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REVIEW PAPER

A systematic review of threshold values of pollen concentrations for symptoms of allergy

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Abstract Pollen threshold values used in public warning systems are intended to inform people of the risk of developing allergy symptoms. However, there is no consensus about which pollen concentrations provoke allergy symptoms. The aim of this systematic review was the evaluation of studies investigating the relationship between pollen concentrations (alder, ash, birch, hazel, mugwort and ragweed) and the number of cases in which participants visited a doctor, drug consumption and allergy symptoms. This systematic literature review is registered in PROSPERO (CRD42019112369). A PubMed search was applied and enriched by consultation with experts and a snowball strategy. The included studies were checked for risk of bias (RoB), and extensive data were extracted and compared. Of 511 studies, 22 were eligible according to the previously established inclusion criteria, and 17 from these showed a low RoB. The strongest evidence was reported for ash (*Fraxinus*) pollen, where an increase of number of doctor's visits at an interquartile range (IQR) of 18–28 grains/m^3 was detected by three studies. Five studies about birch (*Betula*) pollen showed a threshold value of 45 grains/m^3 for increased drug consumption. The evidence of a threshold value was limited for alder (*Alnus*), hazel (*Corylus*), mugwort (*Artemisia*) and ragweed (*Ambrosia*) pollen. The inconsistent results

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concerning all types of pollen, except ash pollen, can be the result of multiple factors, e.g., age, gender, allergen content of pollen and individual sensitivity. These influencing factors should be investigated more closely in future research.

Keywords Aeroallergens · Conjunctivitis · Pollen · Rhinitis · Systematic review · Pollen thresholds

1 Introduction

Pollen is one of the most common aeroallergens causing allergic diseases (Navarro et al., 2009). Allergens from pollen induce the production of immunoglobulin E (IgE) antibodies, which circulate in blood but more importantly are then linked to the surface of mast cells. These mast cells reside in the mucosal membranes. Upon renewed exposure, the allergen is bound to the IgE from the mast cells and triggers the release of inflammatory mediators. Further information on the development of allergic reactions can be found in Janeway et al. (2001). This results in symptoms typical of an allergic reaction (Janeway et al., 2001). IgE antibodies in serum indicate allergic sensitization and are the minimal precondition for the clinical manifestation of allergic diseases (Schoefer et al., 2008).

A genetic predisposition for the development of sensitization to allergens has been confirmed (Bousquet et al., 2001). However, in the last decades, a rising prevalence of allergic diseases that cannot be explained by changes in the genetics of the population was observed (Bergmann et al., 2016; Pawankar et al., 2020; Bousquet et al., 2001). Besides individual predispositions, studies have identified environmental factors promoting the development of allergic reactions, among which is climate change (Pawankar et al., 2020).

In addition, Buters et al. (2012, 2015), found that the sensitivity of population depends on the local flora (and pollen). They concluded if a plant species is widespread in a geographical area, the population can tolerate a higher concentration of this pollen before symptoms occur.

Allergic rhinitis (AR) is the most prevalent allergic disease (Pawankar et al., 2020). AR is an inflammation of the nasal mucosa and frequently associated with ocular symptoms, which is expressed in the term rhinoconjunctivitis (Pawankar et al., 2020). People suffering from AR have a lower quality of life in comparison with the general population (Navarro et al., 2009).

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The first attempts to establish threshold pollen concentrations values for informing the people of potential allergy symptoms date back to 1970s in Sweden. From clinical experience, Swedish physicians had defined the risk of pollen-induced symptoms to be low between 0 and 10 pollen grains/m^3, middle—between 10 and 30, high—between 30 and 100 and very high—for more than 100 grains/m^3. Later on, the neighboring country Denmark adopted the British threshold values, defining a low risk between 0 and 30, middle between 30 and 50, high between 50 and 150 and very high for more than 150 grains/m^3 (summarized by Kiotseridis et al. (2013)). Meanwhile, the European Academy of Allergy and Clinical Immunology (EAACI) determined the so-called high pollen days and further characteristics defining pollen season for five different pollen types (Pfaar et al., 2017) based on a narrative review of threshold values for pollen-induced symptoms (De Weger et al., 2013). A high ragweed pollen day, for example, was defined with at least 50 pollen/m^3, respectively, and a high birch pollen day with 100 pollen/m^3. However, these values had been disputed, as more recent studies highlighted that threshold values may strongly depend on regional conditions such as vegetation and climate and on individual conditions (De Weger et al., 2013).

The aim of this study was to perform a systematic review of studies investigating the relationship between pollen concentrations (alder, ash, birch, hazel, mugwort, ragweed) and the number of doctor's visits, drug use and allergy symptoms.

2 Methods

This systematic literature review is registered in PROSPERO (registration number: CRD42019112369) since January 24, 2019. The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (Moher et al., 2009) were considered (Electronic Supplementary Material 1). The reviewer team included two researchers, one main and one second reviewer, and was supported by an expert team (co-authors), contributing as advisors.

2.1 Article sources

A complex search string including terms related to the categories: exposure, allergy symptoms and association (Table 1), was used by the reviewer team in the database PubMed (Electronic Supplementary Material 2). The search was conducted on August 14, 2018. The date of publication was not restricted and included literature published in English and German. In addition, on May 28, 2020, the authors performed an update of the systematic literature search for the period 2018-2020. Additionally, the expert team was consulted to include further relevant literature.

The authors found many studies dealing with threshold values of grass pollen. Therefore, the results concerning grass pollen were excluded from this paper and will be presented in detail in a following paper (LUPO2).

2.2 Review process

Two reviewers independently performed the title, abstract and full-text screening. The main reviewer extracted the data of the included studies. Both reviewers were involved in the derivation and application of the rules for RoB assessments. Finally, a snowball strategy was applied meaning the reference lists of all identified literature were screened for further important references. EndNote X8 was used to process the literature references.

In addition to the PubMed search, sources for relevant studies were expert consultations, screenings of reference lists and the systematic screening of the book Allergenic Pollen (Sofiev and Bergmann, 2013). This book deals with the production, distribution in the atmosphere, release of allergens from pollen and health effects as well as monitoring and forecast of different pollen types. At the time, it was the only book that summarized studies examining pollen thresholds. These studies were not systematically researched.

2.3 Eligibility criteria for included studies

Eligibility of studies was assessed according to the inclusion and exclusion criteria listed in Table 2 by abstract and full-text screening. The search results were summarized according to the PRISMA flow diagram (Moher et al., 2009) (Fig. 1). Reasons for exclusion were listed with the name of the category of criteria for inclusion and exclusion (Table 2). If several analyses (e.g., additionally stratified by age) were presented, the non-stratified results were extracted and are included in the tables.

Table 1 Search term

	Search term	August 14, 2018	May 28, 2020
Original search term	Pollen [tiab]	511 hits	68 hits
	AND		
	ragweed OR Ambrosia OR “Ambrosia artemisiifolia” OR mugwort OR Artemisia OR “Artemisia vulgaris” OR birch OR Betula OR alder OR Alnus OR ash OR Fraxinus OR grass OR Poaceae OR hazel OR Corylus OR rye OR Secale		
	AND		
	“pollen threshold” OR “pollen thresholds” OR “pollen level” OR “pollen levels” OR “pollen load” OR “pollen count” OR “pollen counts” OR “pollen quantification” OR “pollen quantifications” OR “pollen concentration” OR “pollen concentrations” OR “aeroallergen concentration” OR “aeroallergen concentrations” OR “aeroallergen level” OR “aeroallergen levels” OR “atmospheric pollen counts” OR “symptom load index” OR “pollen symptom score” OR “pollen symptoms score”		
	AND		
	(“pollen induced allergy” OR “pollen-associated allergic risk” OR allergy OR allergies OR “pollen allergy” OR “pollen allergies” OR “seasonal allergy” OR asthma OR “allergic asthma” OR “asthma exacerbation” OR “asthma exacerbations” OR rhinitis OR “allergic rhinitis” OR rhinoconjunctivitis OR “allergic rhinoconjunctivitis” OR conjunctivitis OR “allergic conjunctivitis” OR “conjunctival symptoms” OR “seasonal conjunctivitis” OR hayfever OR “hay fever” OR pollinosis OR rhinitis OR “seasonal rhinitis” OR “pollen-induced rhinitis” OR “allergic rhinitis” OR “seasonal allergic rhinitis” OR “allergic reaction” OR “allergic reactions” OR “allergic symptoms” OR “allergic symptoms” OR “allergic response” OR “allergic responses” OR “clinical response” OR “clinical symptoms” OR “clinical symptom” OR wheeze OR “hospital admission” OR “hospital admissions” OR “emergency department” OR “learning ability” OR “working ability” OR “working capacity” OR “allergy symptoms” OR “initiation of symptoms” OR “conjunctival symptoms” OR “nasal symptoms” OR “bronchial symptoms” OR “ocular symptoms” OR “respiratory symptoms” OR “itchy eyes” OR “itchy-watery eyes” OR “blocked nose” OR “runny blocked nose” OR “itchy nose” OR sneezing OR “itchy skin” OR wheeze OR wheezing OR “whistling in the chest” OR “shortness of breath” OR “chest tightness” OR “persistent cough” OR cough OR asthma OR “allergic symptoms” OR “atopic eczema” OR “asthma medication” OR “allergy medicines” OR “rescue medication” OR antihistamine)		
	AND		
	association OR associated OR relationship OR related OR relation OR significant OR significance OR correlation OR correlated		
	NOT		
	Animals		
	NOT		
	Placebo		
	Filters: english[la] OR german [la] OR french[la] OR spanish[la]		

