ratio	1.03 (0.98–1.09)	
			Standard deviation 3 rd quartile	10	Lag 2–4		1.03 (0.98–1.09)	
					Lag 2–4		1.03 (0.97–1.09)	
					Lag 2–4		1.05 (1.00–1.11)	
			Level with strongest sig	11	Lag 2–4			

Table 3 continued

Study	Population	Outcome	Concentration category	Grains/ m ³	Lag (days)	Measure of effect	Effect (lower CI; upper CI)	Covariates
Hospital Admission								
Babin et al. (2007)	Paediatric emergency department visits in several hospitals	Asthma (ICD-9; 493.XX) (in one of the first 3 of 9 possible diagnosis fields)	Concentration Increase	10	Lag 0	Mean Percentage Change	0.7 (− 7.4 to 9.5)	Long-term seasonal trends Interactions among O ₃ , PM _{2.5} and different types of pollen were analysed (no sig. interactions found)
Dales et al. (2004)	Emergency hospitalisations of all hospitals in respective city	Asthma (ICD-9; 493.XX)	Concentration increase	14	Between 0 and 5	Mean Percentage Change	1.95 (1.08–2.83)	Long-term trends, day of the week, meteorologic variables, air pollution (presented results without air pollution → did not affect results by more than 1%)
Guilbert et al. (2018)		Asthma (ICD-9; 493.XX)	IQR increase	12	Cum. (lag 0–6)	Percentage change	5.9 (0.0–12.0)	Seasonal and long-term trend, public holidays, day of the week, mean temperature, humidity
Osborne et al. (2017)	In-patient admissions within Greater London to NHS-Hospitals	Asthma (ICD-10 J45 J46)	0-95th percentile increase	104	Lag 0	Percentage change	− 6.18 (− 14.69 to 2.33)	Temperature, precipitation, humidity, day of week, public holidays, PM ₁₀ , NO ₂ , O ₃ , SO ₂
					Lag 1		− 6.69 (− 16.19 to 2.82)	
					Lag 2		6.2 (− 3.28 to 15.69)	
					Lag 3		1.24 (− 7.67 to 10.25)	
					Lag 4		17.23 (17.23–25.54)	
					Lag 5		14.11 (6.22–22.01)	
					Lag 6		5.95 (− 2.04–13.94)	
					Lag 7		3.31 (− 4.21–10.83)	
Silver et al. (2018)	Admissions to all public hospitals in Greater Melbourne	Till 1998: Asthma (ICD-9; 493.XX) After 1998: Asthma (ICD-10 AM J45 J46)	Average concentration	Average of 100 in last three days	Lag 3	Additional admissions	4	Day of the year, relative humidity, temperature, precipitation, north–south wind component, east–west wind component, non-grass pollen (consider lagged variable over different times), O ₃ , PM _{2.5}
Tobias et al. (2003)	Admissions to one hospital in Madrid	Diagnosis of: Asthma or asthmatic bronchitis or Spastic bronchitis or bronchospasm	PVariation in range between the 95th and 99th percentile	98.4	Lag 3	Percentage change	17.1 (3.2–32.8)	Air pollutants (PM ₁₀ , SO ₂ NO ₂ , O ₃), temperature, humidity, acute respiratory infections, day of the week, public holidays, other pollen

ARC allergic rhinitis and conjunctivitis, Avg average, cum cumulated, IQR Interquartile range, SAR seasonal allergic rhinitis, SGS Symptomatic Global Score, sig. significant; URI upper respiratory infections

Table 4 Rules for the Risk of Bias (RoB) assessment

Criteria	Question	Assessment possibilities*	Rules for the assessment (topic-related rules were established by the authors based on the general rules defined by OHAT (OHAT, 2015a, 2015b) and Lam et al. (2016) (supplementary file “Instructions for making risk of bias determinations”))
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	+ +	If the following five confounders, defined as most important by the authors of the systematic review “LUPO”, were at least considered: nitrogen dioxide (NO ₂), ozone (O ₃), particulate matter (PM), relative humidity/precipitation, wind speed
		+	If three or four of the most important confounders were considered
			If three or four confounders were considered but not all included in the final model
		–	Information should be available but is missing
			If one or two of the most important confounders were considered
			If none of the most important confounders but other relevant confounders were considered
Detection bias: exposure characterisation	Can we be confident in the exposure characterisation?	– –	No consideration of confounder
			The authors assume or even declare the bias
		+ +	Daily exposure characterisation AND There is direct evidence that exposure characterisation is adequate for the study population (e.g. residence and pollen trap in same city)
		+	More than weekly but not daily exposure characterisation AND/OR There is no direct evidence that exposure characterisation is adequate for the study population
		–	Weekly or less exposure characterisation AND/OR Information should be available but is missing
		– –	Exposure was inappropriately assessed (e.g. unserious source of exposure assessment) AND/OR The authors assume or even declare the bias
Detection bias: outcome assessment	Can we be confident in the outcome assessment?	+ +	Self-reported symptom(s)/symptom diary, diagnosed by a doctor, emergency visits, hospitalisations, intake or prescriptions or sales of medication, AND Daily assessment of the outcome AND ICD code of outcome was reported and used
		+	Outcome was not self-reported or reported by a doctor but by a third person (e.g. mother) AND/OR Outcome was assessed not daily but several times a week AND/OR ICD code of outcome was not used/reported
		–	Information should be available but is missing AND/OR Outcome was assessed once a week or less often AND/OR Outcome definition was inappropriate (e.g. a mixture of several outcomes), but outcome was appropriately measured AND/OR Content of symptom scores was not described
		– –	Outcome (appropriate or inappropriate definition) was inappropriately measured (e.g. inconsistent definition or data collection) AND/OR The authors assume or even declare the bias

