



Interactive effects of allergens and air pollution on respiratory health: A systematic review

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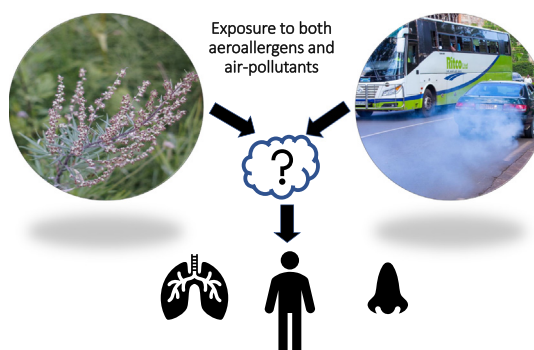
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HIGHLIGHTS

- Whether allergen and pollutants interact to affect respiratory health is unknown.
- A systematic review of epidemiological studies was conducted.
- Studies in English were searched from the MEDLINE, EMBASE and Scopus databases.
- There was no consensus as to which allergen or pollutant is likely to interact.
- Evidence of allergen-pollutant interactions on respiratory health is weak.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Studies have demonstrated an adverse role of outdoor allergens on respiratory symptoms. It is unknown whether this effect is independent or synergistic of outdoor air pollutants.

Methods: We systematically reviewed all epidemiological studies that examined interaction effects between counts of outdoor airborne allergens (pollen, fungal spores) and air pollutants, on any respiratory health outcome in children and adults. We searched the MEDLINE, EMBASE and Scopus databases. Each study was summarized qualitatively and assessed for quality and risk of bias (International Prospective Register for Systematic Reviews, registration number CRD42020162571).

Results: Thirty-five studies were identified (15 timeseries, eight case-crossovers, 11 panels and one cohort study), of which 12 reported a significant statistical interaction between an allergen and air pollutant. Eight interactions were related to asthma outcomes, including one on lung function measures and wheeze, three to medical consultations for pollinosis and one to allergic symptoms (nasal, ocular or bronchial). There was no consensus as to which allergen or air pollutant is more likely to interact. No study investigated whether interactions are stronger in atopic individuals.

Conclusion: Despite strong evidence from small experimental studies in humans, only a third of studies identified significant allergen-pollutant interactions using common epidemiological study designs. Exposure misclassification, failure to examine subgroups at risk, inadequate statistical power or absence of population-level effects are possible explanations.

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1. Introduction

The effects of outdoor airborne allergens on respiratory health have been evaluated in many epidemiological studies. A recent systematic review and meta-analysis concluded that outdoor pollen exposure is an important trigger for childhood asthma exacerbations requiring emergency department attendance (Erbas et al., 2018). Outdoor air pollutants, which coexist with airborne allergens, have also been widely studied for their adverse effects on respiratory health, in particular on asthma (Orellano et al., 2017). However, despite the substantial evidence supporting the existence of independent effects of allergens and air pollution on respiratory health, it remains unclear whether these environmental factors may also act synergistically.

Outdoor air pollutants have been shown to modify the allergenic potential of plant pollen and fungal spores via chemical modifications, increase allergen release from pollen grains and fungal spores and facilitate the transport of allergens into the airways. Air pollutants may also exert direct effects on individuals that could enhance the response to allergens, such as inducing epithelial damage which could increase oxidative stress and inflammation, and skewing the immune system towards an allergic response (Eguiluz-Gracia et al., 2020; Reinmuth-Selzle et al., 2017; Sedghy et al., 2018; Sénéchal et al., 2015; Smiljanic et al., 2019). Indeed, many small experimental studies conducted on humans have shown adverse synergistic effects of allergens and air pollutants on biological outcomes. For example, co-exposures to allergens and air pollution induce DNA methylation (Clifford et al., 2017), increase allergen-induced inflammatory and cellular immune responses (Hosseini et al., 2016), alter protein expression in lung (Mookherjee et al., 2018) and impair lung function (Wooding et al., 2019). Results from epidemiological studies, however, which assess allergen-pollutant interactions at ambient level appear less consistent (Anderson et al., 1998; Babin et al., 2008; Babin et al., 2007; Cakmak et al., 2012; Chen et al., 2016; Dales et al., 2004; Darrow et al., 2012; Erbas et al., 2012; Ghosh et al., 2012; Krmpotic et al., 2011; Lewis et al., 2000; Tham et al., 2017a; Tham et al., 2017b; Weisel et al., 2002).

Understanding allergen-pollutant interactions is especially relevant for urban areas where there are drives to increase green spaces and where the concentrations of some air pollutants tend to be high (Sousa-Silva et al., 2020). The assessment of co-exposures to pollen and pollutants in urban centres is an active area of research (Mücke et al., 2014; Ørby et al., 2015). As climate change is expected to increase

pollen and fungal spore counts (Galán et al., 2016; Ziello et al., 2012) and influence their spread (Storkey et al., 2014), in addition to raising the concentrations of some air pollutants (e.g. carbon monoxide (CO), ozone, extreme dust events), it is vital that we understand how co-exposures to allergens and pollutants influence respiratory health (Schiavoni et al., 2017).

This systematic review expands on the work by Erbas et al. (2018) (focused specifically on asthma exacerbations and outdoor pollen) (Erbas et al., 2018), and is the first to review and summarize the current epidemiological evidence on the interaction effects of outdoor airborne allergens and air pollutants on any respiratory health outcome.

2. Material and methods

2.1. Search strategy

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher et al., 2009, 2015) guidelines. A protocol was developed and uploaded to PROSPERO (International Prospective Register for Systematic Reviews, registration number CRD42020162571).

The literature was searched using three computerised bibliographic databases, MEDLINE, EMBASE and Scopus (search last updated April 27th, 2020). The search terms used in MEDLINE are listed in Table 1. Very similar but adapted terms were used in EMBASE (e.g. Emtree sub-headings) and Scopus (Supporting Information, Tables S1–S2). The search terms were grouped into four categories (respiratory health, outdoor allergens, air pollution and study design) and linked with the Boolean operator “AND”. Reference lists of included studies were searched to find additional studies.

2.2. Study selection and eligibility criteria

All identified articles were downloaded into an electronic systematic review manager (Covidence, n.d.). Duplicates were deleted using the software's function. The titles and abstracts of the remaining articles were reviewed for eligibility by two researchers (HL, EF). Studies were retained if an outdoor allergen and air pollutant was mentioned in the abstract/title (or when it was suspected that both environmental factors were considered in the analysis). Subsequently, to identify studies that examined an interaction effect between an allergen and air pollutant,

Table 1
Search terms used to identify articles in MEDLINE.

Category	Search terms
Respiratory health	MeSH terms: Asthma OR Bronchitis OR Cough OR Forced Expiratory Volume OR Pulmonary Ventilation OR Respiratory Sounds OR Rhinitis OR Respiratory Disorders OR Spirometry OR Vital Capacity Free text: airway* OR asthma* OR breath* OR bronchi* OR cough* OR exacerbation* OR hayfever OR hay fever OR lung OR pulmonary OR respiratory OR rhinoc* OR wheez*
Outdoor allergens	MeSH terms: Allergens OR Alternaria OR Cladosporium OR Fungi OR Pollen OR Spores, Fungal Free text: aeroallergen* OR aero allergen or aero allergens OR allergen* OR aspergillus OR cedar OR OR grass OR birch OR pollen* OR mould* OR mold* OR parietaria OR ragweed OR spore*
Air pollution	MeSH terms: Air Pollution OR Air Pollutants OR Ozone OR Nitrogen Dioxide OR Particulate Matter OR Sulfur Dioxide OR Traffic-Related Pollution OR Vehicle Emissions Free text: air quality OR carbon monoxide OR emission* OR exhaust OR freeway* OR highway* OR motorway* OR nitrogen dioxide OR particulat* OR particle* OR pollut* OR road* OR sulphur dioxide OR traffic* OR ozone
Study design	MeSH terms: Case-Control Studies OR Cross-Over Studies OR Cohort Studies OR Longitudinal Studies Free text: case control OR casecontrol OR case crossover OR cohort OR daily OR longitudinal OR panel OR timeseries OR time series

a text search was conducted for “interact*”, “stratif*” and “modi*”, and each publication’s tables and figures were screened. The full texts of the publications retained were evaluated for data extraction and quality assessment by two researchers (HL, EF). Disagreements at all stages were resolved by a third author (DJ).