Table 1 continued

	Search term	August 14, 2018	May 28, 2020
Later addition to the search term	Pollen [tiab]		
	AND		
	ragweed OR Ambrosia OR "Ambrosia artemisiifolia" OR mugwort OR Artemisia OR "Artemisia vulgaris" OR birch OR Betula OR alder OR Alnus OR ash OR Fraxinus OR grass OR Poaceae OR hazel OR Corylus OR rye OR Secale		
	AND		
	"pollen threshold" OR "pollen thresholds" OR "pollen level" OR "pollen levels" OR "pollen load" OR "pollen count" OR "pollen counts" OR "pollen quantification" OR "pollen quantifications" OR "pollen concentration" OR "pollen concentrations" OR "aeroallergen concentration" OR "aeroallergen concentrations" OR "aeroallergen level" OR "aeroallergen levels" OR "atmospheric pollen counts" OR "symptom load index" OR "pollen symptom score" OR "pollen symptoms score"		
	AND		
	("drug consumption")		
	AND		
	association OR associated OR relationship OR related OR relation OR significant OR significance OR correlation OR correlated		
	NOT Animals		
	NOT Placebo		
	Filters: english[la] OR german [la] OR french[la] OR spanish[la]		

2.4 Assessment of the risk of bias

The risk of bias (RoB) of each included study was assessed to evaluate their internal validity. The assessment was done on the study level and—if more than one outcome was investigated—on the outcome level (Moher et al., 2009). The RoB tool of the Office of Health Assessment and Translation (OHAT), National Toxicology Program of the US Department of Health and Human Services designed for cohort, case–control and cross-sectional studies was selected as the starting point, supplemented and adapted to the needs of the review. As done previously (Zhao et al., 2018), the tool was also used for time-series and case-crossover studies.

The available instructions for the ratings of the OHAT criteria were considered (OHAT, 2015a; b), but adapted to the topic in agreement with the expert team to formulate precise rules for the RoB assessment. An extensive catalogue of rules for the RoB assessment was developed (Table 3) and used for an objective and replicable study assessment (Table 4, Electronic Supplementary Material 3). The same answer possibilities as applied by OHAT were used, and these are "definitely low RoB (+ +)," "probably low RoB (+)," "probably high RoB (-)," "definitely high RoB (- -)" and "not applicable (NA)."

Studies with a high or probably high RoB in any category except one (category: conflict of interest, CoI) were omitted from results synthesis and consequently not described in "Result" section. Studies with no information about CoI were included, but the corresponding probably high RoB due to CoI was mentioned explicitly in "Results" section.

Table 2 Criteria for inclusion and exclusion

Criteria		Inclusion	Exclusion
PECO/ PICOS	Population	General human population showing pollen-related allergy symptoms, any gender, age, nationality	Population never showing pollen-related allergy symptoms
Exposure	Pollen type	Alder, ash, birch, hazel, mugwort, ragweed or rye	Other pollen than the included, e.g., grass (Cyperaceae and Poaceae); a mixture of the included pollen grass (Cyperaceae and Poaceae) was initially included and was part of the search term, and however, finally it was excluded and moved to a separate paper)
	Pathway	Airborne	Any other than airborne
	Origin	Natural exposure	Allergen challenge, pollen chamber
	Unit	Pollen concentrations (grains/m^3)	Exposure estimated without pollen concentration measurement; pollen concentrations are not reported
	Time reference	Data of Exposure was assessed with periodicity, which not exceeded 1 week	Exposure data from more than one week was summarized (e.g., monthly or yearly)
	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 acute allergy symptoms, bronchial (e.g., allergic asthma), nasal (e.g., seasonal allergic rhinitis, SAR) and ocular (e.g., rhinoconjunctivitis)	Not pollen-related allergy 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, tests of sensitization (e.g., IgE value or skin prick test);
	Additional outcome	Pollen-related hospital admissions, emergency department visits, visits to physician, 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 symptoms or indicating in which range of pollen counts symptoms occur	Health outcomes not measured, measured by symptoms scores indicating a change of the score but not a range of pollen counts with symptoms occurring
	Time reference	Daily or weekly (including averaged values and lag days)	Values summarized per month, year, etc.
Study design*	Design	Epidemiological observational studies, control groups of intervention studies	Epidemiological experimental studies, basic research studies regarding new technologies or applications, 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 analyzed. 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
Others			
	Language	English, German	All other languages
	Publication year	All publication years	No exclusion

Table 2 continued

Criteria		Inclusion	Exclusion
	Reference place	All places/countries	No exclusion

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

EOE Eosinophilic esophagitis, *IgE* immunoglobulin E, *SAR* Seasonal allergic rhinitis, *PAR* Perennial allergic rhinitis, *PECO/PICO* Population, Exposure/Intervention, Comparison, Outcome

2.5 Data synthesis

Data synthesis was done in a qualitative way, arranged according to pollen type and health outcome. The reported increases of pollen concentrations always assumed a baseline of 0 grains/m^3. All following pollen threshold values are based on daily averages.

3 Results

The literature search in PubMed yielded 454 hits. Additionally, 57 studies were identified by the expert team or the snowball strategy, resulting in 511 indicated studies. From these, 22 studies met the inclusion criteria (Table 2 and Fig. 1). Five of them had to be excluded due to high or probably high RoB (Table 4, Electronic Supplementary Material 3). Thus, the data of final 17 studies were synthetized.

The update of the literature search retrieved 68 hits. The vast majority of them (66 references) were excluded in title and abstract screening due to exclusion criteria. After full-text screening of the two remaining references, both were excluded due to the exclusion criteria (Table 2 and Fig. 1).

Table 5 summarizes key aspects of the final 17 studies (pollen type, country and health outcome), and Table 6 gives more detailed characteristics. Ash (n = 9) and ragweed (n = 8) were the mainly examined pollen types. Ten studies focused on the number of doctor's visits (either on hospital admissions or emergency department or visits to physician) in association with pollen concentrations. Six studies analyzed drug consumption (for details see in Electronic Supplementary Material 4) and two the occurrence of symptoms in connection with pollen concentrations. The time period for data collection started in 1993 in the oldest case and ended in 2014 in the most recent study. The following subgroups were analyzed: only children (n = 4 studies), only adults (n = 3), only individuals being 65 years or older (n = 1), all individuals except infants (n = 4) and all individuals without restrictions regarding age (n = 5) (for details see Tables 6 and 7). All studies included male and female subjects. The sample size was a lot larger in the studies focusing on the number of doctor's visits (n = 502 up to n=60,066) or drug sale data (n = 6,780 up to n = 118,723) and rather small in studies focusing on symptoms (n = 30 and 61) (Table 6 and Table 7). From all the 17 pollen outcome analyses included in this review, eight were published with a CoI statement and nine without (Table 6).

Table 7 shows the study results and corresponding necessary information. The results were subsequently described per pollen type. An overview of pollen types, kind of health outcome, studies and significance is provided in Fig. 2.

3.1 Studies on alder pollen

Four studies analyzed the association between *alder* and the occurrence of health outcomes (Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Guilbert et al., 2018; Guilbert et al., 2016). Guilbert et al. (2018) observed the number of doctor's visits due to asthma and three other studies reported drug consumption for allergic rhinoconjunctivitis (D. M. Caillaud et al., 2015; Zeghnoun et al., 2005; Guilbert et al., 2016). Only Zeghnoun et al. (2005) found statistically significant results for a population aged 65 years and older, for which an interquartile range (IQR) increase of 19 grains/m^3 resulted in an increase of prescriptions for an oral antihistamine on the same day (RR = 1.14) (Zeghnoun et al., 2005). For all other age groups (Zeghnoun et al., 2005) and for the other three studies such as Caillaud et al. (2015) (IQR = 35.5 grains/m^3), Guilbert et al., (2018) (IQR = 9 grains/m^3) and

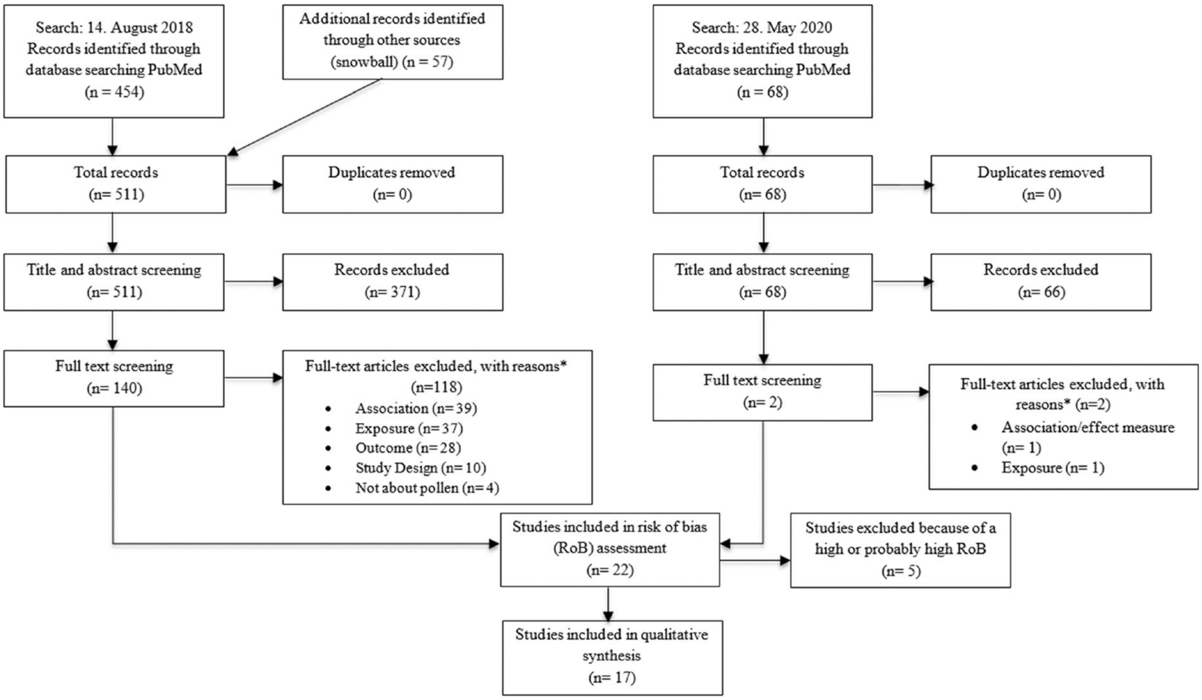

Fig. 1 PRISMA flowchart (adapted from (Moher et al., 2009)). *The first obvious reason for exclusion was listed, while multiple reasons are possible. The reasons listed correspond to the criteria for inclusion (Table 1). For example, the reason "association/effect measure" means that the study does not match with one or more of the criteria for inclusion in these categories (e.g., no reporting of odds ratios but reporting of correlation coefficients)

Guilbert et al. (2016) (IQR = 18.25 grains/m^3), no statistically significant results were shown.