Table 4 continued

Criteria	Question	Assessment possibilities*	Rules for the assessment (topic-related rules were established by the authors based on the general rules defined by OHAT (OHAT, 2015a, 2015b) and Lam et al. (2016) (supplementary file “Instructions for making risk of bias determinations”))
Attrition bias	Were outcome data complete without attrition or exclusion from analysis?	+ +	There was no or a low attrition or exclusion (< 10%) (Genaidy et al. 2007; OHAT, 2015b) AND Reasons were documented, when subjects were removed from the study or excluded from analysis
		+	There was no or a low attrition or exclusion (< 10%) (Genaidy et al. 2007; OHAT, 2015b) AND Reasons were not documented, when subjects were removed from the study or excluded from analysis AND/OR There was an acceptable attrition or exclusion (between 10 and 20% (Genaidy et al. 2007; OHAT, 2015b)) AND Reasons were documented, when subjects were removed from the study or excluded from analysis
		–	Information should be available but is missing (to be distinguished from NA) AND/OR There was an acceptable attrition or exclusion (between 10 and 20% (Genaidy et al. 2007; OHAT, 2015b)) AND Reasons were not documented, when subjects were removed from the study or excluded from analysis AND/OR There was an unacceptable large attrition or exclusion (> 20% (Genaidy et al. 2007; OHAT, 2015b)) AND Reasons were documented, when subjects were removed from the study or excluded from analysis
		– –	There was unacceptable large attrition or exclusion (> 20%) AND Reasons were not documented, when subjects were removed from the study or excluded from analysis The attrition/exclusion rate is unknown The authors assume or even declare the bias
		NA	Not applicable: if secondary data (e.g. insurance or hospital data) is analysed, every case is considered separately what prevents information about attrition. If specific cases of secondary data were excluded by the authors (e.g. specific age groups), then the attrition bias should be assessed
Selective reporting bias	Were all measured outcomes reported?	+ +	All measured outcomes (summarised scores as well as all components; as described in the method section) are reported (in the results section)
		+	It seems that all measured outcomes (summarised scores as well as all components; as described in the method section) are reported (in the results section) OR A summarised outcome (e.g. a score) is reported and all previously described components were included but were not presented separately
		–	Information should be available but is missing OR It is not understandable, if all measured outcomes were presented OR It is not understandable, how the results were derived
		– –	Results of important measured outcomes were not reported AND/OR Some of the outcomes were summarised in a score while others were excluded from the score without reasonable explanation. AND/OR Only significant or a selection of the best findings were reported

Table 4 continued

Criteria	Question	Assessment possibilities*	Rules for the assessment (topic-related rules were established by the authors based on the general rules defined by OHAT (OHAT, 2015a, 2015b) and Lam et al. (2016) (supplementary file “Instructions for making risk of bias determinations”))
Conflict of interest	Do the authors declare no conflict of interest?	+ +	“Study authors make a claim denying conflicts of interest”. “The study did not receive support from a company, study author, or other entity having a financial interest in the outcome of the study” (Lam et al. 2016)
		+	“There is insufficient information to permit a judgement of low risk of bias, but there is indirect evidence that suggests” no conflict of interest. (Lam et al. 2016)
		–	Information should be available but is missing AND/OR “There is insufficient information to permit a judgement of high risk of bias, but there is indirect evidence that suggests” a conflict of interest. (Lam et al. 2016)
		– –	“The study received support from a company, study author, or other entity having a financial interest in the outcome of the study”. (Lam et al. 2016)

*Assessment possibilities: + + definitely low RoB, + probably low RoB, -probably high RoB, – definitely high RoB, NA not applicable

et al., 2003). The observed outcomes of these studies were HA (Dales et al., 2004; Guilbert et al., 2018; Osborne et al., 2017; Silver et al., 2018; Tobias et al., 2003) and ED visits (Cirera et al., 2012; Darrow et al., 2012; Gleason et al., 2014; Heguy et al., 2008; Sun et al., 2016) due to an asthma diagnosis. Only the study of Babin et al. (2007) presented results for both outcomes. Most studies identified asthma cases based on the ICD-9 493 asthma code as a diagnosis, while few studies (Osborne et al., 2017; Silver et al., 2018) used solely or additionally the ICD 10 J45, J46 codes. Further deviations from the ICD-codes are indicated in Table 3.

Five out of six studies investigating the association between asthma-related ED visits and grass pollen exposure found a statistically significant correlation. Both Babin et al. (2007) and Heguy et al. (2008) found a statistically significant percentage increase of 2.6% and 1.7%, respectively, in ED visits. In both studies, the ED visits followed a three-day lag after exposure to a 10 grains/m³ increase in grass pollen concentrations. For the same increase in exposure (increase in grass pollen by 10 grains/m³), Darrow et al. (2012) and Gleason et al. (2014) found minimal but statistically significant associations with ED visits: Darrow et al. (2012) reported a RR of 1.02 (95% CI: [1.01–1.03]), Gleason et al. (2014) an adjusted OR of 1.02 (95% CI:

[1.01–1.03]). Cirera et al. (2012) reported a statistically significant risk of 7.2% for ED visits for a pollen concentration of 10–28 grains/m³ and a no statistically significant risk of a pollen concentration of 0–10 grains/m³. No statistically significant effect on ED visits for 10 grains/m³ was also found by Sun et al. (2016). In summary, both statistically significant and non-significant risks of ED visits could be found for the grass pollen threshold of 10 grains/m³. In summary, for pollen concentrations of 10 grains/m³ a risk of 1.7–2.6% can be derived for ED visits.

Various studies have found a statistically significant association between the number of HA due to asthma and grass pollen counts (Dales et al., 2004; Guilbert et al., 2018; Osborne et al., 2017; Tobias et al., 2003). They reported a percentage increase in HA due to asthma cases between 1.95 and 17.23%, with different numbers of lag days. The lowest percentage increase of 1.95% of HA due to asthma was found by Dales et al. (2004) for grass pollen concentration of 14 grains/m³. In contrast, Guilbert et al. (2018) observed a larger percentage increase in HA (5.9%) at a concentration of 12 grains/m³. Osborne et al. (2017) reported a statistically significant percentage increase in HA of 14.11% and 17.23% for 104 grains/m³. Tobias et al. (2003) also found a similar statistically significant percentage increase in HA

Table 5 Criteria for a low RoB assessment

Bias	Criteria for low RoB assessment
Confounding bias	NO ₂ , O ₃ , PM, humidity/precipitation and wind speed considered as confounder
Detection bias (exposure)	Pollen concentration collected daily with pollen sampler at appropriate location
Detection bias (outcome)	Outcome reported daily by patient him-/herself, diagnosed by doctor, documented as visits of health facilities, or documented as medication intake, prescriptions or sales
Attrition bias	Attrition or exclusion below 10% and reasons for attrition or exclusion documented
Selection bias	Day of the week and a variable about time/seasonal trends considered (If secondary data analysed, assessment of attrition bias was not applicable)
Selective reporting bias	All measured outcomes reported in the results section (e.g. Including single components of summarised scores)
Conflict of interest	A declaration of no conflicts of interest

(17.1%) for a pollen concentration of 98.4 grains/m³. Furthermore, Silver et al. (2018) found that grass pollen had a statistically significant effect, when mean concentrations of pollen exceeded 100 grains/m³ for three successive days. In contrast, Babin et al. (2007) found no statistically significant association between HA and a same-day exposure of 10 grains/m³ of grass pollen. In summary, all analysed studies reported a statistically significant percentage increase in hospital admissions above a pollen threshold of 12 grains/m³. Furthermore, it was observed that the percentage increase in hospital admissions grows with increasing pollen concentrations.