Studies had to meet the following three criteria to be included: (1) assess the interaction between at least one measured outdoor allergen and one air pollutant in relation to a respiratory health outcome in humans; (2) be conducted using a study design listed in Table 1; (3) be written in English. Studies conducted exclusively in laboratory settings or involving occupational allergens or indoor allergens were excluded. We included all potential interactions and made no assumptions of the nature of interactions.

Correspondingly, aligning with the PICO model, our population (P) of interest was all population groups, the intervention/exposure (I) was outdoor allergens and air pollutants, the comparison (C) made was different levels of exposure to these environmental factors, and the outcomes (O) considered were any respiratory health outcome.

2.3. Data extraction

We extracted the following information from each study: author names, publication year, study design, information on the study population (general/at risk, age, location, time period, sample size), allergens, air pollutants and health outcomes considered, outcome and exposure assessment methods, statistical analysis, adjustment factors, effect estimates and their corresponding 95% confidence intervals for the main effects of allergens and air pollutants, as well as their interaction, and whether effect modification by atopy was examined.

2.4. Study quality and risk of bias

The quality of each study was assessed using a modified version of a validated study quality instrument flexible enough to be applied to various study designs (Zaza et al., 2000). This instrument collects information on sample description and sampling method, outcome and exposure assessment, appropriateness of the statistical analysis and interpretation of the results. We further collected information on which allergen-pollutant interactions were tested (to assess potential reporting bias and multiple testing) and qualitatively, on the statistical power of the study to assess interactions. Consideration was given to study-level risk of bias and outcome-level risk of bias.

3. Results

3.1. Search results

The search yielded 1530 unique articles. Title and abstract screening led to the exclusion of 1322 articles. The remaining 208 articles were searched for whether an interaction effect between an allergen and air pollutant appeared to have been tested, which was the case in 38 articles. After fulltext reading, two articles were excluded as they ultimately did not test an interaction, two were excluded as they did not provide information on the results of the interactions tested and one new article was found through a manual search of reference lists and included, leading to a final number of 35 articles (flow chart provided in Fig. 1). The descriptive characteristics of these 35 studies and their findings related to allergen-pollutant interactions are summarized in Table 2 (additional information is provided in the Supporting Information, Table S3).

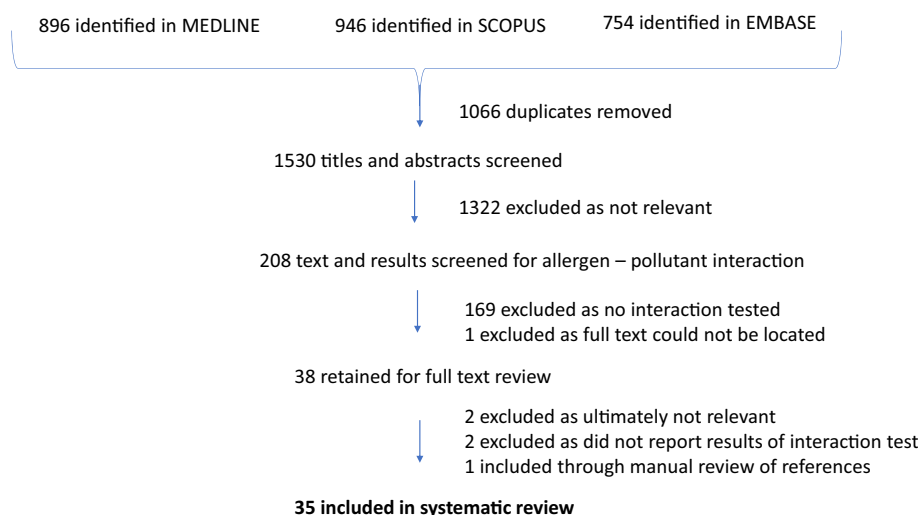


Fig. 1. Flow chart of study selection.

Table 2
Characteristics of studies ordered by study design (timeseries and case-crossover studies, panel studies, cohort study) and year.

Author, year	Type of study	Population, location	Time period	Outcome	Allergens	Air pollutants	Allergen - pollutant interactions	Atopic status
Guilbert et al., 2018	Timeseries	Residents of Brussels-Capital Region, Belgium	01/01/2008 to 31/12/2013	Daily number of asthma hospital admissions	Daily counts of 11 pollen taxa (alder, hazel, yew, Cupressaceae, ash, hornbeam, birch, oak, plantain, grasses, mugwort) and two fungal spore taxa (<i>Alternaria</i> , <i>Cladosporium</i>)	NO ₂ , O ₃ , PM _{2.5} , PM ₁₀	Interactions tested between all allergens and air pollutants. Significant interactions found, notably risks higher for grass and birch pollen counts on days with high PM ₁₀ and O ₃ levels, respectively ($p = 0.05$). Interactions also found in the unexpected direction between <i>Alternaria</i> and PM ₁₀ and PM _{2.5} , oak and NO ₂ and hazel and O ₃ ($p = 0.06$).	No information
Phosri et al., 2017	Case-crossover	Residents of Fukuoka City, Japan, attending 10 otolaryngology and ophthalmology clinics	2002 to 2012 (01/02–30/04 only)	Daily number of medical consultations for pollinosis	Daily counts of pollen (comprises Japanese cedar and cypress pollen)	PM _{2.5} mass and its components (NO ₃ ⁻ , non-sea-salt-SO ₄ ²⁻ , sea-salt-Ca ²⁺)	Interactions tested between pollen and all pollutants. Cumulative effect of pollen greater on days with high non-sea-salt Ca ²⁺ ($p < 0.01$) and, for some models, non-sea-salt SO ₄ ²⁻ and NO ₃ ⁻ . Pollen effects (unexpectedly) greater on days with moderate (compared to high) total PM _{2.5} mass ($p < 0.01$).	No information
Sakata et al., 2017	Timeseries	Residents of Fukuoka City, Japan, attending four otorhinolaryngology clinics	1989 to 2012 for Clinic I and III, 1994–2012 for Clinic II, 1989–2001 for Clinic IV (February to April only)	Daily number of medical consultations for pollinosis	Daily counts of pollen (comprises Japanese cedar and cypress pollen)	Asian dust days (visibility <10 km), SPM	Interactions tested between Asian dust days and pollen and were consistently significant for all lags in 3 out of 4 clinics ($p < 0.01$). Interactions also tested between SPM and pollen and were significant for all four clinics during Asian dust-free days ($p < 0.01$).	No information
Tham et al., 2017a	Case-crossover	Asthmatic children (2–18 years) attending Campbelltown, Camden or Liverpool hospitals, Sydney, Australia	29/05/2008 to 03/05/2013	Daily number of asthma hospital admissions	Counts of total fungal spores and 20 fungal spore taxa	NO ₂ , O ₃ , PM _{2.5} , PM ₁₀	Interactions tested between pollutants and allergens. None significant.	No information
Tham et al., 2017b	Case-crossover	Melbourne Air Pollen Children and Adolescent (2–17 years) study participants (hospitalized for asthma in Melbourne, Australia)	09/2009 to 12/2011	Daily number of asthma hospital admissions	Counts of total fungal spores and 12 fungal spore taxa (<i>Alternaria</i> , <i>Cladosporium</i> , <i>Ganoderma</i> , <i>Leptosphaeria</i> , <i>Pleospora</i> , <i>Sporormiella</i> , <i>Pithomyces</i> , smuts, <i>Coprinus</i> , <i>Drechslera</i> , <i>Stemphylium</i> , <i>Periconia</i>)	NO ₂ , O ₃ , PM _{2.5} , PM ₁₀	Interactions tested between pollutants and allergens. None significant.	Information available for 630 participants. Analyses stratified by sensitization (8.9% to <i>Alternaria</i> only, 6.5% to <i>Cladosporium</i> only, and 13.7% to both). No information
Chen et al., 2016	Timeseries and case-crossover	Residents of Adelaide, South Australia	01/07/2003 to 30/06/2013	Daily number of asthma hospital admissions	Daily total pollen counts	NO ₂ , O ₃ , PM _{2.5} , PM ₁₀	Unclear which interactions tested but reported that none significant.	No information
Gleason et al., 2014	Case-crossover	Children (3–17 years) in New Jersey, USA	2004 to 2007 warm season (01/04 to 30/09 only)	Daily number of asthma emergency department visits	Daily counts of tree pollen, weed pollen, grass pollen and ragweed	O ₃ , PM _{2.5}	Stated that interactions tested between quintiles of O ₃ and PM _{2.5} with high vs low categories of each pollen type, although no interaction terms formally reported. Stratified models indicate effect of O ₃ and PM _{2.5} greater on days with high 3-day average weed pollen counts. Interactions tested between pollen counts and PM _{2.5} and SPM. Effect of 5-day average cumulative pollen count greater on days with high	No information
Konishi et al., 2014	Case-crossover	Residents of Chiyoda ward, Tokyo, Japan, attending one general practice	2001 to 2011 (January to May only)	Daily number of initial doctor consultations for pollinosis	Daily counts of pollen (comprises Japanese cedar and cypress pollen)	CO, NO ₂ , O ₃ , PM _{2.5} , SO ₂ , SPM	Interactions tested between pollen counts and PM _{2.5} and SPM. Effect of 5-day average cumulative pollen count greater on days with high	No information