3.2 Studies on ash pollen

Nine studies analyzed *ash* pollen (Ito et al., 2015; Motreff et al., 2014; Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Fuhrman et al., 2007; Guilbert et al., 2018; Osborne et al., 2017; Dales et al., 2008; Guilbert et al., 2016). Four studies analyzed the number of doctor's visits due to asthma (Guilbert et al., 2018; Osborne et al., 2017; Dales et al., 2008; Ito et al., 2015). Guilbert et al., (2018) observed a 4 grains/m^3 increase of ash pollen with no statistically significant effects. Osborne et al. (2017) and Dales et al. (2008) reported threshold values between 18 and 20 grains/m^3 with low statistically significant percentage increases. Ito et al. (2015) mentioned a statistically significant cumulative rate ratio of 1.7 (95% CI 1.5–1.9) for an increase of 223 grains/m^3. Six studies observed drug consumption due to increasing pollen concentrations (Ito et al., 2015; Motreff et al., 2014; Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Fuhrman et al., 2007; Guilbert et al., 2016). Guilbert et al. (2016) showed that an IQR of 24.5 grains/m^3 yielded statistically significantly increased medication sales in the 19-39 and 40-64 age groups. An increase of 28 to 223 grains/m^3 showed significant results in non-age restricted populations (D. M. Caillaud et al., 2015; Fuhrman et al., 2007; Ito et al., 2015; Motreff et al., 2014; Zeghnoun et al., 2005). Zeghnoun et al., (2005) reported a statistically significant cumulative relative risk of 1.22 (95% CI 1.13–1.31) for a change in pollen concentration of 28 grains/m^3. Fuhrman et al., (2007) observed a statistically significant increase of 7.3% for drug consumption for an increasing IQR of 33 grains/m^3 (95% CI 4.6–10.1). Caillaud et al., (2015) found a statistically significant increased risk of drug consumption associated with an IQR of 41 grains/m^3 (RR = 1.019, 95% CI 1.004–1.033). Motreff et al., (2014) observed a statistically significant RR in one of two project areas

Table 3 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 (2015b, a) and Lam et al., (2016)
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
		– –	No consideration of confounder
			The authors assume or even declare the bias
Detection bias: exposure characterization	Can we be confident in the exposure characterization?	+ +	Daily exposure characterization AND
			There is direct evidence that exposure characterization is adequate for the study population (e.g., residence and pollen trap in same city)
		+	More than weekly but not daily exposure characterization AND/OR
			There is no direct evidence that exposure characterization is adequate for the study population
		–	Weekly or less frequent exposure characterization 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, hospitalizations, 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 3 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 (2015b, a) and Lam et al., (2016)
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) are analyzed, 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 (summarized scores as well as all components, as described in "Method" section) are reported (in "Results" section)
		+	It seems that all measured outcomes (summarized scores as well as all components, as described in "Method" section) are reported (in "Results" section) OR
			A summarized 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 summarized in a score, while others were excluded from the score without reasonable explanation. AND/OR
			Only significant or a selection of the best findings was reported

Table 3 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 (2015b, a) and Lam et al., (2016)
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 judgment 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 judgment 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

ICD International Statistical Classification of Diseases and Related Health Problems *NA* not applicable, NO_2 nitrogen dioxide; O_3 ozone; *OHAT* Oral Health Assessment Tool, *PM* particulate matter

when a 60 grains/m^3 pollen increase was detected (RR = 1.02, 95% CI 1.01–1.03). Ito et al., (2015) reported a statistically significant cumulative rate ratio of 1.9 (95% CI 1.7–2.1) for a change of 223 grains/m^3.

3.3 Studies on birch pollen

Eight studies (Ito et al., 2015; Fuhrman et al., 2007; Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; D. Caillaud et al., 2014a; Osborne et al., 2017; Guilbert et al., 2016; Guilbert et al., 2018) analyzed *birch* pollen in association with different health outcomes. Three studies investigated the number of doctor's visits following asthma (Ito et al., 2015; Osborne et al., 2017; Guilbert et al., 2018) symptoms. No statistically significant results were reported by Osborne et al. (2017) for a percentile increase of 195 grains/m^3. Guilbert et al. (2018) found a statistically significant increase in the number of doctor's visits for a change of 3.2% (95% CI 1.1, 5.3) with an interquartile range increase of 40 grains/m^3. Ito et al. (2015) showed a cumulative rate ratio of 1.3 (95% CI 1.19-1.48) for 98th percentile increase of 1680.3 grains/m^3. Regarding drug consumption, five studies (Ito et al., 2015; Fuhrman et al., 2007; Zeghnoun et al., 2005; Caillaud et al., 2015; Guilbert et al., 2016) were included, while all show positive statistically significant results at least in some subgroups. Zeghnoun et al., (2005) observed that an IQR increase of 45 gains/m^3 resulted in an increase of drug consumption (RR = 1.22, 95% CI 1.11–1.35). Caillaud et al. (2015) showed an increasing risk of drug consumption (RR=1.030, 95% CI 1.005–1.055) with an IQR of 58 grains/m^3. Ito et al., (2015) reported a cumulative rate ratio of 2.0 (95% CI 1.8–2.2) per 0–98th percentile increase of 1680.3 grains/m^3. Fuhrman et al. (2007) found a statistically significant increase of 7% (95% CI 3.8–10.4) with an IQR increase of 45 grains/m^3. Guilbert et al. (2016) showed statistically significant results in age subgroups for a threshold value of 85 grains/m^3. They observed the highest increase in risk of drug consumption (RR = 1.05, 95% CI 1.04–1.06) for birch pollen among the 19–39-year-old men. The smallest increase of risk (RR = 1.02, 95% CI 1.01–1.04) was found among the 13–18-year-old girls and the 6–12-year-old boys. Nasal, ocular and bronchial symptoms were analyzed in one study (D. Caillaud et al., 2014a) in association with an increase in pollen concentration of 10 grains/m^3. Odds ratios were statistically significant, when the increase was below but not above a certain concentration (110 grains/m^3 for nasal symptoms, 70 grains/m^3 for ocular and bronchial each).

3.4 Studies on hazel pollen

Exposure to *hazel* pollen was investigated in five studies (Fuhrman et al., 2007; Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Guilbert et al., 2018; Guilbert et al., 2016). The study of Guilbert et al. (2018) on the number of doctor's visits due to hazel pollen exposure yielded no statistically significant results (IQR=4 grains/m^3). Drug consumption in association with hazel pollen exposure was analyzed in four studies (Fuhrman et al., 2007; Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Guilbert et al., 2016). Fuhrman et al. (2007) reported a statistically significant increase of 2.3% (95% CI 0.4–4.3) with an IQR increase of 23 grains/m^3. Zeghnoun et al., (2005) showed statistically significant risk (RR = 1.08, 95% CI 1.00–1.15) with an IQR of 15 grains/m^3 among the over 65 years old. Caillaud et al. (2015) (IQR = 31 grains/m^3) and Guilbert et al. (2016) (IQR = 9 grains/m^3) found no statistically significant effects.

3.5 Studies on mugwort pollen

Five studies analyzed *mugwort* pollen (Motreff et al., 2014; Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Guilbert et al., 2018; Tobias et al., 2003). Guilbert et al. (2018) (IQR = 1 grain/m^3) and Tobías et al. (2003) (IQR = 2.1 grains/m^3) focused on the number of doctor's visits (Guilbert et al., 2018; Tobias et al., 2003) and yielded no statistically significant results. Drug consumption was surveyed in three studies (Motreff et al., 2014; Zeghnoun et al., 2005; D. M. Caillaud et al., 2015). Motreff et al. (2014) observed a statistically significant RR in one of two project areas when a pollen increase of 3 grains/m^3 was analyzed (RR = 1.09, CI 1.05–1.13). Zeghnoun et al., (2005) (IQR = 7 grains/m^3) and Caillaud et al. (2015) (IQR = 6.5 grains/m^3) reported no statistically significant results.

3.6 Studies on ragweed pollen

Ragweed pollen were investigated in eight studies (Gleason et al., 2014; Heguy et al., 2008; Villeneuve et al., 2006; Zhong et al., 2006; Cakmak et al., 2002; D. Caillaud et al., 2014b; Motreff et al., 2014; D. M. Caillaud et al., 2015). The increased number of doctor's visits are the outcome in five ragweed studies focusing on asthma (Gleason et al., 2014; Heguy et al., 2008; Zhong et al., 2006) or allergic rhinitis (Villeneuve et al., 2006), rhinitis or sinusitis (Cakmak et al., 2002) and conjunctivitis (Cakmak et al., 2002). Cakmak et al., (2002) found a statistically significant positive association between an increase of 72 grains/m^3 and an increase of 11.4% (95% CI 3.36–19.43) for frequency of doctor's visits due to sinusitis and conjunctivitis. Villeneuve et al., (2006) investigated an interquartile increase of 22.6 grains/m^3 and ten days average of the number of doctor's visits for allergic rhinitis and found a statistically significant increase of 6.4%. Regarding asthma, the results are very diverse: Zhong et al., (2006) observed a statistically significant risk of an increase in the frequency of doctor's visits at pollen concentrations above 100 grains/m^3 (RR = 1.54, 95% CI 1.02–2.33). In contrast, Gleason et al. (2014), who investigated children, reported a protective effect, where asthma-related emergency department visits were observed in combination with a tenfold pollen increase the same day (Gleason et al., 2014). Heguy et al., (2008) found no statistically significant effect for visits to physician due to higher ragweed pollen concentrations (Heguy et al., 2008). Regarding drug consumption, the studies of Caillaud et al., (2015) (IQR=5 grains/m^3) and Motreff et al., (2014) (IQR = 5 grains/m^3) were included, but both studies did not find significant results. Caillaud et al., (2014b) investigated the relation of nasal, ocular and respiratory symptoms with pollen season and found mostly positive associations (up to RR = 1.33) if an increase of 10 pollen grains/m^3 was observed.