3.1.2 Medication and prescription data

Four studies investigating the association between the outcome medication and prescription data (drug consumption/medication sales) and grass pollen concentrations reported statistically significant RRs between 1.04 and 1.13 (Table 3) (Caillaud et al., 2015; Fuhrman et al., 2007; Guilbert et al., 2016; Motreff et al., 2014). These studies report pollen concentrations using an interquartile range (IQR). All these studies examined a different period of lag days

from 0 to 10 lag days. Caillaud et al. (2015) showed a statistically significant relative risk of 1.04 for drug consumption/medication sales at an IQR of 38 grains/m³ (95% CI: [1.038–1.050]). Motreff et al. (2014) observed a statistically significant RR of 1.11 (95% CI: [1.08–1.14]) for an IQR of 31 grains/m³ for the French city Montpellier. In contrast, for the French city Nimes, Motreff et al. (2014) found a statistically significant RR of 1.11 (95% CI: [1.07–1.14]) for an IQR of already 14 grains/m³. A percentage increase of 8.7% (RR = 1.087; 95% CI: [1.069–1.105]) was reported for an IQR of 41 grains/m³ by Fuhrman et al. (2007). Guilbert et al. (2016) found statistically significant RRs between 1.04 and 1.13 for an IQR of 20 grains/m³ for all sex and age groups younger than 65 years except for females aged 13–18 years. In summary, the results and possible threshold values are difficult to derive. A statistically significant increase in medication consumption was found for all observed pollen concentrations. Additionally, Motreff et al. (2014) showed that different pollen concentrations (14 grains/m³ and 31 grains/m³) at two different locations (Nimes and Montpellier) show the same RR of 1.11 (95% CI: [1.08–1.14]) for drug consumption/medication sales.

3.1.3 Pollen-related symptoms

Three studies investigated the association between the concentration of grass pollen and self-reported health symptoms. Annesi-Maesano et al. (2012) showed an OR of 1.08 (95%-CI: [1.04–1.11]) for pollen-related symptoms at a pollen threshold value for 60 grains/m³. DellaValle et al. (2012) reported an OR of 1.80 (95% CI: [1.31–2.47]) for self-reported health symptoms starting at a threshold value of 3–4 grains/m³. In addition, DellaValle et al. (2012) observed that increasing pollen levels let the OR for pollen-related symptoms rise:

- 5–8 grains/m³: (OR = 2.09; CI: [1.31–3.33]);
- 9–15 grains/m³: (OR = 2.58; CI: [1.60–4.18]);
- > 15 grains/m³: (OR = 2.64; CI: [1.55–4.49]).

Feo Brito et al. (2007) found no statistically significant association between grass pollen concentration (IQR = 99 grains/m³) and intensity of pollen-related symptoms. In summary, it is difficult to derive possible threshold values from the results. DellaValle et al. (2012) found a statistically significant OR of 1.80

Table 6 Heatmap of the Risk of Bias (RoB) assessment

Nb	Authors (year)	Key criteria			Other criteria			
		Confounding bias	Detection bias: exposure characterisation	Detection bias: Outcome assessment	Attrition bias	Selective reporting bias	Conflict of interest	In- or exclusion from data synthesis
1	Annesi-Maesano et al. (2012)	+	+	+	NA	+	–	Inclusion
2	Babin et al. (2007)	+	+	+	NA	+	+	Inclusion
3	Caillaud et al. (2015)	+	+	+	NA	+	+	Inclusion
4	Cirera et al. (2012)	+	+	+	NA	+	+	Inclusion
5	Dales et al. (2004)	+	+	+	NA	+	–	Inclusion
6	Darrow et al. (2012)	+	+	+	NA	+	–	Inclusion
7	DellaValle et al. (2012)	+	+	+	+	+	–	Inclusion
8	Feo Brito et al. (2007)	+	+	+	+	+	–	Inclusion
9	Fuhrman et al. (2007)	+	+	+	+	+	+	Inclusion
10	Gleason et al. (2014)	+	+	+	NA	+	+	Inclusion
11	Guilbert et al. (2016)	+	+	+	NA	+	+	Inclusion
12	Guilbert et al. (2018)	+	+	+	NA	+	+	Inclusion
13	Héguy et al. (2008)	+	+	+	NA	+	–	Inclusion
14	Motreff et al. (2014)	+	+	+	NA	+	–	Inclusion
15	Osborne et al. (2017)	+	+	+	NA	+	–	Inclusion
16	Silver et al. (2018)	+	+	+	NA	+	+	Inclusion
17	Sun et al. (2016)	+	+	+	NA	+	+	Inclusion
18	Tobias et al. (2003)	+	+	+	NA	+	+	Inclusion

+ + definitely low RoB (dark green), + probably low RoB (lime green), -probably high RoB (orange), – definitely high RoB (red), NA not applicable (white)

for symptoms from a pollen concentration of 3–4 grains/m³. The observed ORs increased steadily with increasing pollen concentration. In contrast, Annesi-Maesano et al. (2012) found a statistically significant OR of 1.08 for a pollen concentration of 60 grains/m³.

3.2 Confounding variables

The RoB assessment showed that all studies included confounders in their analysis. However, only two (DellaValle et al., 2012; Guilbert et al., 2018) reported a possible effect of confounding or effect modification by age groups, air pollution, influenza epidemics and respiratory viral infections (DellaValle et al., 2012; Guilbert et al., 2018). Several studies excluded air pollutants after no effect was found, or when included in the model, the size of the effect was not further investigated (Table 3).

3.3 Lags

Table 8 gives an overview of the in the studies reported lag days. Most studies calculated the effect starting at the same day up to the third day after exposure. Longer lags were rarely reported. A lag of 3 days showed the highest number of statistically significant results.