Cakmak et al., 2012	Timeseries	Residents of 11 cities in Canada.	01/04/1994 to 31/03/2007	Daily number of asthma hospital admissions	Daily counts of weed, trees and grass pollen and Basidiomycetes, Ascomycetes and Deuteromycetes fungal spores.	CO, NO ₂ , O ₃ , PM _{2.5} , PM ₁₀ , SO ₂	PM _{2.5} (consistently) or SPM levels (less consistently), compared to days with moderate pollutant levels. Results less clear when considering single-day pollen effects.	No information
Darrow et al., 2012	Case-crossover	Residents of Atlanta metropolitan area, USA, attending 41 acute-care hospitals	1993 to 2004 Analyses limited to pollen season for each taxa (2–5 months), 01/09/2003 to 31/12/2003	Daily number of emergency department visits for asthma and wheeze	Daily counts of four tree pollen taxa (Betulaceae, Cupressaceae, Quercus, Pinaceae), grasses and Ambrosia	CO, NO ₂ , O ₃ , PM _{2.5} , PM ₁₀ , SO ₂	Interactions tested between all pollutants and all allergens. Effect of allergens greater on days with high air pollution levels in several cases, especially for PM ₁₀ . Interaction terms significant ($p < 0.05$) between ascomycetes and CO and PM ₁₀ , basidiomycetes and CO, NO ₂ , SO ₂ and PM ₁₀ , deuteromycetes and CO, NO ₂ , SO ₂ and PM ₁₀ , trees and PM _{2.5} , weeds and PM ₁₀	No information
Erbas et al., 2012	Timeseries	Children (<15 years) living in Melbourne, Australia	01/09/2003 to 31/12/2003	Daily number of asthma emergency department visits for asthma	Daily counts of grass pollen	NO ₂ , O ₃ , airborne particle index	Interactions tested between grass pollen count and the Airborne Particle index and NO ₂ . Neither significant.	No information
Ghosh et al., 2012	Timeseries	Residents of Kolkata, India, with a diagnosed respiratory allergy attending a hospital allergy clinic (catchment area of 2 hospitals included)	2004 to 2009	Number of asthma-related hospital admissions recorded in 10-day time-slots.	Daily counts of five pollen types (<i>Areca</i> , <i>Carica</i> , <i>Chenopodiaceae</i> , <i>Cocos</i> , <i>Phoenix</i> , <i>Cyperaceae</i> , <i>Poaceae</i>), 7 fungal types (<i>Alternaria</i> , <i>Aspergilli</i> , <i>Basidiospores</i> , <i>Cladosporium</i>) and total fungal spores	NO ₂ , SO ₂ , SPM, respirable particulate matter, O ₃ (latter only for two years)	Unclear which interactions tested but reported that none significant.	No information
Krmpotic et al., 2011	Timeseries	Residents of Zagreb, Croatia	01/01/2004 to 31/12/2006	Daily number of asthma hospital admissions	Daily alder, hazel, birch, hornbeam, oak, grasses and ragweed pollen counts	CO, NO ₂ , PM ₁₀	Interactions tested between all pollutants and pollen variables. None significant.	No information
Babin et al., 2008	Timeseries	Residents of Washington, DC, USA, on Medicaid health plan	01/10/1994 to 22/11/2005	Daily number of asthma-related acute care visits	Daily tree, grass, weed pollen counts and total mold spore counts.	O ₃ , PM _{2.5} , PM ₁₀	Unclear which interactions tested but reported that none significant.	No information
Babin et al., 2007	Timeseries	Residents of Washington, DC, USA.	10/2001 to 09/2004 (except 12/2002)	Daily number of asthma-related pediatric emergency department visits and admissions	Daily tree, grass, weed pollen counts and total mold spore counts	O ₃ , PM _{2.5}	Interactions tested between both pollutants and all allergens but none significant.	No information
Carracedo-Martinez et al., 2008	Case-crossover	Residents of the City of Vigo, Spain	1996–1999	Daily number of medical emergency calls for cardiovascular and respiratory causes	20 types of pollen counts	Black smoke, SO ₂	Unclear which interactions tested but reported that none significant.	No information
Villeneuve et al., 2006	Timeseries	Elderly (≥65 years) residents of Toronto, Canada.	01/01/1995 to 31/12/2000	Daily number of primary care visits for allergic rhinitis	Daily ragweed counts	NO ₂ , O ₃ , PM _{2.5} , PM ₁₀ , PM _{2.5-10} , SO ₂	Interactions tested between ragweed and all pollutants except O ₃ . None significant.	No information
Dales et al., 2004	Timeseries	Residents of 10 cities in Canada.	01/04/1993 to 31/03/2000 (only months with pollen/fungal counts >0)	Daily number of asthma hospital admissions	Daily counts of weed, trees and grass pollen and Basidiomycetes, Ascomycetes and Deuteromycetes fungal spores.	NO ₂ , O ₃ , SO ₂ , coefficient of haze	In combined analyses, only interaction term between O ₃ and tree pollen count was significant ($p < 0.05$). City-specific interactions also observed between O ₃ and certain allergens (basidiomycetes in 3 cities,	No information

(continued on next page)

Table 2 (continued)