3.7 Sub-analyses by age

For alder, the only statistically significant result regarding drug consumption was found for people aged 65 years and older (Zeghnoun et al., 2005). In contrast, Guilbert et al. (2018) observed lower hospitalization effects in the oldest age groups in comparison with young people for mugwort and in a lower degree for birch. Guilbert et al. (2016) (alder, ash, birch, hazel), Fuhrman et al. (2007) (ash, birch, hazel) and Zeghnoun et al. (2005) (ash, birch) identified adults as most affected. Zeghnoun et al. (2005) found other age patterns for other pollen types (not investigated here). Ito et al. (2015) found highest associations between medication sales and tree pollen concentration for children (5–17 years) and weak

Table 4 Heat map of the risk-of-bias (RoB) assessment

Nb.	Authors (year)		key criteria			other criteria			
			Confounding bias	Detection bias: exposure characterization	Detection bias: Outcome assessment	Attrition bias	Selective reporting bias	Conflict of interest	In- or exclusion from data synthesis
1	Caillaud et al. (2014a)		+	++	+	+	++	–	inclusion
2	Caillaud et al. (2014b)		+	++	+	++	+	++	inclusion
3	Caillaud et al. (2015)		+	++	+	NA	++	++	inclusion
4	Cakmak et al. (2002)		+	++	+	++	++	++	inclusion
5	Dales et al. (2008)		+	++	++	NA	++	–	inclusion
6	Darrow et al. (2012)		—	+	++	NA	++	–	exclusion
7	Fuhrman et al. (2007)		+	++	+	++	++	++	inclusion
8	Gleason et al. (2014)		+	+	++	NA	++	++	inclusion
9	Guilbert et al. (2018)		+	++	++	NA	++	++	inclusion
10	Guilbert et al. (2016)		++	++	+	NA	++	++	inclusion
11	Héguy et al. (2008)		+	++	++	NA	++	–	inclusion
12	Hofman et al. (1996)		—	+	–	NA	–	–	exclusion
13	Huynh et al. (2010)		+	–	–	—	++	++	exclusion
14	Ito et al. (2015)	medication sale	+	+	++	NA	++	++	inclusion
		ED visits	+	+	++	NA	++	++	inclusion
15	Lewis et al. (2000)		–	++	++	NA	–	–	exclusion
16	Motreff et al. (2014)		+	++	+	NA	++	–	inclusion
17	Osborne et al. (2017)		+	++	++	NA	++	–	inclusion
18	Ross et al. (2002)	asthma medication use	–	++	+	–	—	–	exclusion
		symptom score	–	++	–	–	—	–	
19	Tobías et al. (2003)		+	++	++	NA	++	++	inclusion
20	Villeneuve et al. (2006)		+	++	++	NA	++	–	inclusion
21	Zeghnoun et al. (2005)		+	++	+	NA	++	–	inclusion
22	Zhong et al. (2006)		+	++	++	NA	++	–	Inclusion

Legend:
Nb. = number; ED = emergency department
Abbreviations: (+ +, *dark green*) Definitely low RoB, (+, *light green*) Probably low RoB, (–, *orange*) Probably high RoB, (—, *red*) Definitely high RoB, (NA, *white*) not applicable

associations for 0–4 years and 65 years and older. Motreff et al. (2014) investigated several pollen types (not all included here) and found in general decreasing allergic rhinitis cases by age. They speculate, if comorbidities of the elderly might hamper the diagnosis and treatment (due to drug interactions (Busse and Kilaru 2009)) of allergic rhinitis. Caillaud et al. (2015) investigated drug consumptions and made sub-analyses by age for ash and found statistically significant results in all but the youngest age group (5-14 years) for pollen threshold value of 41 grains/m^3 and for birch with statistically significant results in all but the 15 to 44 years old for pollen threshold value of 58 grains/m^3. Villeneuve et al. (2006) focused their complete study on the age group 65 years and older; however, this decision was not justified on pollen-related susceptibility but based on a higher susceptibility of the elderly regarding particulate matter (Thurston 1996), which was the main focus of their study (Villeneuve et al., 2006)

Table 5 Summary of the included studies according to kind of pollen, country and health outcome

Characteristics		Total	Number by kind of pollen†					
			Alder	Ash	Birch	Hazel	Mugwort	Ragweed
Total		22	5	10	11	6	6	9
Total used for result synthesis		17	4	9	8	5	5	8
Country	Belgium	1	2	2	2	2	1	0
	Canada	4	0	1	0	0	0	3
	England	1	0	1	1	0	0	0
	France	6	2	4	4	3	3	3
	Spain	1	0	0	0	0	1	0
	USA	3	0	1	1	0	0	2
Health outcome (number of studies with statistically significant results in brackets)	Drug consumption	6	3 (1)	6 (5)	5 (5)	4 (2)	3 (1)	2 (0)
	HA	10	1 (0)	4 (2)	3 (2)	1 (0)	2 (0)	6 (3‡)
	Symptoms	2	0 (0)	0 (0)	1 (1)	0 (0)	0	1 (1)
No conflict of interest declaration		8	1	4	3	1	2	4

HA Hospital admission;

†The sum of the number by kind of pollen is higher than total, because several studies investigate more than one kind of pollen.

‡One of these three significant studies showed protective effects (Gleason, Bielory et al., 2014)

4 Discussion

4.1 Key findings

Threshold values were found for ash, birch and ragweed. A threshold value of 18-28 grains/m^3 could be extracted from four studies examining ash pollen and the number of doctor's visits (Osborne et al., 2017; Dales et al., 2008; Guilbert et al., 2018; Ito et al., 2015). Five studies showed a statistically significant increase in the health outcome of drug consumption beginning at a threshold value of 28 ash grains/m^3 for the whole population (Motreff et al., 2014; Ito et al., 2015; Zeghnoun et al., 2005; Fuhrman et al., 2007; D. M. Caillaud et al., 2015) and 24 grains/m^3 for the 19–64 age group (Guilbert et al., 2016). For birch pollen and drug consumption, a threshold value of 45 grains/m^3 could be extracted from five studies (Guilbert et al., 2016; Ito et al., 2015; Zeghnoun et al., 2005; Fuhrman et al., 2007; D. M. Caillaud et al., 2015). A threshold value of 22.6 grains/m^3 could be worked out from four studies examining ragweed pollen and the number of doctor's visits (Villeneuve et al., 2006; Gleason et al., 2014; Zhong et al., 2006; Cakmak et al., 2002).

4.2 Pollen-specific data

Of four studies on alder pollen (Guilbert et al., 2018; Guilbert et al., 2016; D. M. Caillaud et al., 2015; Zeghnoun et al., 2005), only one study found a statistically significant result. An increased risk of oral antihistamine prescription in combination with an increase in alder pollen concentration of 19 grains/m^3 was found for the age group over 65 years (Zeghnoun et al., 2005). A possible shift in the daily pollen concentration and the time of purchase of oral antihistamine was not considered in the analysis (Zeghnoun et al., 2005). The authors conclude from this that the results of the study are not reliable. The statistically significant result should be viewed critically, because the result could be confounded by the possible shift in pollen concentration and purchase of pharmaceutical. Additionally, other studies could not find statistically significant results for the age group over 60 years (Guilbert et al., 2018; Guilbert et al., 2016).

Thus, based on drug consumption (D. M. Caillaud et al., 2015; Guilbert et al., 2016; Ito et al., 2015; Fuhrman et al., 2007; Motreff et al., 2014; Zeghnoun et al., 2005) and hospitalization studies (Osborne et al., 2017; Dales et al., 2008; Guilbert et al., 2018; Ito et al.,