3.4 Pollen sampler

The used pollen sampler and the pollen sampler location is shown in Table 2. The pollen stations are located in cities ($n = 12$) or suburban areas ($n = 1$) (Annesi-Maesano et al., 2012; Caillaud et al., 2012; Cirera et al., 2012; Dales et al., 2004; Feo Brito et al., 2007; Fuhrman et al., 2007; Gleason et al., 2014; Guilbert et al., 2016, 2018; Heguy et al., 2008; Motreff et al., 2014; Osborne et al., 2017; Silver et al., 2018). The height at which the pollen stations were located

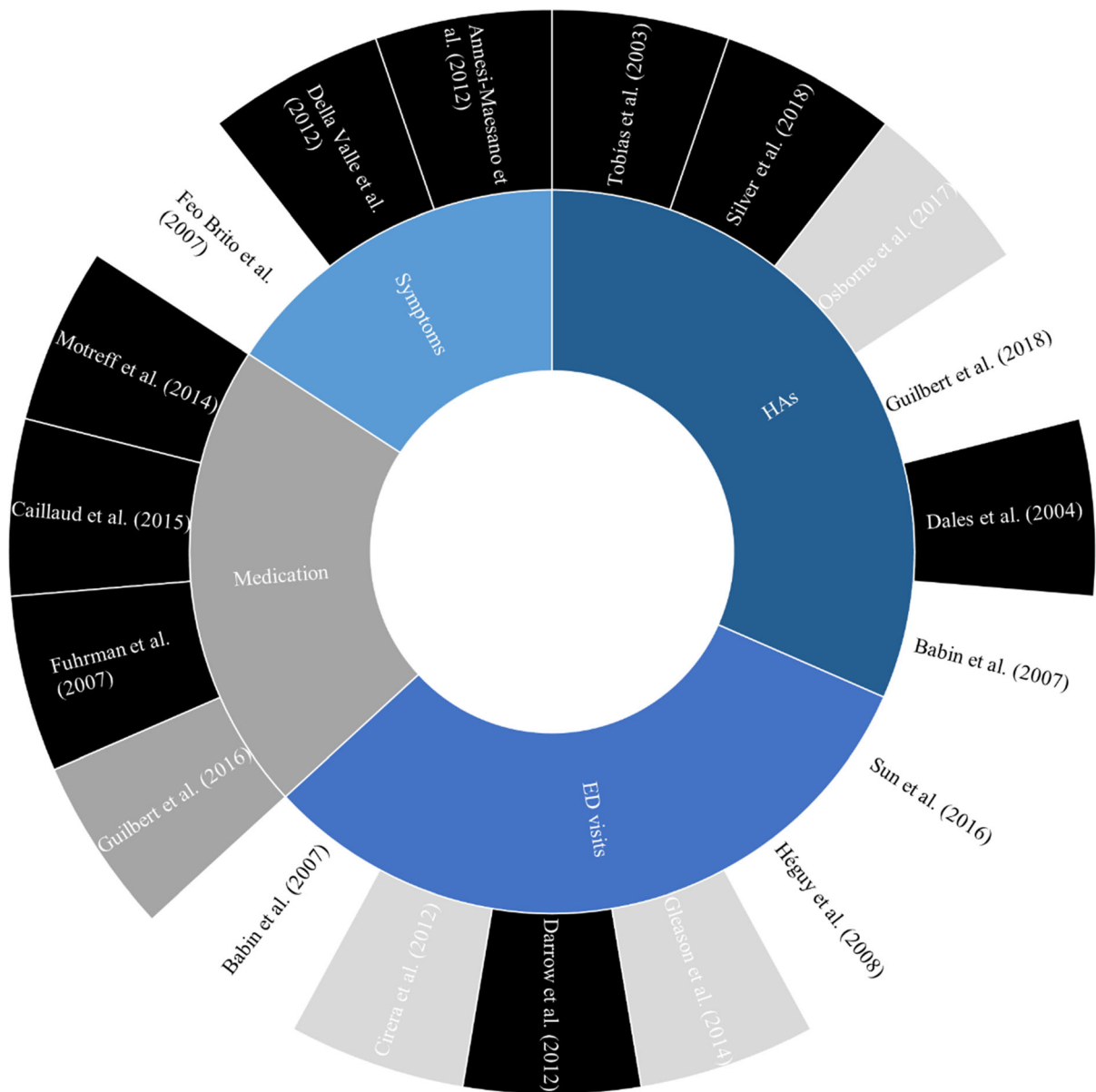


Fig. 2 Circle diagram with kind of health outcome, studies and significance of results. Legend: description of the colours of the outermost ring: black background: studies with significant

results; grey background: studies with significant results only in sub-analyses; white background: studies with non-significant results;

varied between the studies (2.45–30 m). Out of 18 studies, nine did not indicate the height of the pollen station (Annesi-Maesano et al., 2012; Babin et al., 2007; Dales et al., 2004; DellaValle et al., 2012; Feo Brito et al., 2007; Gleason et al., 2014; Osborne et al., 2017; Sun et al., 2016; Tobias et al., 2003).

3.5 Age groups

Eight of 18 studies investigated effects in subgroups such as age groups (Annesi-Maesano et al., 2012; Babin et al., 2007; Caillaud et al., 2015; Darrow et al., 2012; Fuhrman et al., 2007; Guilbert et al., 2016, 2018; Motreff et al., 2014).

Table 7 Summary of included studies according to country and health outcome

Total	28
Total used for result synthesis	18
<i>Country</i>	
Belgium	2
Canada	2
England	1
France	4
Spain	3
USA	5
Australia	1
<i>Health outcome (number of studies with significant results in brackets)*</i>	
Drug consumption	4 (4)
Emergency department visits	6 (5)
Hospital admission	6 (5)
Symptoms	3 (2)
Missing conflict of interest statement	8

*The sum of the number outcomes is higher than total, because one study investigate more than one outcome

3.5.1 Emergency department visits and hospital admissions

Only one of six studies that investigated the association between pollen-related ED visits and grass pollen concentrations analysed the impact on different age groups (Darrow et al., 2012). In the study by Darrow et al. (2012), the subgroups of 5–17-year-olds and 18+ year-olds had a risk of ED visits above a threshold value of 10 grains/m³ (RR = 1.02, CI: [1.01–1.04] and RR = 1.03, CI: [1.02–1.04]). The subgroup of 0–4-year-olds showed no statistically significant risk of ED visits above a threshold of 10 grains/m³ (RR = 1.007; CI: [0.988–1.025]).

Two studies out of six investigating the effect of pollen concentrations on HA analysed different age groups (Babin et al., 2007; Guilbert et al., 2018). Guilbert et al. (2018) found for a pollen value of 12 grains/m³ a statistically significant percentage change of 7.9% for HA in the age group 15–59 years. No statistically significant percentage changes for HA were found in the subgroups of 0–14-year-olds and over 60-year-olds (Guilbert et al., 2018). Babin et al. (2007) found no statistically significant percentage change in different age groups for a threshold of 10 grains/m³. In summary, there were no definitive results found that point to a particular vulnerability of a specific age group for pollen-associated ED visits or HA.