Author, year	Type of study	Population, location	Time period	Outcome	Allergens	Air pollutants	Allergen – pollutant interactions	Atopic status
Lierl and Homung, 2003	Timeseries	Residents of Cincinnati, USA	04/1996 to 10/1996 and 04/1997 to 10/1997 (08/1996 excluded)	Daily number of asthma hospital visits (includes visits and admissions combined)	Daily counts of total pollen and fungal spores	O ₃ , PM ₁₀	deuteromycetes in 3 cities, weeds in 3 cities, trees in 4 cities, grass in 1 city). Interactions tested between pollen counts and air pollutants. No interaction terms formally reported. Stratified models indicate effect of pollen counts greater on high (> 33 µg/m ³) PM ₁₀ days. Interactions tested between pollutants and allergens. None significant.	No information
Sunyer et al., 2002	Case-crossover	Residents of Barcelona, Spain, who attended emergency department for asthma between 1985 and 1989 in the four largest hospitals (covers 80% of population)	1985 to 1995	Number of overall and cause-specific mortality (including respiratory mortality)	Weekly counts of total pollen, grass pollen, total fungal spores, <i>Cladosporium</i> , <i>Alternaria</i> , <i>Epicoccum</i> and <i>Helminthosporium</i>	Black smoke, CO, NO ₂ , O ₃ , SO ₂		No information
Weisel et al., 2002	Timeseries	Residents of central and northern New Jersey, USA	01/05/1995 to 31/08/1995	Daily number of asthma hospital visits and admissions	Daily counts of total pollen and total fungal spores	O ₃	Unclear which interactions tested but reported that none significant	No information
Lewis et al., 2000	Timeseries	Residents of Derby, England	01/1993 to 12/1996	Daily number of asthma hospital admissions and visits (assessed separately)	Daily counts of grass and birch pollen, hyaline basidiospores, coloured basidiospores, <i>Didymella</i> , <i>Alternaria</i> , and <i>Cladosporium</i>	Black smoke, O ₃ , NO ₂	Interactions tested between all pollutants and pollen variables. None significant.	No information
Anderson et al., 1998	Timeseries	Residents of London, UK	1987 to 1992	Daily number of asthma hospital admissions	Daily birch, grass and oak pollen counts	Black smoke, NO ₂ , O ₃ , SO ₂	Interactions tested between all three allergens and pollutants significant in unipollutant models (O ₃ and SO ₂), restricted to warm season. Significant interaction found between SO ₂ and grass pollen counts in 0–14 age group in warm season ($p < 0.01$). Interactions also found between ozone and birch and ozone and oak in unexpected direction in all-ages analysis in the warm season ($p < 0.001$)	No information
DellaValle et al., 2012	Panel	Children (4–12 years) with asthma living in Connecticut, Massachusetts and New York, USA	Recruited 2000 to 2003, each followed for one year.	Daily record of asthma symptoms of wheeze, night symptoms, shortness of breath, chest tightness, persistent cough and rescue medication use ^a	Daily counts of total pollen, and tree, grass and weed pollen	NO ₂ , O ₃ , PM _{2.5} , SO ₂	Interactions tested between O ₃ and all pollen variables, but none significant.	Information available for 319 (74%) subjects. Analyses stratified by sensitization to grass (26%) and weed (22%) pollen.
Chen et al., 2011	Panel	Children (mean age 10.6 years) of three elementary and two middle schools in Taipei Country, Taiwan	09/2007 to 06/2008	Monthly FVC, FEV ₁ , FEF ₂₅ , FEF ₅₀ , FEF ₇₅ , FEF _{25/75}	Daily total fungal spore counts in week of lung function measurement	CO, NO ₂ , O ₃ , PM _{2.5} , PM _{coarse} , SO ₂	Unclear which interactions tested but reported that none significant.	No information
Jalaludin et al., 2004	Panel	Primary school children (mean age 9.6 years) with a history of wheeze attending six primary schools in western and southwestern Sydney.	01/02/1994 to 31/12/1994	Daily record of respiratory symptoms (wheeze, wet cough, dry cough), asthma medication use, visit to a doctor for asthma ^a	Daily counts of total pollen and <i>Alternaria</i>	NO ₂ , O ₃ , PM ₁₀	Interaction terms tested between air pollutants and counts of total pollen and <i>Alternaria</i> , but none significant.	No information

Delfino et al., 2002	Panel	Children/adolescents (9–19 years) with asthma living in Alpine California, USA	01/03/1996 to 30/04/1996	Daily record of asthma symptoms that interfere with daily activities ^a	Daily counts of total pollen and fungal spores	NO ₂ , O ₃ , PM ₁₀	Interactions tested between pollutants and allergens but none significant.	77.3% sensitized to pollens or fungi.
Just et al., 2002	Panel	Children (mean age 10.9 years) diagnosed with asthma who are outpatients at a hospital in Paris, France	01/04/1996 to 30/06/1996	Daily record of incident and prevalent asthma attacks, nocturnal cough, wheeze, irritation symptoms, respiratory infections, use of β_2 -agonist and morning and daily variability in PEF ^a	Daily counts of total pollen	Black smoke, NO ₂ , O ₃ , PM ₁₃ (SO ₂ too low for analysis)	Interaction terms tested between O ₃ and pollen counts. Interaction term significant for incident asthma attacks ($p = 0.002$).	90.2% were atopic.
Ross et al., 2002	Panel	Asthmatics living in East Moline, USA	24/05/1994 to 25/10/1994	Daily record of morning and evening PEF ^a , symptom scores frequency of asthma attacks and asthma medication use ^a	Daily counts of total, grass and ragweed pollen, as well as counts of total, <i>Alternaria</i> , <i>Cladosporium</i> , <i>Curvularia</i> , <i>Drechslera</i> and <i>Epicoccum</i> spores.	O ₃ , PM ₁₀ (only every 6th day), SO ₂	Interactions tested between O ₃ and allergens. None significant.	41–46% sensitized to trees, grasses or ragweed. Analyses stratified by sensitization.
Higgins et al., 2000	Panel	Asthmatics or those with chronic obstructive pulmonary disease who react to methacholine attending two general practices in Halton Health District, UK	28 days from August to mid-September 1991	Daily mean and variability in PEF ^a , presence of wheeze symptoms (data for dyspnoea, cough, throat irritation, eye irritation not usable for analyses) ^a	Daily counts of total fungal spores (measured pollen counts too low for analyses)	NO ₂ , O ₃	Interactions tested between total fungal spore counts and O ₃ and NO ₂ . Interactions observed between fungal spores and O ₃ for daily mean and variability in PEF ^a and wheeze symptoms ($p < 0.02$). Interaction also found between fungal spores and NO ₂ for wheeze but in unexpected direction ($p < 0.05$).	63% atopic. Analyses stratified by sensitization.
Jalaludin et al., 2000	Panel	Primary school children (mean age 9.6 years) with a history of wheeze attending six primary schools in western and southwestern Sydney	01/02/1994 to 31/12/1994	Daily record of evening PEF ^a (daily mean deviation of 3 measurements and maximum)	Daily counts of total pollen and <i>Alternaria</i>	NO ₂ , O ₃ , PM ₁₀	Unclear which interactions tested but reported that none significant	No information
Delfino et al., 1997	Panel	Asthmatics living in Alpine California, USA	09/05/1994 to 03/07/1994	Daily record of responses for asthma symptom severity and inhaler use and morning and evening PEF ^a	Daily counts of total pollen and fungal spores, as well as 12 fungi types (<i>Alternaria</i> , <i>Cladosporium</i> , <i>Helminthosporium</i> , <i>Aspergillus</i> and <i>Penicillium</i> , <i>Coprinus</i> , <i>Periconia</i> , <i>Botrytis</i> , total ascospores, total basidiospores, hyphal fragments, rusts, unidentified spores).	O ₃ , PM ₁₀	Interactions tested between pollen counts, PM ₁₀ and O ₃ with fungal spore counts for all outcomes, but none significant.	All subjects sensitized to ≥ 1 pollen extract. Analyses conducted among 16 subjects sensitized to ≥ 1 of five skin prick tests for fungal spore taxa.
Delfino et al., 1996	Panel	Children/adolescents (9–16 years) with asthma living in Mesa region in San Diego, USA	20/09/1993 to 31/10/1993	Daily record of responses for asthma symptom severity and inhaler use ^a	Daily counts of total pollen and fungal spores, as well as 5 fungi types (<i>Alternaria</i> , <i>Cladosporium</i> , <i>Helminthosporium interseminatum</i> , <i>Aspergillus</i> , <i>Penicillium</i>).	HNO ₁ , HNO ₃ , O ₃ , PM _{2.5} , sulfate and nitrate fractions of PM _{2.5}	Interactions tested between O ₃ and the fungal count variables, but none significant.	All subjects sensitized to ≥ 1 pollen extract. Analyses conducted among 10 subjects sensitized to ≥ 1 of five skin prick tests for fungal spore taxa.
Jones et al., 1994	Panel	Children (mean age 10.6 years) with a respiratory disorder (95% had asthma) attending two private practice offices and one pediatric clinic in Baton Rouge, Louisiana	14/06/1990 to 30/09/1990	Daily record of PEF ^a , respiratory symptom count and rating, activity time and rating, asthma/COPD medication count ^a	Daily counts of total pollen and fungal spores	NO ₂ , O ₃	Two-way interactions tested between both allergens and pollutants, as well as one-three way interaction between O ₃ , NO ₂ and fungal spore counts. None significant.	No information
Kanatani et al., 2016	Longitudinal cohort	Pregnant women (taking part in a larger cohort study) living in Kyoto,	10/2011 to 02/2012 to	Any allergic symptom (nasal, ocular or bronchial; symptom score > 0) ^a	Daily counts of pollen (comprises Japanese cedar and cypress pollen)	Asian dust days (dust level ≥ 0.07 km) compared to	Interaction term tested between dust days (yes/no) and pollen counts, and was significant	57.2% sensitized to Japanese cedar pollen. Analyses stratified by