Table 6 Characteristics of the included studies

Authors (date)	Kinds of pollen	Health outcomes	Region	Time period	Age in years	Analyzed sample size
Caillaud et al. (2014a)	Birch	Bronchial, nasal, ocular, symptoms	France (Nantes, Angers, Tours, Rouen, Chambery, Roussillon, Dijon, Paris, Amiens, Chalon-sur-Saône, Clermont-Ferrand)	2010 (March 22–May 16)	≥ 18	61 individuals
Caillaud et al. (2014b)	Ragweed	Nasal, ocular, respiratory symptoms	France (Grenoble, Lyon, Avignon, Saint-Étienne, Nevers) Switzerland (Geneva)	2009 (July 13–October 4), 2010 (August 2–October 10)	≥ 18	30 individuals
Caillaud et al., (2015)	Alder, ash, birch, hazel, mugwort, ragweed	Drug consumption for SAR. A SAR case: the association between an oral antihistamine and a local (nasal or ocular) antiallergic drug on the same prescription	France (Clermont-Ferrand area)	2003–2012	≥ 5	97,611 cases in total (between 7265 and 11,315 per year)
Cakmak et al., (2002)	Ragweed	Rhinitis or sinusitis-related emergency visits	Canada (eastern Ontario)	1993–1997 (May–September)	Children (mean age: 7.7 (SD: 4.8))	502 patients
		Conjunctivitis-related emergency visits			Children (mean age: 5.12 (SD: 4.8))	1,761 patients
Dales et al. (2008)	Ash	Asthma hospital admissions (ICD-9 493)	Canada (Vancouver, Saint John, Toronto, Edmonton, Winnipeg, Ottawa, Halifax, London, Windsor, Calgary)	1993 (March)–2000 (March)	No restrictions	60,066 admissions
Fuhrman et al. (2007)*	Ash, birch, hazel	Antiallergic drug consumption (oral antihistamine and a local antiallergic drug on the same prescription) as indicator for an episode of treated ARC	France (Clermont-Ferrand area)	2000 (January)–2001 (December) and 2003 (January)–2004 (December)	≥ 5	6,780 individuals per years
Gleason et al. (2014)	Ragweed	Asthma emergency department visits (ICD-9 code 493.xx)	USA (New Jersey)	2004–2007 (April–September)	3–17	21,854 visitors
Guilbert et al. (2016)	Alder, ash, birch, hazel	Reimbursable antihistamines for systemic use sales	Belgium (Brussels-Capital Region)	2005–2011	No restrictions	1,370,535 reimbursable allergy medication purchases by 347,034 distinct individuals
Guilbert et al. (2018)	Alder, ash, birch, hazel, mugwort	Asthma hospital admissions (ICD-9 493)	Belgium (Brussels)	2008–2013 (January-April)	No restrictions	5,094 admissions
Heguy et al. (2008)*	Ragweed	Asthma emergency visits (ICD-9 493)	Canada (Montreal)	1994–2004 (April–October)	≤ 9	43,780 visitors

Table 6 continued

Authors (date)	Kinds of pollen	Health outcomes	Region	Time period	Age in years	Analyzed sample size
Ito et al. (2015)	Ash, birch	Asthma syndrome emergency department visits	USA (New York City)	2002–2011	No restrictions	ED visits reported by 52 hospitals (mean visits per day: 269)
		Medication sale (brand name and generic products, which were classified as allergy medications and other medications described with the word "allergy")				Medication sales reported by 200 stores (mean sales per day: 3,493)
Motreff et al. (2014)	Ash, mugwort, ragweed	ARC cases defined as the association of an oral antihistamine drug and a local (nose or eye) antiallergenic drug on the same medical prescription	France (urban areas of Montpellier and Nîmes)	2004-2007	5	118,723 cases in total in both areas (Montpellier and Nîmes)
Osborne et al. (2017)	Ash, birch	Asthma hospital admissions (ICD-10 J45 and J46)	England (greater London)	2004–2008 (April–August)	16–64	11,984 admissions
Tobías et al. (2003)	Mugwort	Asthma hospital emergencies, diagnoses: asthma, asthmatic bronchitis, spastic bronchitis, bronchospasm	Spain (Madrid)	1995–1998	No restrictions	4,827 admissions
Villeneuve et al. (2006)	Ragweed	Number of doctor's visits for allergic rhinitis (ICD-9-CM rubric 177)	Canada (Toronto)	1995–2000 (July–October)	≥ 65	52,691 visitors
Zeghnoun et al. (2005)	Alder, ash, birch, hazel, mugwort	ARC cases, defined as a person who, on a given day, had a prescription to obtain an oral antihistamine associated with treatment for allergic rhinitis or allergic conjunctivitis, or both	France (Clermont-Ferrand area)	2000/2001	≥ 5	On average 26 cases per day over the entire study period
Zhong et al. (2006)	Ragweed	Asthma emergency room visit or outpatient clinic visit (ICD-9 codes 493-493.91)	USA (Cincinnati area)	2002 (April–October)	1–18	1,254 visitors

[*]Reviewer requests for numerical results from figures or results from not presented sub-analyses were sent to Fuhrman et al. (2007), Ito et al. (2015) and Tobias et al. (2003). Ito et al. (2015) provided the requested data.

ARC allergic rhinoconjunctivitis, *ED* emergency department, *ICD* International Statistical Classification of Diseases and Related Health Problems, *ICD-9 493* Diagnosis Code Asthma, ICD-9-CM rubric 177 classical modification, cause of death; ICD-10 J45 asthma bronchiale; ICD-10 J46 status asthmaticus, *SAR* seasonal allergic rhinoconjunctivitis, *SD* standard deviation

Table 7 Results of the included studies by kind of pollen and health outcome

Pollen	Authors	CoI	Health outcome	Concentration category	Grains/m^3	Lag (days) †	Measure of effect	Effect	CI	Covariates	Stratified results
Alder	Drug consumption										
	Caillaud et al. (2015)	N.A.	SAR case	IQR increase	35.5	Lag 0–1 (avg)	RR	1.00	[0.98; 1.02]	Air pollution, weather, day of the week, long-term trend, season, public holidays, school holidays	None
	Guilbert et al. (2016)	None	Sales of reimbursable antihistamines for systemic use	IQR increase	18.25	Lag 0-10 (cum)	RR	1.00	[0.98; 1.03]	Air pollution (PM_{10}, NO_2, SO_2 and O_3), meteorological conditions, flu, seasonal component, day of the week.	Age Sex NO sign. results
	Zeghnoun et al. (2005)	N.A.	ARC case	IQR increase	19	Lag 0–1 (avg)	RR	0.99	[0.96; 1.02]	Trend and seasonal variation, day of the week, school holidays, temperature, humidity, precipitation, O_3	Age
						Lag 0		1.14	[1.02; 1.27]		+65 years only sign. result
	Visits to physician										
	Guilbert et al. (2018)	None	Asthma HA (ICD-9 493)	IQR increase	9	Lag 0-6 (cum)	Percentage change	0.2	[− 2.2; 2.7]	Seasonal and long-term trends, day of the week, public holidays, mean temperature, relative humidity	Age PM2.5, NO2, O3 Influenza Respiratory infection All not sign.
Ash	Drug consumption										
	Caillaud et al, (2015)	None	Drug consumption for SAR SAR case	IQR increase	41	Lag 0–1 (avg)	RR	1.019	[1.004; 1.033]	Air pollution, weather, day of the week, long-term trend, season, public holidays, school holidays	Age Some sub-groups with sign. results
	Guilbert et al. (2016)	None	Sales of reimbursable antihistamines for systemic use	IQR increase	24.5	Lag 0–10 (cum)	RR	1.05	[1.04; 1.06]	Air pollution (PM_{10}, NO_2, SO_2 and O_3), meteorological conditions (daily minimal temperature and average relative humidity,), flu, seasonal component, day of the week	Age & Sex
								1.03	[1.02; 1.04]		19–39 years, ♀
								1.03	[1.02; 1.04]		40–64 years, ♂
								1.02	[1.01; 1.03]		40–64 years, ♀

Table 7 continued

Pollen	Authors	CoI	Health outcome	Concentration category	Grains/m^3	Lag (days) †	Measure of effect	Effect	CI	Covariates	Stratified results
	Ito et al, (2015)	None	Medication sale	0-98th percentile increase	223.3	Lag 0–3 (cum)	Rate Ratio (cum)	1.91	[1.748; 2.086]	Day of the week, within seasonal trends, humidity, temperature, $PM_{2.5}$, O_3	None
	Fuhrman et al. (2007)	None	Antiallergic drug consumption	IQR increase	33	Lag 0–1 (avg)	Percentage change	7.3	[4.6; 10.1]	Day of the week, public holiday, temperature, relative humidity, O_3	Age
			treated ARC			Lag 0–5 (cum)		12.7	[8.6; 17.0]		Sign. in all age groups
	Motreff et al. (2014)	N.A.	ARC case	IQR increase	60 (Montpellier)	Lag 0–1 (avg)	RR	1.02	[1.01; 1.03]	O_3, NO_2, PM_{10}, day of the week, public holidays and vacation, temperature, humidity/precipitations. No significant effect and therefore not included in the final model: O_3, NO_2, PM_{10}, precipitation	age
						Lag 0–5 (cum)		1.04	[1.02; 1.06]		Sign. in two of four age groups
					9 (Nîmes)	Lag 0–1 (avg)		1.00	[0.98; 1.01]		
						Lag 0–5 (cum)		1.01	[0.99; 1.03]		
	Zeghnoun et al. (2005)	N.A.	ARC case	IQR increase	28	Lag 0–1 (avg)	RR	1.22	[1.13; 1.31]	Trend and seasonal variation, day of the week, school holidays, temperature, humidity, precipitation, O_3	age all sub-groups with sign. result except (65+)
	Visits to physician										
	Dales et al (2008)	N.A.	Asthma HA ICD-9 493	IQR increase	20.18	N.A.	Percentage increase	1.69	[0.38; 3.00]	Other tree pollen types, grasses, fungal spores, NO_2, SO_2 and O_3, day of the week, humidity, temperature, temporal trends	None
	Guilbert et al, (2018)	None	Asthma HA ICD-9 493	IQR increase	4	Lag 0–6 (cum)	Percentage change	0.00	[-0.60; 0.50]	Seasonal and long-term trends, day of the week, public holidays, mean temperature, relative humidity	age PM2.5, NO2, O3 influenza respiratory infection all not sign
	Ito et al. (2015)	None	Asthma syndrome ED visits	0-98th percentile increase	223.3	Lag 0–7 (cum)	Rate Ratio (cum)	1.695	[1.526; 1.883]	Day of the week, within seasonal trends, humidity, temperature, $PM_{2.5}$, O_3	age some sub-groups show sign. results
	Osborne et al, (2017)	N.A.	Asthma HA ICD-10 J45 and J46	0-95th percentile increase	18	Lag 4	Percentage change	3.99	[0.10; 7.89]	Temperature, precipitation, humidity, day of week, public holidays, PM_{10}, NO_2, SO_2 and O_3	none