3.5.2 Medication and prescription data

All four studies about pollen concentration and medication and prescription data (drug consumption/medication sales) analysed the effects in different age groups (Caillaud et al., 2015; Fuhrman et al., 2007; Guilbert et al., 2016; Motreff et al., 2014). Motreff et al. (2014) investigated different age groups (5–14-year-olds, 15–44-year-olds, 45–64-year-olds and over 65-year-olds) in the cities Montpellier and Nîmes. The relative risk of drug consumption was statistically significant for all age groups at a pollen concentration of 14 grains/m³ (Nîmes) and 31 grains/m³ (Montpellier). In Montpellier, analysing all age groups the highest risk of drug consumption/medication sales was found for the 5–14-year-olds at a pollen concentration value of 31 grains/m³ (RR = 1.20; CI: [1.13–1.28]) (Motreff et al., 2014). In Nîmes, the highest estimator for the risk of drug consumption/medication sales was found for the age group 15–44-year-olds at a threshold value of 14 grains/m³ (RR = 1.15; CI: [1.07–1.23]) (Motreff et al., 2014).

In the study of Caillaud et al. (2015), the age groups 5–14-year-olds, 15–44-year-olds, 45–64-year-olds and over 65-year-olds were investigated. The relative risk of drug consumption/medication sales was statistically significant above a threshold value of 38 grains/m³ for all age groups. The 5–14-year-olds had a statistically significant risk (RR = 1.08; CI: [1.07–1.10]) of drug consumption/medication sales

compared to the other age groups. The over 65-year-olds had a statistically significant risk (RR = 1.02; CI: [1.01–1.03]).

Fuhrman et al. (2007) investigated different age groups (5–14-year-olds, 15–34-year-olds, 35–64-year-olds and over 65-year-olds). The relative risk of drug consumption/medication sales was statistically significant above a threshold value of 41 grains/m³ for all age groups. Fuhrman et al. (2007) identified a 6.4% risk of pollen-associated drug consumption/medication sales for the over-65 age group (CI: [4.7–8.1]). The 35–64-year-olds had the lowest statistically significant risk of drug consumption/medication sales (3.8%; CI: [2.4–5.3]) (Fuhrman et al., 2007).

In the study of Guilbert et al. (2016), the age groups 0–5-year-olds, 6–12-year-olds, 13–18-year-olds, 19–39-year-olds, 40–64-year-olds, 65–84-year-olds and over 85-year-olds were investigated stratified by gender. For pollen concentration of 20 grains/m³, the study of Guilbert et al. (2016) showed statistically significant relative risks of drug consumption/medication sales for some age groups, while other age groups had no statistically significant results. The 19–39-year-olds had the highest statistically significant risk of drug consumption/medication sales (female: RR = 1.10; CI: [1.08–1.11] and male: RR = 1.13; CI: [1.11–1.14]). The over 85-year-olds had the lowest risk of drug consumption/medication sales (female: RR = 0.99; CI: [0.96–1.02] and male: RR = 0.98; CI: [0.94–1.03]) (Guilbert et al., 2016).

In summary, no age group could be identified as particularly vulnerable to pollen-related medication intake. Two out of four studies identified the 5–14 age group as vulnerable for high drug consumption/medication sales when exposed to pollen. (Caillaud et al., 2015; Motreff et al., 2014). In contrast, three out of four studies showed a small risk of drug consumption/medication sales among the oldest age group (over 65 years or over 85 years) (Caillaud et al., 2015;

Guilbert et al., 2016; Motreff et al., 2014). Only one study identified the age group over 65 years as vulnerable with the highest risk of drug consumption/medication sales (Fuhrman et al., 2007). These studies show a mixed picture. Based on these results, it is not possible to derive pollen threshold values for a specific age group or to identify a specific age group as particularly vulnerable.

3.5.3 Pollen-related symptoms

One of three studies investigating pollen concentration and symptoms conducted a subgroup analysis by age (Annesi-Maesano et al., 2012). Annesi-Maesano et al. (2012) were able to show an association for over 65-year-olds for pollen count of 60 grains/m³ and pollen-related symptoms (OR = 0.56 (CI: [0.45–0.70])).

3.6 Subgroups by location

The locations of the studies are shown in Table 2.

3.6.1 Emergency department visits and Hospital admissions

Statistically significant associations between a pollen concentration of at least 10 grains/m³ and ED visits could be found in four studies at different locations. Statistically significant associations between pollen-associated ED visits and pollen concentrations of 10 grains/m³ were observed in studies conducted in Montreal (1.7%) (Heguy et al., 2008), in Washington DC (2.6%) (Babin et al., 2007), in New Jersey (RR = 1.02) (Darrow et al., 2012) and in Georgia (OR = 1.02) (Gleason et al., 2014). No association for pollen-associated ED visits and a pollen concentration from 0 to 10 grains/m³ were found in the Spanish city of Cartagena (Cirera et al., 2012). Sun et al. (2016)

Table 8 Overview of lag days that were reported in all studies

	Lag 0	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6	Lag 7
Number	10	7	5	7	3	3	2	1
Percentage	0.56	0.39	0.28	0.39	0.17	0.17	0.11	0.06
Significant results	3	3	1	5	1	1	0	0
Percentage of significant results	0.30	0.43	0.20	0.71	0.33	0.33	0	0

*Reports of cumulative results are not included in this table

found no association of pollen concentrations above 10 grains/m³ and ED visits in Wake County (North Carolina). For the sub-analyses by location with regard to ED visits, it can be concluded that both statistically significant and non-significant effects with ED visits are observed at a pollen concentration of 10 grains/m³ and above. And secondly, the pollen-induced risk of ED visits varies according to location.