(continued on next page)

Table 2 (continued)

Author, year	Type of study	Population, location	Time period	Outcome	Allergens	Air pollutants randomly selected control days (dust level < 0.07/km)	Allergen - pollutant interactions ($p < 0.001$)	Atopic status sensitization.
		Toyama and Tottori, Japan	05/2012, 10/2012 to 11/2012, 02/2013 to 05/2013					

CO = carbon monoxide; NO₂ = nitrogen dioxide; O₃ = ozone; PEFR: peak expiratory flow rate; PM_{2.5} = particulate matter ≤2.5 µm in aerodynamic diameter; PM₁₀ = particulate matter ≤10 µm in aerodynamic diameter; SO₂ = sulphur dioxide; SPM = suspended particulate matter.

^a Self-reported.

3.2. Study characteristics

Of the 35 included studies, there were 15 timeseries, eight case-crossovers, 11 panel and one cohort study. The most common health outcome was daily number of asthma hospital emergency department admissions or visits, assessed in timeseries and case-crossover studies ($n = 17$). Daily records of self-reported asthmatic, allergic (nasal, ocular or bronchial) or respiratory symptoms ($n = 10$) followed by changes in daily measurements of lung function ($n = 7$) were the next most frequently investigated outcomes, assessed in panel studies. All timeseries and case-crossover studies used administrative respiratory health data whereas information on respiratory symptoms was collected using self-completed (or parent-completed) questionnaires or diaries in the panel studies. Most studies were conducted in the United States ($n = 12$), Australia ($n = 6$), Japan ($n = 4$), Canada ($n = 3$) and the United Kingdom ($n = 3$). Fourteen studies were conducted in children/adolescents, four exclusively in adults and 17 in both children and adults.

Interactions with total pollen and total fungal spore counts were examined in 12 and 13 studies, respectively, whereas specific pollens (e.g. grasses, ragweed) and fungal types were examined in 22 and 13 studies, respectively. Most studies ($n = 24$) defined daily allergen exposure for the entire study area as the daily mean count obtained from one monitoring site. Measurements were most commonly made using a volumetric trap (Burkard/Hirst), although the measurement device was not always reported. A few studies used data from several monitoring sites to calculate daily exposures for the study area (two (Jalaludin et al., 2000, 2004), three (Ross et al., 2002) or nine (Konishi et al., 2014) monitoring sites) or assigned daily exposures to home addresses using data from the closest monitoring site from participants' home (Kanatani et al., 2016) or a spatial-temporal model (DellaValle et al., 2012). Only the data provider of the allergen information was provided in five studies (Babin et al., 2008; Babin et al., 2007; Just et al., 2002; Krmpotic et al., 2011; Weisel et al., 2002).

Similar methods were used to assign air pollution exposures as those used to assign allergen exposures, although usually data from a larger number of monitoring sites were available. Notable exceptions included the use of a spatial-temporal model which provided daily estimates of pollutants at a 12 km square grid scale (Gleason et al., 2014) and personal samplers to assign ozone exposures in two studies (Delfino et al., 1996, 1997).

3.3. Allergen and air pollutant interactions

Of the 35 studies that examined allergen-pollutant interactions (summarized in Tables 2 and S3), 12 reported at least one significant interaction effect: nine in timeseries and case-crossover studies, two in panel studies and one in a cohort study.

3.3.1. Timeseries and case-crossover studies

Six timeseries or case-crossover studies reported allergen-pollutant interactions for daily number of asthma hospital admissions or visits.

In a five-year timeseries study in London, two pollutants (ozone and SO₂) showed main effects on daily number of asthma hospital admissions, and interactions were tested with daily birch, grass and oak pollen counts. Only the interaction between SO₂ and grass pollen counts was statistically significant (and in the hypothesized direction) among 0–14 year-olds in the warm season (April to September) ($p < 0.01$). Two other interactions were noted in the all-ages analysis in the warm season (between ozone and birch and ozone and oak, $p < 0.001$), but these were in the unexpected direction, as results suggested stronger adverse effects of ozone on days with no pollen (Anderson et al., 1998).

In a second timeseries study using data on daily weed, tree and grass pollen counts, counts of three fungal classes (Basidiomycetes, Ascomycetes, Deuteromycetes), as well as NO₂, ozone, SO₂ concentrations and a coefficient of haze in ten Canadian cities over seven years, an

interaction term between ozone and tree pollen counts was significant for overall daily number of asthma hospital admissions in analyses including all data ($p < 0.05$). Additional interactions were observed between ozone and counts of certain allergens in city-specific analyses (basidiomycetes in three cities, deuteromycetes in three cities, weeds in three cities, trees in four cities, grass in one city) (Dales et al., 2004). A further Canadian timeseries study which examined the same allergens reported a larger effect of several fungal and pollen allergen counts on days with high air pollution concentrations, especially PM_{10} . Interaction terms were significant ($p < 0.05$) between ascomycetes counts and CO and PM_{10} , basidiomycetes counts and CO, NO_2 , PM_{10} , and SO_2 , deuteromycetes counts and CO, NO_2 , PM_{10} , and SO_2 , tree pollen counts and $PM_{2.5}$, as well as weed pollen counts and PM_{10} (Cakmak et al., 2012). It is worth noting the substantial overlap in data between these two Canadian studies: Dales et al. (2004) (Dales et al., 2004) reported allergen-pollutant interactions over seven years (01/04/1993 to 31/03/2000) in ten cities and Cakmak et al. (2012) (Cakmak et al., 2012) examined the same allergens over 13 years (01/04/1994–31/03/2007) in the same ten cities plus one other.

In a six-year timeseries study, interactions were tested between daily counts of 11 pollen taxa and two fungal spore taxa and NO_2 , ozone, $PM_{2.5}$, PM_{10} in relation to overall daily number of asthma hospital admissions in the Brussels-Capital Region, Belgium (Guilbert et al., 2018). Several significant interactions were found, although only two were in the expected direction; the adverse effects of grass and birch pollen counts were higher on days with high PM_{10} and ozone concentrations, respectively ($p = 0.05$). Results in the opposite direction (i.e. lower asthma hospitalizations associated with increasing allergen counts) were observed for Alternaria on days with high PM_{10} and $PM_{2.5}$ concentrations, oak on days with high NO_2 concentrations and hazel on days with high ozone concentrations ($p = 0.06$).