Table 7 continued

Pollen	Authors	CoI	Health outcome	Concentration category	Grains/m^3	Lag (days) †	Measure of effect	Effect	CI	Covariates	Stratified results
Birch	Drug consumption										
	Caillaud et al. (2015)	None	Drug consumption for SAR	IQR increase	58	Lag 0–1 (avg)	RR	1.03	[1.005; 1.055]	Air pollution, weather, day of the week, long-term trend, season, public holidays, school holidays	Age
			SAR case								some sub-groups with sign. results
	Fuhrman et al. (2007)	None	Antiallergic drug consumption	IQR increase	45	Lag 0–1 (avg)	Percentage change	7	[3.8; 10.4]	Day of the week, public holiday, temperature, relative humidity, O_3	age
			treated ARC			Lag 0–5 (cum)		11	[5.9; 16.3]		sign. in all but the 65+ age group
	Guilbert et al. (2016)	None	Sales of reimbursable antihistamines for systemic use	IQR increase	84.75	Lag 0–10 (cum)	RR	1.02	[1.01; 1.04]	Air pollution (PM_{10}, NO_2, SO_2 and O_3), meteorological conditions (daily minimal temperature and average relative humidity), flu, seasonal component, day of the week	Age
											sex 6–12 years, ♂
								1.03	[1.01; 1.04]		13–18 years, ♂
								1.02	[1.01; 1.04]		13–18 years, ♀
								1.05	[1.04; 1.06]		19–39 years, ♂
								1.03	[1.02; 1.04]		19–39 years, ♀
								1.04	[1.03; 1.04]		40–64 years, ♂
								1.03	[1.02; 1.03]		40–64 years, ♀
	Ito et al. (2015)	None	Medication sale	0–98th percentile increase	1680.3	Lag 0–3 (cum)	Rate Ratio (cum)	2.01	[1.831; 2.205]	Day of the week, within seasonal trends, humidity, temperature, $PM_{2.5}$, O_3	none
	Zeghnoun et al. (2005)	N.A.	ARC case	IQR increase	45	Lag 0–1 (avg)	RR	1.22	[1.11; 1.35]	Trend and seasonal variation, day of the week, school holidays, temperature, humidity, precipitation, O_3	Age
											all sub-groups with sign. results
	Visits to physician										
	Guilbert et al. (2018)	None	Asthma HA	IQR increase	40	Lag 0–6 (cum)	Percentage change	3.2	[1.1; 5.3]	Seasonal and long-term trends, day of the week, public holidays, mean temperature, relative humidity	age,
			(ICD-9 493)								PM2.5, NO2, O3
											influenza
											respiratory infections

Table 7 continued

Pollen	Authors	CoI	Health outcome	Concentration category	Grains/m^3	Lag (days) †	Measure of effect	Effect	CI	Covariates	Stratified results all not sig
	Ito et al. (2015)		Asthma syndrome ED visits	0-98th percentile increase	223.3	Lag 0–7 (cum)	Rate ratio (cum)	1.324	[1.184; 1.479]	Day of the week, within seasonal trends, humidity, temperature, $PM_{2.5}$, O_3	age some sub-groups show sign. results
	Osborne et al. (2017)	N.A.	Asthma HA (ICD-10 J45 and J46)	0-95th percentile increase	195	Lag 4	Percentage change	3.1	[− 5.56; 11.78]	Temperature, precipitation, humidity, day of week, public holidays, PM_{10}, NO_2, O_3, SO_2	none
	Symptoms										
	Caillaud et al. (2014a)	N.A.	Symptoms Nasal	Up to 110 grains/m^3	10	Either lag 0, lag 1 or lag 0–1 (avg). The most sign. lag was retained.	OR	1.07	[1.03; 1.12]	Temperature, humidity, wind speed, NO_2, O_3, PM_{10}, age, geographical area of participant	None
				above 110 grains/m^3				1	[0.99; 1.01]		
			Ocular	up to 70 grains/m^3				1.17	[1.08; 1.27]		
				above 70 grains/m^3				1	[0.99;1.00]		
			bronchial	up to 70 grains/m^3				1.12	[1.03; 1.21]		
				above 70 grains/m^3				0.99	[0.98; 1.00]		
Hazel	Drug consumption										
	Caillaud et al. (2015)	None	Drug consumption for SAR SAR case	IQR increase	31	Lag 0–1 (avg)	RR	1	[0.982; 1.013]	Air pollution, weather, day of the week, long-term trend, season, public holidays, school holidays	None
	Fuhrman et al. (2007)	None	drug consumption	IQR increase	23	Lag 0–1 (avg)	Percentage change	2.3	[0.4; 4.3]	Day of the week, public holiday, temperature, relative humidity, O_3	Age sign. only in the 35–64 years old
			Treated ARC			Lag 0–5 (cum)		2.4	[− 0.4; 5.2]		
	Guilbert et al. (2016)	None	Sales of reimbursable antihistamines for systemic use	IQR increase	9	Lag 0–10 (cum)	RR	0.97	[0.94;1.00]	Air pollution (PM_{10}, NO_2, SO_2 and O_3), meteorological conditions, flu, seasonal component, day of the week.	Age Sex no sign. results
	Zeghnoun et a (2005)	N.A.	ARC case	IQR increase	15	Lag 0–1 (avg)	RR [age ≥5]	1.02	[0.99; 1.06]	Trend and seasonal variation, day of the week, school holidays, O_3, temperature, humidity, precipitation,	65+ age group with sign. results
							RR [age 65+]	1.08	[1.00; 1.15]		

Table 7 continued

Pollen	Authors	CoI	Health outcome	Concentration category	Grains/m^3	Lag (days) †	Measure of effect	Effect	CI	Covariates	Stratified results
	Visits to physician										
	Guilbert et al. (2018)	None	Asthma HA	IQR increase	4	Lag 0–6 (cum)	Percentage change	0.5	[-2.5; 3.6]	Seasonal and long-term trends, day of the week, public holidays, mean temperature, relative humidity	Age PM2.5, NO2, O3 influenza respiratory infections
			ICD-9 493								all not sign.
Mugwort	Drug consumption										
	Caillaud et al. (2015)	None	Drug consumption for SAR	IQR increase	6.5	Lag 0–1 (avg)	RR	0.96	[0.912; 1.003]	Air pollution, weather, day of the week, long-term trend, season, public holidays, school holidays	None
			SAR case								
	Motreff et al. (2014)	N.A.	ARC case	IQR increase	3 (Montpellier)	Lag 0–1 (avg)	RR	1.09	[1.05; 1.13]	PM_{10}, NO_2, O_3, day of the week, public holidays and vacation, temperature, humidity/precipitations. No significant effect and therefore not included in the final model: PM_{10}, NO_2, O_3, precipitation	Age sign. in all except age group +65
						Lag 0–5 (cum)		1.08	[1.05; 1.11]		None
					2 (Nîmes)	Lag 0–1 (avg)		1.01	[0.97; 1.04]		None
						Lag 0–5 (cum)		1.02	[0.97; 1.08]		None
	Zeghnoun et al. (2005)	N.A.	ARC case	IQR increase	7	Lag 0–1 (avg)	RR	1.02	[0.95; 1.09]	Seasonal variation, O_3 , day of the week, school holidays, humidity, temperature, precipitation	age all not sign
	Visits to physician										
	Guilbert et al. (2018)	None	Asthma HA	IQR increase	1	Lag 0–6 (cum)	Percentage change	1.4	[–4.4; 7.6]	Seasonal and long-term trends, day of the week, public holidays, mean temperature, relative humidity	age, $PM_{2.5}$, NO_2, O_3 influenza respiratory infections
			(ICD-9 493)								all not sign.
	Tobías et al. (2003)	None	Asthma hospital emergencies, diagnoses	Range btw 95th and 99th percentile	2.1	Lag 1	Percentage change	4.4	[–6.6; 16.7]	Air pollutants (PM_{10}, SO_2, NO_2, O_3), meteorological data, acute respiratory infections, day of the week, public holidays, other pollen	One pollutant model
Ragweed	Drug consumption										
		None		IQR increase	5	Lag 0–1 (avg)	RR	1	[0.981; 1.012]		None

Table 7 continued

Pollen	Authors	CoI	Health outcome	Concentration category	Grains/m^3	Lag (days) †	Measure of effect	Effect	CI	Covariates	Stratified results
	Caillaud et al. (2015)		Drug consumption for SAR							Air pollution, weather, day of the week, long-term trend, season, public holidays, school holidays	
			SAR case								
	Motreff et al. (2014)	N.A.	ARC case	IQR increase	5 (Montpellier)	Lag 0–1 (avg)	RR	0.99	[0.96; 1.02]	O_3, NO_2, PM_{10}, day of the week, public holidays and vacation, temperature, humidity/precipitations. No significant effect and therefore not included in the final model: O_3, NO_2, PM_{10}, precipitation	None
						Lag 0–5 (cum)		0.98	[0.93; 1.03]		
					5 (Nîmes)	Lag 0–1 (avg)		1	[0.97; 1.02]		
						Lag 0–5 (cum)		1.03	[0.99; 1.07]		
	Visits to physician										
	Cakmak et al.(2002)	None	Rhinitis or sinusitis ED visits	Increase in allergen conc. equal to their mean	72	N.A.	Percentage increase	9.3	[– 11.1; 29.68]	Long-term trends, meteorological and air pollution variables (daily and weekly changes, O_3, NO_2, SO_2, daily sulfates, temperature, relative humidity, barometric pressure)	none
			Conjunctivitis ED visits					11.4	[3.36; 19.43]		
	Gleason et al., (2014)	None	Asthma ED visits ICD-9 493	Conc. increase	10	Lag 0	OR	0.97	[0.96; 0.97]	Holiday, school in session, temperature, humidity	By further lags (all not significant)
	Heguy et al. (2008)	N.A.	Asthma ED visits ICD-9 493	Conc. increase	10	Lag 0	MPC	0.08	[-0.48; 0.63]	Minimum temperature, change in barometric pressure over the previous 24 h, maximum O_3, maximum NO_2	By further lag days (all not sign.)
	Villeneuve et al. (2006)	N.A.	Physician visits for AR ICD-9-CM 177	IQR increase	22.6	Lag 0–10 (avg)	Percentage change	6.4	[0.7; 12.4]	Temperature, humidity, influenza	By further lag days (all not sign.)
	Zhong et al. (2006)	N.A.	Asthma ED Outpatient clinic ICD-9 493–493.91	Conc. increase	100	Lag 5	RR	1.54	[1.02; 2.33]	Effects of season, day of the week, temperature, humidity, O_3, $PM_{2.5}$	None
	Symptoms										
	Caillaud et al., (2014b)	None	Nasal symptom (WD, 2009)	Increase per conc.	10	Either lag 0, lag 1 or lag 0–1 (avg). The most sign. lag was retained.	OR	1.13	[0.99; 1.28]	Temperature, humidity, wind speed, O_3, PM_{10} , age variables were tested and retained when significant (no information which variables were retained) treatment	Another model without adjustment for treatment
			Nasal symptom (WE, 2009)					1.02	[0.98; 1.05]		
			Ocular symptom (2009)					1.26	[1.11; 1.43]		
			Respiratory symptom 2009					1.12	[1.01; 1.25]		
			Nasal symptom (WD, 2010)					1.33	[1.07; 1.65]		