Statistically significant associations of pollen concentrations above 11 grains/m³ and HA were observed in studies conducted in Halifax, London (in Canada), Windsor (in Canada), Madrid, London, Melbourne and Brussel (Dales et al., 2004; Guilbert et al., 2018; Osborne et al., 2017; Silver et al., 2018; Tobias et al., 2003). Dales et al. (2004) compared pollen-associated number of HA between ten Canadian cities. A statistically significant increase in pollen-associated HA of 3.19% was observed in Halifax at a pollen concentration of 11 grains/m³ (Dales et al., 2004). A statistically significant increased risk of HA (5.8% and 6.5%) was found for pollen concentrations of 12.2 and 18.7 grains/m³ in London and Windsor (Dales et al., 2004). A statistically significant increase in HA (17%) was found for pollen concentration of 98.4 grains/m³ and 104 grains/m³ in Madrid and London (England) (Osborne et al., 2017; Tobias et al., 2003). A value of 12 grains/m³ results in an increased risk of HA (5.9%) in a study in Brussel (Guilbert et al., 2018). No statistically significant results for an increased risk of HA were found for pollen concentration values of 10 grains/m³ in a study in Washington DC (Babin et al., 2007). In summary, it can be concluded that statistically significant associations of ED visits and HA and pollen concentrations of 11 grains/m³ can be observed. The level of risk of HA starting from a value of 11 grains/m³ varies depending on the location.

3.6.2 Medication and prescription data

All French studies in this review showed a statistically significant increase in drug consumption/medication sales at different pollen concentration levels in each case. Caillaud et al. (2015) reported a statistically significant RR of 1.04 (CI: [1.038–1.050]) for a pollen concentration of 38 grains/m³ in Clearmont-Ferrand. In contrast, also in Clearmont-Ferrand, Fuhrman et al. (2007) identified a statistically significant percentage of 8.7% for a pollen concentration of 41 grains/m³.

Furthermore, Motreff et al. (2014) identified the same relative risk of drug consumption/medication sales at different threshold values in two French cities. In the French city of Nimes, a statistically significant relative risk of 1.11 (CI: [1.07–1.14]) for drug consumption/medication sales was found at a threshold value of 14 grains/m³. In contrast, in the French city of Montpellier, a statistically significant relative risk of 1.11 (CI: [1.08–1.14]) for drug consumption/medication sales could be found at a pollen concentration of 31 grains/m³ (Motreff et al., 2014). For the sub-analysis by location, it can be summarised that statistically significant associations can be observed for pollen concentrations above 14 grains/m³ with drug consumption/medication sales.

3.6.3 Pollen-related symptoms

Among the included studies, the only statistically significant association of pollen concentrations above 60 grains/m³ with symptoms was found for metropolitan France (OR = 1.08; CI: [1.04–1.11]) (Annesi-Maesano et al., 2012). Considering the association of pollen concentration and the occurrence of symptoms, no effects could be shown in the northeast of the USA for different threshold values (3–4 grains/m³ (OR = 1.20; CI: [0.84–1.73]), 5–8 grains/m³ (OR = 1.37; CI: [0.94–2.01]), 9–15 grains/m³ (OR = 1.34; CI: [0.91–1.98]) above 15 grains/m³ (OR = 1.48; CI: [0.98–2.23])) (DellaValle et al., 2012). Feo Brito et al. (2007) found no statistically significant percentage changes for a threshold value of 99 grains/m³ in the Spanish cities Ciudad Real and Puertollano. For the sub-analysis of pollen-related symptoms by location, it can be concluded that the pollen concentrations at which symptoms are observed vary from location to location. Moreover, it is not always possible to specify concrete pollen concentrations.

4 Discussion

This systematic review summarises literature on grass pollen-induced health outcomes like hospital admissions, emergency department visits, drug consumption and allergic symptoms. The aim was to give an overview of several outcomes and to identify potential pollen concentrations at which outcomes occur.

4.1 Key findings

By including a wide range of health outcomes and study populations, this review provides a unique accumulation and aggregation of data on the effects of grass pollen on health outcomes. The results of 18 studies with a low RoB were investigated and summarised, presenting results for pollen-associated ED visits, HAs, drug consumption and symptoms. The risk of ED visits due to pollen concentrations of 10 grains/m³ varied from 1.7 to 2.6% in the included studies (Babin et al., 2007; Cirera et al., 2012; Darrow et al., 2012; Gleason et al., 2014; Heguy et al., 2008; Sun et al., 2016). A statistically significant percentage increase in hospital admissions could be observed at pollen concentration values of 12 grains/m³ (Babin et al., 2007; Dales et al., 2004; Guilbert et al., 2018; Osborne et al., 2017; Silver et al., 2018; Tobias et al., 2003). Possible pollen threshold values are difficult to summarise from the studies focussing on drug consumption/medication sales (Caillaud et al., 2015; Fuhrman et al., 2007; Guilbert et al., 2016; Motreff et al., 2014) and symptoms (Annesi-Maesano et al., 2012; DellaValle et al., 2012; Feo Brito et al., 2007). In addition, it could be shown that more HA was counted at higher pollen concentrations.

This review did not identify any age group as vulnerable for pollen-associated health outcomes (Annesi-Maesano et al., 2012; Babin et al., 2007; Caillaud et al., 2015; Darrow et al., 2012; Fuhrman et al., 2007; Guilbert et al., 2016, 2018; Motreff et al., 2014). For the sub-analysis by location, it can be summarised that the level of pollen concentrations leading to more ED visits, HA, medication use and symptoms varied.

4.2 Health outcome-specific data

4.2.1 Emergency department visits and hospital admissions

Out of six studies investigating an exposure of 10 grains/m³, four studies found a statistically significant increase in ED visits (Babin et al., 2007; Darrow et al., 2012; Gleason et al., 2014; Heguy et al., 2008). The results found in this review strengthen the assumption that grass pollen exposure of 10 grains/m³ leads to pollen-associated health outcomes, while Sun et al. (2016) documented no significant effect of pollen

concentration of 10 grains/m³ and ED visits. This could be an indication that the allergic reaction depends on the properties of the individual pollen, as well as on the environmental conditions. Considering the present studies, it can be concluded that there is a risk of ED visits above a threshold of 10 grains/m³ (Babin et al., 2007; Cirera et al., 2012; Darrow et al., 2012; Gleason et al., 2014; Heguy et al., 2008; Sun et al., 2016).

From the six studies dealing with grass pollen and HA, a threshold value at 12 grains/m³ can be derived. A pollen concentration value of 12 grains/m³ resulted in a higher probability of pollen-associated HA of 2–6%. A value of 100 grains/m³ increased the probability by 17%. The higher the pollen concentration, the higher the risk of pollen-associated HA can get. No association between pollen concentrations below 10 grains/m³ and ED visits or HA could be observed. This concentration might be too low to cause severe symptoms leading to ED and HA triggered by allergic asthma.