Although no formal interaction terms were provided, another timeseries study reported that the adverse effect of total pollen counts on daily number of asthma hospital visits in children (including 14 months of combined data on visits and admissions from Cincinnati, USA) was greater on high PM_{10} days (but not high ozone days) using stratified analyses (Lierl and Hornung, 2003). Of note, the authors state "We found significant interactions between season and pollen count and between pollen count and measured particulate level" but do not present the results of the interaction term. A three-year case-crossover study also used stratified analyses to demonstrate increasing adverse effects of ozone and $PM_{2.5}$ on daily number of asthma emergency department visits in children on days with high (but not low) three-day average weed counts during the warm season in New Jersey, United States. No difference in ozone and $PM_{2.5}$ effects were observed on high tree, grass or ragweed pollen days (Gleason et al., 2014). Although no formal interaction tests were reported for these latter two studies (Gleason et al., 2014; Lierl and Hornung, 2003), we here consider them as having found allergen-pollutant interactions based on the author's interpretation of the data.

In contrast to the above six studies which reported significant allergen-pollutant interactions on daily number of asthma hospital admissions or visits, eleven similar timeseries or case-crossover studies did not find significant interactions (Chen et al., 2016; Darrow et al., 2012; Erbas et al., 2012; Ghosh et al., 2012; Lewis et al., 2000; Tham et al., 2017a; Tham et al., 2017b; Babin et al., 2008; Babin et al., 2007; Krmpotic et al., 2011; Weisel et al., 2002). Combined, these studies cover various parts of the world and assessed interactions between both total and specific pollen and fungal spore counts and several pollutants. Although a few had rather short time-frames (≤ 3 years; (Babin et al., 2007; Erbas et al., 2012; Krmpotic et al., 2011; Tham et al., 2017b; Weisel et al., 2002)), this was not a universal trend in this group of studies reporting null findings for allergen-pollutant interactions.

Three Japanese studies examined interactions between measures of air pollutants and pollen counts comprising Japanese cedar and

Japanese cypress pollen on medical consultations for pollinosis, all of which reported significant interactions. First, in a case-crossover study using ten years of data from one ward in Tokyo, the adverse effect of 5-day average cumulative pollen was greater on days with high $PM_{2.5}$ mass compared to days with more moderate levels ($p = 0.02$) (Konishi et al., 2014). Results were similar but less consistent for suspended particulate matter. Second, in a timeseries analysis, consistent interactions between pollen counts and Asian dust days (visibility < 10 km) were reported in three out of four clinics in Fukuoka City ($p < 0.01$), as well as between pollen counts and suspended particulate matter in all four clinics during Asian dust-free days ($p < 0.01$) (Sakata et al., 2017). Third, interactions were tested between pollen counts and $PM_{2.5}$ total mass and its components (NO_3^- , non-sea-salt- SO_4^{2-} , sea-salt- Ca^{2+}) in a ten-year timeseries study using data from ten clinics in Fukuoka City (Phosri et al., 2017). The adverse two-day cumulative effect of pollen was greater on days with high non-sea-salt Ca^{2+} levels ($p < 0.01$) and less consistently, high non-sea-salt SO_4^{2-} and NO_3^- levels. However, the adverse effect of pollen was also unexpectedly greater on days with moderate compared to high total $PM_{2.5}$ mass ($p < 0.01$).

Finally, one four-year timeseries study in Vigo, Spain, assessed interactions with various pollen counts and black smoke and SO_2 on daily number of medical emergency calls for cardiovascular and respiratory cases (Carracedo-Martinez et al., 2008), one six-year timeseries study of elderly residents in Toronto, Canada, assessed interactions with ragweed counts and several air pollutants on daily number of primary care visits for allergic rhinitis (Villeneuve et al., 2006), and one ten-year case-crossover study of asthmatics in Barcelona, Spain, assessed interactions with pollen and fungal spore counts and several pollutants on overall and case-specific mortality (Sunyer et al., 2002). All three of these analyses yielded null findings.

3.3.2. Panel and cohort studies

The six timeseries and case-crossover studies that reported allergen-pollutant interactions on daily number of asthma hospital visits or admissions are weakly supported by the results of only two panel studies. First, among 35 adult patients with asthma or chronic obstructive pulmonary disease followed for four weeks during late summer (August to mid-September) in the United Kingdom, increasing total fungal spore counts were associated with reduced daily mean peak expiratory flow rate and increased daily variability in peak expiratory flow rate and reported wheeze symptoms, and these effects were greater the higher the prior (24–48 h) ozone level ($p < 0.02$) (Higgins et al., 2000). However, an interaction effect between fungal spore counts and NO_2 for wheeze was also found in the unexpected direction ($p < 0.05$). Second, in a three-month panel of 82 children diagnosed with asthma (90.2% atopic and all outpatients at a hospital in Paris, France), an interaction was found between ozone and total pollen count for daily records of self-reported incident asthma attacks ($p = 0.002$). Significant interactions were not found for daily records of self-reported respiratory symptoms, medication use or measures of peak expiratory flow rates (Just et al., 2002).

Of the nine panel studies that did not find significant allergen-pollutant interactions, seven assessed asthma or respiratory symptoms or medication use as outcomes (five included children/adolescents (Delfino et al., 2002; Delfino et al., 1996; DellaValle et al., 2012; Jalaludin et al., 2004; Jones et al., 1994) and two included participants of all ages (Delfino et al., 1997; Ross et al., 2002)), and five considered peak expiratory flow rate measures as outcomes (three included asthmatics of all ages (Delfino et al., 1997; Jones et al., 1994; Ross et al., 2002), one included children with wheeze (Jalaludin et al., 2000) and one included children with asthma, allergic rhinitis or healthy controls (Chen et al., 2011)).

Finally, in a Japanese cohort study of 3328 pregnant women followed for a total of 12 months of Asian dust seasons (February to May and October to November) (over three years), an interaction ($p < 0.001$) was found between the presence of Asian dust days (dust

level $\geq 0.07/\text{km}$) and pollen counts for developing any allergic symptom (nasal, ocular or bronchial symptoms, symptom score > 0) reported using a mobile phone questionnaire (Kanatani et al., 2016).

3.4. Effect modification by atopy

Of the total 35 studies, nine presented information on the atopic status of participants (six panel, one case-crossover and one cohort study). Of these nine, one included nearly exclusively atopic individuals (90.2%, (Just et al., 2002)) and eight included a mix of atopic and non-atopic individuals (Delfino et al., 2002; Delfino et al., 1996, 1997; DellaValle et al., 2012; Higgins et al., 2000; Kanatani et al., 2016; Ross et al., 2002; Tham et al., 2017b). Of these latter eight studies which could conduct analyses stratified by atopic status, four reported some stronger main effects of allergens or air pollutants among atopic subgroups (Delfino et al., 1997; DellaValle et al., 2012; Kanatani et al., 2016; Tham et al., 2017b) but none assessed whether allergen-pollutant interactions may be stronger among atopic individuals.

3.5. Quality assessment and risk of bias

Most studies were of good quality (quality assessment conducted summarized in the Supporting Information, Table S4). Selection bias is unlikely in the timeseries and case-crossover studies as these tended to include hospitals comprehensively covering the intended study areas. Loss to follow-up is more of a concern for the panel studies, although only two included $<80\%$ of initially recruited participants (Delfino et al., 1996; Ross et al., 2002). Variation in effect estimates by individual-level factors was rarely considered. Only one study assessed allergen-pollutant interactions by age group (Anderson et al., 1998) and none examined allergen-pollutant interactions by atopic status. Multiple testing and reporting bias are likely as multiple lags and several allergen-pollutant combinations were frequently tested but interaction effect estimates or p-values reported for only a subset of these analyses. Although difficult to assess, limited statistical power to test allergen-pollutant interactions is suspected in several studies.