Table 7 continued

Pollen	Authors	CoI	Health outcome	Concentration category	Grains/m^3	Lag (days) †	Measure of effect	Effect	CI	Covariates	Stratified results
			Nasal symptom (WE, 2010)					1.20	[1.00; 1.44]		
			Ocular symptom (2010)					1.09	[1.01; 1.07]		
			Respiratory symptom 2010					1.02	[0.97; 1.08]		

AR allergic rhinitis, *ARC* allergic rhinoconjunctivitis, *ARC case* allergic rhinoconjunctivitis (ARC) cases, defined as a person who, on a given day, had a prescription to obtain an oral antihistamine associated with treatment for allergic rhinitis or allergic conjunctivitis, or both; *avg* average, *btw* between, *conc* concentration, *cum* cumulated, *ED* emergency department, *f* female, *HA* hospital admission, *IQR* interquartile ranges, *m* male, *MPC* mean percent change, *OR* odds ratio, *RR* relative risk, *SAR* seasonal allergic rhinoconjunctivitis, *SAR case* seasonal allergic rhinoconjunctivitis case was defined as the association between an oral antihistamine and a local (nasal or ocular) antiallergic drug on the same prescription (Caillaud et al. (2015)), *sign*. significant; treated *ARC* oral antihistamine and a local antiallergic drug on the same prescription as indicator for an episode of treated ARC; *WD* Weekdays, *WE* Weekends

†Explanation of information regarding lag days:

♂ male

♀ female

Lag 0: Outcome and exposure measurements from the same day were compared.

Lag 1: Outcome measurements were compared with exposure measurements from the day before.

Lag 2: Outcome measurements were compared with exposure measurements from two days before.

Lag 0–1 (averaged): Outcome measurements were compared with the average of the exposure measurements from the same day and the day before.

Lag 2–3 (averaged): Outcome measurements were compared with the average of the exposure measurements from two days earlier and three days earlier.

Lag 0–3 (cumulated): Outcome measurements were compared with the cumulated exposure measurements from the same day, the day before, two days earlier and three days earlier

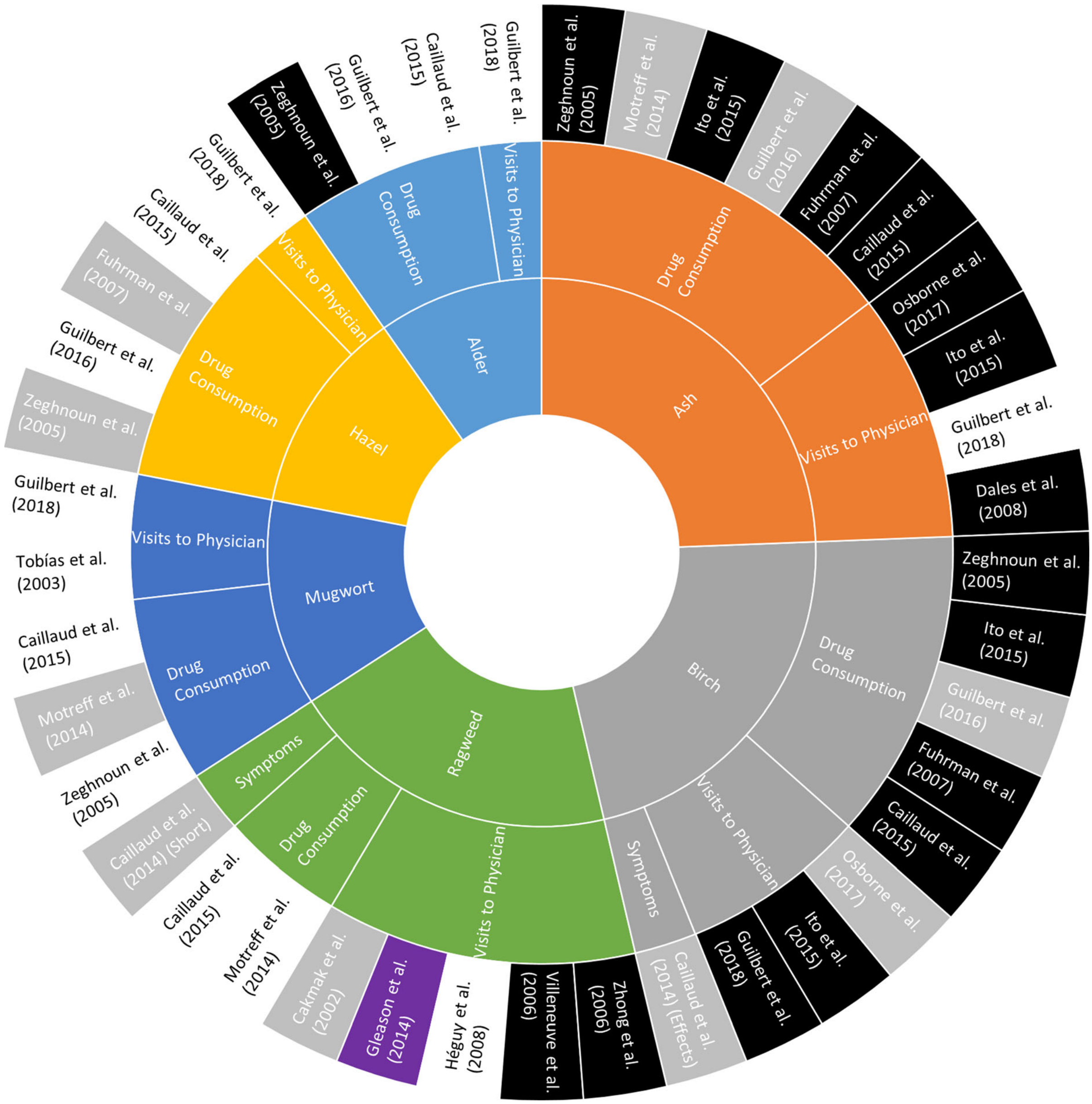

Fig. 2 Circle diagram with kind of pollen, kind of health outcome, studies and significance of results. This figure was created using program Microsoft Excel 2016. Black background: studies with statistically significant results; gray background: studies with statistically significant results only in sub-analyses; white background: studies with statistically nonsignificant results; purple background: study with significant protective effect of visits to physician

2015), it seems that an increase in ash pollen of around 18-28 grains/m^3 results in a statistically significant increase in antiallergic drug sales or cases of visits to physician. Studies investigating a lower pollen concentration (4 grains/m^3 (Guilbert et al., 2018) and 9 grains/m^3) showed no statistically significant results. Based on these results, the authors can conclude that there is plausibility to pollen threshold values. Therefore, the authors recognize a threshold value for ash pollen of 18 grains/m^3 for the outcome "visits to physician" and a threshold value of 28 grains/m^3 for "drug consumption."

The majority of the studies on threshold values of birch pollen show statistically significant results

(Zeghnoun et al., 2005; Fuhrman et al., 2007; Ito et al., 2015; Guilbert et al., 2016; D. M. Caillaud et al., 2015) and indicated an increasing risk of taking medication above a threshold value of 45 grains/m^3. Nevertheless, one study showed no statistically significant results (Osborne et al., 2017). The authors attribute this to confounding or limitations in the study design. Caillaud et al., (2014a) identified statistically significant birch pollen threshold values of 110 grains/m^3 for the occurrence of nasal symptoms, 70 grains/m^3 for the occurrence of ocular symptoms and 70 grains/m^3 for the occurrence of bronchial symptoms. The author's results further indicate that for pollen concentrations above the threshold values just mentioned, the occurrence of symptoms decreases again. This result indicates a nonlinear relationship between birch pollen concentrations and symptoms.

The results of hazel pollen threshold values (Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Guilbert et al., 2018; Guilbert et al., 2016; Fuhrman et al., 2007), mugwort pollen threshold values (Zeghnoun et al., 2005; D. M. Caillaud et al., 2015; Guilbert et al., 2018; Motreff et al., 2014; Tobias et al., 2003) and ragweed pollen threshold values (D. M. Caillaud et al., 2015; D. Caillaud et al., 2014b; Zhong et al., 2006; Cakmak et al., 2002; Heguy et al., 2008; Villeneuve et al., 2006; Motreff et al., 2014; Gleason et al., 2014), respectively, gave a mixed picture. Statistically significant and statistically nonsignificant results were found for both high and low concentrations. Therefore, the authors cannot identify a threshold value for hazel, mugwort and ragweed pollen. From the results identified, it can be concluded that sensitivity is strongly dependent on the individual sensitization of the individual person.