4.2.2 Medication and prescription data

All four studies on grass pollen exposure and drug consumption found statistically significant associations (Caillaud et al., 2015; Fuhrman et al., 2007; Guilbert et al., 2016; Motreff et al., 2014). But the authors were not able to derive an overall pollen threshold value from the study results. However, it could be observed that the risk of medication intake increased with pollen concentration values. With further increasing concentrations, the effects decreased or remained constant. Above a value of 14 grains/m³, a higher risk of drug consumption is to be expected. However, the effects do not develop linearly to the threshold values.

4.2.3 Pollen-related symptoms

The results of the three studies on symptoms and grass pollen showed inconsistent results. This could be due to the subjective assessment of symptoms in the studies. Which pollen concentrations can lead to allergic symptoms cannot be answered with the available studies, as the reported exposure concentrations varied.

4.3 Subgroup analyses

The authors could not identify specific age groups at higher risk of any of the health outcomes. Darrow et al. (2012) and Guilbert et al. (2018) concluded that allergies are difficult to detect in an age group under five years. Therefore, the evaluation of allergy-induced ED visits and HAs in very young children may be biased. The non-stratified results of the included studies differed from the results of the subgroup-analyses stratified by age with regard to associations of grass pollen concentrations and health outcomes. Following the findings of Darrow et al. (2012) and Guilbert et al. (2018), the authors expect a bias in the results of the very young age groups (0–5 years). According to the report “Guidelines for the Diagnosis and Management of Asthma”, the diagnosis of asthma is particularly difficult in 0–4-year-olds because objective measurements of lung function are not possible in this age group (National Asthma Education and Prevention Program, 2007). Thus, the younger age groups may often have undiagnosed pollen allergy or asthma and are at higher risk of symptoms. The low vulnerability of the oldest age group (over 65 years) could be explained by the limited mobility of the patients. Patients with limited mobility are less likely to spend time outdoors and thus less likely to be exposed to pollen. In the future studies, socio-demographic factors and the average length of time spent outdoors should be taken into account when analysing pollen concentrations and their impact on health.

The results of the subgroup-analyses stratified by geographical location were also not consistent. The authors could not identify specific geographical location that showed a higher risk of any of the health outcomes. The study by Motreff et al. (2014) calculated relative risks of pollen-associated drug consumption/medication sales in the cities of Montpellier and Nîmes. In Nîmes, the relative risk (RR = 1.11; CI: [1.07–1.14]) of pollen-associated drug consumption/medication sales was reached at a pollen concentration of 14 grains/m³ and in Montpellier at a pollen concentration of 31 grains/m³ (RR = 1.11; CI: [1.08–1.14]). This could lead to the conclusion that the population in Nîmes might be more vulnerable to grass pollen than the population in Montpellier. Another explanation could be that pollen in Montpellier might have less potential to cause allergies.

In this review, the results of the subgroup analysis stratified for age and geographical location showed a similarly inconsistent picture as the non-stratified results. Those deviations indicated that environmental aspects such as region, climate or weather events as well as individual aspects such as one’s own sensitivity or the allergenic potential of pollen can influence health outcomes. This indicates that other factors and possible influences besides geographical location should be considered more closely in the future research.

4.4 Further explanations

Several factors that may have led to inconsistent results are presented below.

Buters et al. (2012) and Jantunen et al. (2012) concluded that the allergen content per pollen grain may differ substantially. Additionally Schäppi et al. (1997) derived the size of allergen carrying particles (ruptured pollen) as an influencing factor. Thus, more information about pollen itself should be collected and analysed (Bastl et al., 2014; Buters et al., 2012). Furthermore, the authors suggest that the accuracy of pollen concentration data may vary between the analysed studies. Rojo et al. (2020) showed that measured pollen concentrations can vary due to the height of the pollen station. Pollen stations should be set up at an average height of ten metres (Buters et al., 2018). In this review, the height of the pollen stations varied between 2.45 and 30 m. This height difference could bias the results.

Individual differences in tolerance levels leading to allergic reactions could also explain differences in results of the studies investigated. In the study of Jantunen et al. (2012), a higher tolerance for birch pollen of people from Finland in comparison with people from Austria was found. Due to the different vegetation in Finland and Austria, birch pollen counts in Finland are generally much higher than in Austria (Buters et al., 2012; Jantunen et al., 2012). Buters et al. (2012) concluded from the results of Jantunen et al. (2012) that in Finland a local adaptation of the population to the high birch pollen concentration might have occurred. As a result, the population in Finland could be less sensitive to birch pollen. The same symptom score was observed in Austria at a pollen concentration of 250 grains/m³ while it was 600 grains/m³ in Finland (Buters et al., 2012).

Werchan et al. (2017) refer to further factors that influence people's symptom perception and behaviour (e.g. own variable bronchial hyperreactivity, degree of sensitisation, influence of drugs, own perception of symptoms, etc.). Damialis et al. (2019a) found that similar pollen concentrations can cause different intensities of symptoms under different environmental conditions.

Another possible factor that could explain the inconsistent results is the timing of the pollen measurement. There may be a difference in allergen content of pollen in the early season and pollen in the late season (de Weger et al., 2011; Sofiev & Bergmann, 2013). Buters et al. (2015) attribute this difference in allergen release to the natural variability between pollen-producing species. The observations of D'Amato et al. (2001) also support the assumption of a different allergen content of the pollen. D'Amato et al. (2001) observed that the prevalence and severity of health effects in certain patients increased over time even though the pollen concentration in the air remained the same. A possible explanation is air pollution which may have an effect on the allergenicity of pollen (Mur Gimeno et al., 2007). The aspect of air pollution was identified as a confounder in some studies included in this review and considered in the risk of bias analysis. These possible influencing factors may explain the inconsistent results and emphasises the lack of sufficient data on this topic (Kiotseridis et al., 2013).

In general, it should be noted that the date of medication sales or consumption cannot be correlated with the date of pollen counts, as there may be delays in medication sales and consumption. However, medication sales and consumption can be used as an indicator of the prevalence of SAR and allergy symptoms. For example, the found results show an increase in drug sales for SAR and allergy symptoms (Caillaud et al., 2015; Fuhrman et al., 2007; Guilbert et al., 2016), indicating that pollen-related diseases increase with pollen concentration in the investigated populations. This is coherent with recent literature, documenting an increase in asthma, SAR and other allergy-related diseases (Kiotseridis et al., 2013; Shea et al., 2008; von Mutius et al., 1998). Despite a rising prevalence, a rising number of diagnoses and increased treatment of mild cases could also lead to an increase in medication sales (Fuhrman et al., 2007). Further, determining health outcomes based on

medications sales is not ideal because use of medication highly depends on the affected person's attitude. Preventive medication might be purchased and taken in advance (Dales et al., 2008; Zeghnoun et al., 2005). Therefore, an underestimation of the effect of grass pollen on individuals is likely. Thus, reported associations between grass pollen count and health outcomes could also underestimate the effect of grass pollen on health.