4. Discussion

In this systematic review including 35 epidemiological studies that tested allergen-pollutant interactions in the context of respiratory health, we identified 12 studies that found a significant statistical interaction. Eight interactions were related to asthma outcomes, including one on lung function measures and wheeze, three to medical consultations for pollinosis and one to allergic symptoms. There was no consistency as to which allergen or air pollutant is more likely to interact and no study investigated whether allergen-pollutant interactions may be stronger in atopic individuals. There were no apparent systematic differences in terms of population studied (e.g. adults vs. children), outcome and exposures examined, assessment strategies used, sample size or length of follow-up between the 12 studies that reported finding an allergen-pollutant interaction and the 23 that did not.

As the relative majority (six) of allergen-pollutant interactions were identified for daily number of asthma hospital admissions or visits (Anderson et al., 1998; Cakmak et al., 2012; Dales et al., 2004; Gleason et al., 2014; Guilbert et al., 2018; Lierl and Hornung, 2003), this may indicate that such interactions primarily influence severe asthma symptoms requiring hospitalization. However, it is possible that outcome misclassification is lower for severe symptoms compared to more moderate symptoms, the latter of which are usually captured using self-reported questionnaires which are subject to recall bias, or surrogate measures such as medication use. This is supported by the results of a panel study on children with asthma which reported a pollen-ozone interaction for daily incident asthma attacks but not for the less severe outcomes considered (daily records of respiratory symptoms, medication use or measures of peak expiratory flow rates) (Just et al., 2002).

In this review, the proportion of studies reporting significant allergen-pollutant interactions was higher among those using medical records (9/25) than those using self-reported health outcomes (3/10). However, it should be noted that the studies relying on self-reported health outcomes were all panel or cohort studies with smaller sample sizes and shorter follow-up times than the studies using medical records (i.e. timeseries and case-crossover studies). Disease misclassification is nonetheless possible for hospital administrative data but is unlikely to explain the interactions observed as coding errors or preferences (including missingness) are likely independent of daily changes in allergen or pollution concentrations.

Four interactions were observed for allergic outcomes (three for medical consultations for pollinosis (i.e. allergic rhinitis due to pollen) and one for any allergic (nasal, ocular or bronchial) symptom), which supports a role of allergen-pollutant interactions on allergic pathways. Indeed, even for the outcomes not exclusively related to allergy (e.g. asthma), one must assume that the observed increases in these outcomes on days with high allergen counts are driven by persons who are sensitized to the allergen in question. Among the 12 studies that reported allergen-pollutant interactions, the atopic status of participants is unknown in the six timeseries and case-crossover studies on asthma (Anderson et al., 1998; Cakmak et al., 2012; Dales et al., 2004; Gleason et al., 2014; Guilbert et al., 2018; Lierl and Hornung, 2003) and assumed to be 100% in the three timeseries and case-crossover studies on medical consultations for pollinosis (Konishi et al., 2014; Phosri et al., 2017; Sakata et al., 2017). For the remaining three panel studies, stratification by atopic status was not possible in one as 90.2% of participants were atopic (Just et al., 2002) and the other two with more balanced distributions (63% and 57.2% atopic in (Higgins et al., 2000) and (Kanatani et al., 2016), respectively) did not assess whether allergen-pollutant interactions may be stronger among atopic individuals.

Overall, the epidemiological evidence for allergen-pollution interactions found in this systematic review was relatively weak and inconsistent. Only the interactions between Japanese pollen counts (comprising Japanese cedar and Japanese cypress pollen) and measures of high desert dust levels or particulate matter were reported by more than one study (Kanatani et al., 2016; Konishi et al., 2014; Phosri et al., 2017; Sakata et al., 2017). This contrasts with the rather strong and consistent evidence from large epidemiological studies suggesting independent effects of air pollution (Orellano et al., 2017) and allergens (Erbas et al., 2018) on respiratory health, as well as that from small experimental studies in humans demonstrating that allergen and air pollution (particularly diesel exhaust particles) co-exposures alter immune responses as well as gene and microRNA expression, induce epigenetic changes, increase inflammation and reduce lung function in allergic and asthmatic individuals (Barck et al., 2002; Carlsten et al., 2016; Clifford et al., 2017; Hosseini et al., 2016; Mookherjee et al., 2018; Rider et al., 2016; Svartengren et al., 2000; Wooding et al., 2019).

There are several reasons that may explain the predominantly null and inconsistent epidemiological findings observed. Inadequate statistical power to detect interactions is suspected in some studies, as larger sample sizes are typically required to observe a statistical interaction than a main effect of equal magnitude (Hunter, 2005; VanderWeele and Knol, 2014). Although most of the timeseries and case-crossover studies that reported significant allergen-pollutant interactions had large sample sizes and long follow-ups, this was also the case for several of the studies that did not report significant interactions. As small sample sizes, few daily cases or a short follow-up period all contribute to low statistical power, these may be reasons why interactions were more commonly detected in the timeseries or case-crossover studies than in the panel studies, the latter of which are more likely to suffer from these issues. However, well-designed panel studies conducted in high risk (i.e. atopic) individuals could nonetheless be sufficiently powered if conducted in areas and during months with high levels and variation in allergen and pollutant concentrations over short periods of time. Indeed, several authors highlighted low levels or small

variation in exposures as limitations of their analyses (Babin et al., 2008; Babin et al., 2007; Darrow et al., 2012; Delfino et al., 2002; Delfino et al., 1997; Jalaludin et al., 2000; Krmpotic et al., 2011; Lewis et al., 2000; Lierl and Hornung, 2003; Villeneuve et al., 2006). Peak allergen and air pollution times may also not coincide for certain combinations, which may explain why interactions are observed for some allergens but not others (Cakmak et al., 2012).

For most studies reviewed, daily allergen and pollution exposures were assessed using data from one or a few central monitoring sites and a single value assigned to the whole study area, which is unlikely to capture true variation in individual-level exposures. Error in attributing exposure based on this method would likely be random, however it is difficult to confirm how this would affect the allergen-pollutant interactions tested (e.g. reductions in available statistical power). The size of this measurement error will vary by study area due to heterogeneity of exposure sources, weather conditions and physical barriers that affect transport of allergens or pollutants, and is expected to be larger for primary pollutants that vary more over smaller spatial scales (e.g. those from traffic emissions) than secondary pollutants (e.g. ozone). Most studies used volumetric traps (Burkard/Hirst) to collect allergen data while some used Rotorod, Durham or Cour samplers, in addition to other methods. These samplers have been shown to be comparable, although the Rotorod is less efficient at sampling small particles ($<10\ \mu\text{m}$ in diameter) (Frenz, 1999). Hence, fungal spore counts in studies which used Rotorod samplers may be underestimated (Jones et al., 1994; Lierl and Hornung, 2003; Ross et al., 2002).

Further sources of exposure misclassification relate to individual-behaviour (e.g. time-activity patterns and time spent indoors/outdoors). The potential confounding effect of other outdoor allergens (i.e. fungal allergens on pollen allergen associations and vice versa) as well as indoor allergens was rarely considered, which may not be an issue in all study areas as various allergen species have peak concentrations at different times of the year.

It is worth noting that all studies included in this systematic review (and that recently conducted on the main effects of outdoor pollen on asthma emergency department presentations (Erbas et al., 2018)) used daily pollen grain or fungal spore counts as the measure of allergen exposure, rather than measured airborne allergen levels (amount of airborne bioallergenic material). Each pollen grain can release a different amount of pollen allergen into the air (up to a ten-fold daily variation) related to an interplay of external and meteorological variables and in response to various environmental factors (Buters et al., 2015; Plaza et al., 2016). Similar observations have been made for fungal spores (e.g. *Alternaria* (Grewling et al., 2019)). The role of air pollutants on this day-by-day variation in allergen levels remains poorly understood. Allergen levels are also likely to differ by species/cultivars (Jung et al., 2018). The lack of precise information on allergen levels in the air may have contributed to the null findings. It is also possible that peaks in allergen levels (or allergen counts) are more important than daily averages and future studies may consider more temporally resolved data to account for hourly exposures.