4.3 Sub-analyses by age

The results of the sub-analyses by age of the included studies show a mixed picture. No clear age patterns can be concluded for the observed results. Overall, health effects of pollen and/or the help-seeking behavior determined by exposure to pollen might be influenced by age. However, no clear age patterns were identified.

4.4 Sub-analyses by sex

There was just one study stratifying the results by sex. Guilbert et al. (2016) found stronger associations for males aged 19–64 years. In general, allergic rhinitis is more prevalent in males than in females, which was reviewed by Chen et al. (2008). Thus, differences between males and females regarding pollen-related allergic effects and help-seeking behavior should be investigated in more detail. This could be an explanatory factor for contrasting study results.

4.5 Health outcomes—advantages and restrictions

It must be remarked that the health outcomes mostly investigated (drug consumption and visits to physician) are only proxies for the occurrence of symptoms. Physician's diagnoses underestimate the real number of allergy symptoms because of self-diagnoses and self-treatment, and access to health care (Salo et al., 2011). The determination of health outcomes by the request for prescriptions is sensitive to the preventative behavior of the people affected. They might buy antiallergic drugs in advance or use residual products, for example, over-the-counter medicine (Zeghnoun et al., 2005). It should be noted that in most countries, antihistamines, which are the first-line allergic rhinitis therapy, are over-the-counter or OTC medicine. They might also use medications preventively, before the occurrence of symptoms (Fuhrman et al., 2007). In addition, not every person affected is using drugs or might use another product or alternative therapies than observed by the studies. Another factor influencing the disposal of antiallergic drugs and the documentation of symptoms is a misinterpretation of pollen-related symptoms (Zeghnoun et al., 2005) due to similar effects like common cold diseases and influenza (D'Amato et al., 2007). The considerably lower prevalence of allergy symptoms diagnosed by a physician in contrast to self-reported symptoms was already discussed in the literature (Wise et al., 2018; Salo et al., 2011).

In many cases, symptoms themselves as well as help-seeking behavior do not occur on the same day of exposure but a few days later (Kiotseridis et al., 2013). Thus, the exposure from the days before the outcome is commonly considered. Several possibilities of the consideration of lag days were reported and uniformly abbreviated as described in the footnote of Table 7.

4.6 Threshold values

Our results indicate that deriving of threshold values for pollen concentrations resulting in allergic reactions in affected people seems to be much more complex than historically thought and handled in respective pollen forecasts. Thus, the same amount of pollen resulted in different reactions in people (Bastl K et al., 2014; Sofiev and Bergmann 2013) and temporal and regional differences were observed (Bastl K et al., 2014).

Several reasons may be responsible for these differences. To begin with, the allergen content per pollen grain may differ substantially (Buters et al., 2012; Jantunen et al., 2012) and the size of allergen-carrying particles (ruptured pollen) may be a factor that could influence study results (Schappi et al., 1997). Thus, much information about pollen itself should be collected and analyzed (Bastl K et al., 2014; Buters et al., 2012). Furthermore, the accuracy of pollen concentration data may vary between the analyzed studies. Rojo et al. (2020) showed that the measured pollen concentrations can vary due to the height of the pollen station. Additionally, pollen stations are usually set up at an average height of ten meters (Buters et al., 2018). Thus, the exposure of the pollen concentration to an individual at ground level could be underestimated (Buters et al., 2018).

Individual differences in tolerance levels leading to allergic reactions could also explain differences in results of the studies investigated. Jantunen et al. (2012) found a higher tolerance for birch pollen of people from Finland in comparison with people from Austria regarding birch pollen. Birch pollen counts from Finland are generally much higher than in Austria, which might result in a local adaptation (Buters et al., 2012). Indeed, the same symptom score was reached in Austria at 250 grains/m^3 and Finland at 600 grains/m^3 (Buters et al., 2012). Furthermore, symptom awareness and behavior of individuals are influenced by multiple factors (own variable bronchial hyperreactivity, degree of sensitization, influence of drugs, own perception of symptoms, etc.) (Werchan et al., 2017). Additionally, similar pollen concentrations might cause different intensities of symptoms under varying environmental conditions (Damialis et al., 2019). Different pollen types showed different effects. For example, grass pollen induced a stronger effect than the same amount of tree pollen (Wise et al., 2018). While temperature and other weather conditions are influencing factors for allergy symptoms (e.g., thunder asthma) (Thien et al., 2018; Sofiev and Bergmann 2013), there might also be a difference between pollen in the early season in contrast to pollen in the late season (De Weger et al., 2011; Sofiev and Bergmann 2013). This difference in allergen release is to be expected given the natural variability between the pollen-producing species (Buters et al., 2015). It was observed, that—without an increase in the amount of pollen per m^3 of air—the prevalence and severity of its health effects on certain patient has increased with time (D'Amato et al., 2001). 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 the current review. In addition, the consideration of air pollution was included in the risk-of-bias analysis. Thus, consideration of air pollution as confounder had been fixed as a rule for the risk-of-bias assessment in the current review. These possible influencing factors may explain the mostly inconclusive results found in the literature for this review and emphasizes the lack of sufficient data on this topic (Kiotseridis et al., 2013).

The aim of this study was to identify pollen threshold values in relation to symptoms of allergy. Many pollen warning systems use the colors of traffic light to indicate the risk for pollen allergy patients. Such a color scale ranges from green (no risk of developing symptoms due to pollen) to red (high risk of developing symptoms due to pollen). Based on our results, such categorization should be avoided, as even low pollen concentrations can be a high burden for a pollen allergy patient. The results show that pollen allergies should be examined and treated individually, as health outcomes are influenced by different influencing factors such as pollen type, air temperature, region and individual sensitivity. Future studies should focus these influencing factors.

4.7 Assessment of RoB: relevance of the conflict of interest criteria for study outcomes

Of the 17 included studies in this review, eight studies published with a CoI (Fuhrman et al., 2007; Guilbert et al., 2018; Ito et al., 2015; Guilbert et al., 2016; Tobias et al., 2003; Cakmak et al., 2002; Gleason et al., 2014; D. Caillaud et al., 2014b) statement and nine studies without (Osborne et al., 2017; D. Caillaud et al., 2014a; Zeghnoun et al., 2005; Dales et al., 2008; Heguy et al., 2008; Zhong et al., 2006; Villeneuve et al., 2006; D. M. Caillaud et al., 2015; Motreff et al., 2014). The eight studies that provided a CoI statement declared that there are no conflicts of interest. It is noticeable that 83% of the analyses published without CoI show statistically significant results, while only half of the analyses (52%) published with CoI show statistically significant results. Woodruff and Sutton (2014) have summarized evidence that a funding source can influence the study outcome. Thus, it is important to declare whether an external influence is possible.

4.8 Strengths and limitations

Our study had some limitations. The definition of AR, the severity of symptoms, visits to physician and drug consumption vary in the included studies. This variation makes it difficult to compare the results. Therefore, the authors cannot draw general conclusions from the found results. Future studies should define AR, the severity of symptoms, visits to physician or drug consumption in a comparable way.

To the best of our knowledge, the broad scope of this review is unique. There are different reviews on this topic, but our review is uniquely covering a wide variety of allergenic pollen types and health outcomes. One strength of our study is that we had no restricted inclusion criteria regarding the study populations.

Another strength of the study is the broad view on six kinds of pollen types and three categories of health outcomes. A broad search strategy was constructed and applied to PubMed that is recognized as “the primary tool for searching biomedical literature” (Lu 2011). However, the snowball strategy revealed further literature that is not listed in PubMed (Hofman et al., 1996; Motreff et al., 2014) or that is listed in PubMed but was not found with the search term applied (Guilbert et al., 2016; Gleason et al., 2014; Heguy et al., 2008; Ross et al., 2002; Villeneuve et al., 2006).

5 Conclusion

In conclusion, the authors were able to derive indications for pollen threshold values for ash and birch. Due to the many inconsistent results in this review, the factors influencing the association between pollen concentration and health outcomes should be investigated more closely. In this review, the influencing factors age, gender, allergen content of pollen and individual sensitivity could be identified. These influencing factors should be examined more closely in future research.

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Authors' contributions NS-M, HM, IM, PS, JB, K-CB, SB-O, JB, AD, JH, MK, DN, SW-R, AW, MZ, CH, SK and SH contributed to conceptualization. NS-M, HM and IM performed the literature search. NS-M, HM, IM, PS, K-CB, SB-O', JB, AD, JH, MK, DN, AW, CH, SK and SH were involved in methodology. NS-M, HM, IM, PS, AW, CH, SK and SH analyzed the data. NS-M, HM, IM and SK drafted the article. IM, PS, JB, K-CB, SB-O'R, JB, AD, JH, MK, DN, SW-R, AW, MZ, CH, SK and SH revised the article. NS-M, HM, IM, PS, JB, K-CB, SB-O', JB, AD, JH, MK, DN, SW-R, AW, MZ, CH, SK and SH contributed to final approval. NS-M, HM, IM, PS, JB, K-CB, SB-O', JB, AD, JH, MK, DN, SW-R, AW, MZ, CH, SK and SH contributed to agreement to account for all aspects of the work. NS-M, K-CB, SB-O', AD, JH, DN, CH, SK and SH were involved in supervision. NS-M and HM are the first authors. SK and SH are the senior authors

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Data availability All listed tables, figures and supplements are included in the paper or available in Electronic Supplementary Material.

Declarations

Conflict of interest K.C. Bergmann who is the author of paper (Bergmann et al., 2016), J. Buters who is the author of papers (Buters et al., 2018), (Buters et al., 2015) and (Buters et al., 2012) and A. Damialis who is the author of paper (Damialis et al., 2019) included in this review declare that there is no conflict of interest.

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