An important factor is the considered lag of outcomes. Most data were reported for same-day exposure ($n = 10$) up to a three-day lag ($n = 7$). Results suggested that the highest increase in outcomes can be expected on the third day after exposure. Of those studies which included outcome measurements of the third day after exposure, over 70% showed statistically significant results (Table 8). This is coherent with the fact that symptoms as well as help-seeking behaviour mostly do not occur on the same day of exposure, but a few days delayed (Kiotseridis et al., 2013). Such symptom data can be best documented with a pollen app. Pfaar et al. (2020) used a pollen app, which used a symptom and medication score, to collect grass-induced symptom loads in AR. They found a correlation between pollen concentration peaks and pollen-induced symptom loads (Pfaar et al., 2020). This highlights the necessity for the wide use of pollen apps in the future studies. In general, the reporting of lag days can be described as highly selective. Often, only statistically significant lags are reported and sometimes the effect of lags were cumulated. Further, it was not always exactly indicated which lag was reported, making comparisons and aggregation of data difficult. To gain a more coherent view of lag effects, a more consistent reporting of all lag days is necessary.

A majority of the studies examined the association of pollen concentration on health outcome as a linear correlation. For example, Tobias et al. (2003) examined the relationship between pollen concentrations and HA as a linear effect. Later, Tobias et al. (2004) published a second paper, based on the same study population, where a nonlinear relationship of grass pollen increase and HAs was investigated in more detail. They found that the percentage change of HAs due to asthma increases approximately up to a pollen count of 60 grains/m³, then stagnates for a while and increases further up from a grass pollen level of around 125 grains/m³ (Tobias et al., 2004). Unfortunately,

several other studies reporting such thresholds could not be included in this review, due to a probably high or high RoB (Caillaud et al., 2012; Feo Brito et al., 2010; Hofman et al., 1996; Huynh et al., 2010; Johnston et al., 2009; Kiotseridis et al., 2013; Lewis et al., 2000; Lipiec et al., 2005; Rosas et al., 1998; Ross et al., 2002). Therefore, the suggestion of the study of Davies and Smith (1973) that all sensitive individuals will experience allergic symptoms on days when grass pollen count exceeds 50 grains/m³ could not be confirmed by all studies (Davies & Smith, 1973). Further research is needed, to verify such results.

While general thresholds for large populations seem difficult to define, pollen information services could be useful for individual use (Glattacker et al., 2020). The number of active pollen monitoring stations is increasing worldwide (Buters et al., 2018). Allergy sufferers are interested in daily pollen concentrations and the risk of personal symptoms. Despite the existence of clearly specified threshold values, avoiding direct contact with the allergens is the most effective way to minimise allergic symptoms (Kiotseridis et al., 2013). Therefore, the combination of exact pollen monitoring and precise individual symptom documentation to daily pollen concentrations could enable patients to avoid negative health outcomes in the future. For example, smartphone applications that combine individual symptom data and pollen concentrations could be used to determine personalised pollen thresholds that forecast health outcomes more reliably than generalised thresholds. Bousquet et al. (2018) prove the benefits of collecting symptoms via a mobile app. This facilitates access to and evaluation of the collected data (Bousquet et al., 2018). A pollen allergy sufferer who uses pollen information services could estimate his or her own allergic reaction based on the pollen concentrations. Pollen allergy sufferers would be able to set their own individual thresholds based on their own observation of pollen concentrations and associated symptoms.

None of the studies differentiated between different species of grass pollen, as with the currently available biomonitoring techniques it is practically impossible. It needs to be considered that local variations in pollen types, levels and combinations can have different effects (Erbaş et al., 2018). Therefore, these possibly influencing factors need to be analysed in more detail (Kiotseridis et al., 2013).

In addition, it should be noted that despite the identified threshold values, patients with AR react individually to different pollen (Damialis et al., 2019a). Thus, personal limit values are possible. The immune system reacts cumulatively to the total sum of all aeroallergens (Damialis et al., 2019a). Every person is exposed to a variety of bioaerosols, including allergenic pollen and fungal spores, but the effects of the co-exposure are not well explored to date, especially under co-sensitisation with dust mites and other allergens. The combination of aeroallergens and other environmental factors such as air pollution or relative humidity can lower the threshold values for individual patients and among different localities (Damialis et al., 2019a). For this reason, the results of this work should be considered with caution.

4.5 Strength and limitations

Our study has some limitations. The definition of AR, ED visits, HAs, medications and severity of symptoms vary between the included studies. These differences reduce the comparability of the results. Therefore, the authors cannot draw general conclusions from the results found. Future studies should define AR and health outcomes in a comparable way.

A strength of the study is the broad view on several categories of health outcomes. A comparable review is not yet available. PubMed, as ‘the primary tool for searching biomedical literature’ (Lu, 2011), was used to apply the broad search term. Further literature was identified by snowball strategy and expert’s consultations. Even though absolute completeness is hardly ever reached, a high effort has been directed into the identification of relevant studies.

High priority was given to the risk of bias assessment of the studies, which met the criteria for inclusion. An extensive catalogue of rules for the RoB assessment was developed (Table 4) and used for an objective and replicable study assessment.

5 Conclusion

In conclusion, grass pollen exposure results in allergic symptoms, leading to medication use, ED visits and HAs. Based on the present literature, an indication of a threshold value for grass pollen could be identified. More ED visits could be observed at a pollen

concentration value of 10 grains/m³ and more HA at a value of 12 grains/m³. In addition, some studies have shown that between concentrations of 10 grains/m³ and 14 grains/m³, there appeared to be more pollen-associated ED visits, HA and drug consumption/medication sales. Several influencing factors (e.g. age, sex, allergen content of pollen, different personal and population reactivity and location of pollen samplers) should be investigated in more detail in the future research. Individual threshold values could be more useful than general threshold values. With the help of applications, for example, pollen data could be linked to individual symptoms of allergy sufferers.

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Data availability All listed tables, figures and supplements are included in the paper or available in the online supplementary.

Declarations

Conflict of interest Damialis is author of a few paper (Damialis et al. 2019a, 2019b) included in this review. The authors declare that there is no conflict of interest. Buters is author of the paper (Buters et al. 2018) included in this review. The authors declare that there is no conflict of interest.

Ethical approval This review was performed in line with the principles of the PRISMA and Prisma-P.

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