The search strategy used in this systematic review allowed a broad review of studies investigating all potential allergen-pollutant interactions on respiratory health. It was not designed to capture all studies examining independent effects of air pollutants or allergens on respiratory health. One difficulty of conducting systematic reviews on interaction effects is that testing for interactions is frequently done as a secondary analysis (17/35 of the included studies mentioned “interactions” in their study aims). Hence, we may have missed studies that tested for allergen-pollutant interactions but did not report the results (during our search we identified at least three such studies (Caillaud et al., 2014a; Caillaud et al., 2014b; Delfino et al., 1998)). Furthermore, as we restricted our search to studies that evaluated interactions with measured outdoor allergen counts, we excluded those that assessed interactions with “season” only, as a “season” term could be a marker of several environmental factors, and those that used various methods to

define pollen seasons (e.g. Google Trends (Bédard et al., 2020) or predictive modelling (Di Menno di Bucchianico et al., 2019)).

Although a meta-analysis was originally envisioned, this was not possible as so few studies reported effect estimates for all interaction terms tested. Several studies reported interaction terms as simply “non-significant”. Of the studies that did report numerical results, very few overlapped in terms of allergen and pollutant considered and all reported at least some significant interactions, suggesting that any combined meta-analytic result would be subject to reporting bias and consequently be biased towards a significant finding. Even comparing available studies at a descriptive level is challenging due to differences in the study period and population, outcomes and exposures considered, and assessment methods used, as well as the statistical strategy pursued. Differences in the prevalence of atopy, cultural habits regarding medication and hospital services use, heterogeneity in allergen species and allergenicity as well as air pollution concentrations and sources further complicate any geographical comparisons.

5. Conclusions

In summary, the epidemiological evidence supporting interactions between allergens and air pollutants in the context of respiratory health at the population-level is relatively weak. A third of studies reviewed reported statistically significant interactions, nearly half of which were from timeseries/case-crossover studies on daily number of asthma hospital admissions or visits. Future studies investigating allergen-pollutant interactions should ensure sufficient statistical power, conduct subgroup analysis by atopic status, be designed to capture peaks in both allergen counts and pollutant concentrations and investigate variations in the biological allergenic potential (i.e. allergen levels) of the air. As climate change will influence the amount, allergenicity and geographical spread of allergens and increase the concentrations of some pollutants, any adverse effects of air pollutants on the respiratory response to allergens will be relevant for the development of environmental protection policies.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2020.143924>.

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SUPPORTING INFORMATION

Interactive effects of allergens and air pollution on respiratory health: A systematic review

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Search strategy for additional databases

EMBASE

Subject headings have been slightly adapted as “best fit” for EMBASE, by comparing those used in MeSH for Medline

Table S1: Search terms used to identify articles in EMBASE

Category	Search terms
Respiratory health	Subject headings: Asthma OR Bronchitis OR Coughing OR Forced Expiratory Volume OR Lung Ventilation OR Abnormal Respiratory Sound OR Rhinitis OR Respiratory Tract Disease OR Spirometry OR Vital Capacity Free text: Airway* OR asthma* OR breath* OR bronchi* OR cough* OR exacerbation* OR hayfever OR hay fever OR lung OR pulmonary OR respiratory OR rhinoc* OR wheez*
Outdoor allergens	Subject headings: Allergen OR Alternaria OR Cladosporium OR Fungus OR Pollen Free text: aeroallergen* OR aero allergen OR aero allergens OR allergen* OR aspergillus OR cedar OR grass OR birch OR pollen* OR mould* OR mold* OR parietaria OR ragweed OR spore*
Air pollution	Subject headings: Air Pollution OR Air Pollutant OR Ozone OR Nitrogen Dioxide OR Particulate Matter OR Sulfur Dioxide OR Traffic Pollution OR Exhaust Gas Free text: air quality OR carbon monoxide OR emission* OR exhaust OR freeway* OR highway* OR motorway* OR nitrogen dioxide OR particulat* OR particle* OR pollut* OR road* OR sulphur dioxide OR sulfur dioxide OR traffic OR ozone
Study design	Subject headings: Case Control Study OR Crossover Procedure OR Cohort Analysis OR Longitudinal Study Free text: case control OR casecontrol OR case crossover OR cohort OR daily OR longitudinal OR panel OR timeseries OR time series

Scopus

As no subject headings are used in SCOPUS, all relevant subject headings changed to keywords

Table S2: Search terms used to identify articles in SCOPUS

Category	Search terms
Respiratory health	airway* OR asthma* OR breath* OR bronchi* OR cough* OR exacerbation* OR hayfever OR "hay fever" OR lung OR pulmonary OR respiratory OR rhinitis OR rhinoc* OR spirometry OR wheez*
Outdoor allergens	aeroallergen* OR "aero allergen" OR "aero allergens" OR allergen* OR alternaria OR aspergillus OR cedar OR cladosporium OR fung* OR grass OR birch OR pollen* OR mould* OR mold* OR parietaria OR ragweed OR spore*
Air pollution	"air quality" OR "carbon monoxide" OR emission* OR exhaust OR freeway* OR highway* OR ozone OR motorway* OR "nitrogen dioxide" OR particulat* OR particle* OR pollut* OR road* OR "sulphur dioxide" OR "sulfur dioxide" OR traffic OR ozone
Study design	"case-control" OR "case control" OR casecontrol OR "cross-over" OR "case crossover" OR cohort OR daily OR longitudinal OR panel OR timeseries OR "time series"

Table S3: Additional characteristics of studies ordered by study design (timeseries and case-crossover studies, panel studies, cohort study) and year

Author, year	Type of study	Age group	Sample size	Outcome summary	Allergen measurement method	Air pollutant measurement method	Covariates [†]	Main effects of allergen and air pollutants
Guilbert et al. 2018 (1)	Timeseries	All ages; also stratified into: 0-14, 15-59, ≥60 years	1.0 to 1.1 million; 5094 asthma hospitalizations	Overall mean daily asthma admissions: 2.3	One monitoring site in center of study area (Hirst-type volumetric trap)	Daily estimate informed by monitoring sites (N=10) and land-use regression model. One population-weighted daily estimate used for whole study area.	Seasonal and long-term trends, day of the week, public holidays, mean temperature and relative humidity. Influenza and respiratory infections tested in sensitivity analyses.	Asthma admissions associated with grass, birch and hornbeam pollen counts. Effects stronger for those < 60 years for several pollen taxa.
Phosri et al. 2017 (2)	Case-crossover	Age not specified; assumed whole population.	5.1 million residents (health data from 10 clinics); 73,995 visits	Overall mean daily pollinosis clinic visits: 96	One monitoring site (Durham method)	PM _{2.5} mass from mean of central monitoring sites [‡] . PM _{2.5} component data from one monitoring site on Fukuoka University roof.	Mean temperature and relative humidity (day of the week, long-term trends and season effects controlled by design).	Visits for pollinosis associated with pollen counts.
Sakata et al. 2017 (3)	Timeseries	Age not specified; assumed whole population.	Size of at-risk population not reported; 65,488 visits; asian dust days on 238 of 3,630 days	Overall mean daily pollinosis clinic visits: 9.2	One monitoring site (Durham method)	Asian dust days (yes/no) provided by Japan Meteorological Agency. Mean of 4 monitoring sites for suspended particulate matter.	Day of the week, public holidays, mean temperature and relative humidity, month and year.	Visits for pollinosis associated with presence of asian dust days and (more weakly) suspended particulate matter.
Tham et al.	Case-	2-18 years	Size of at-risk	Total of 1180, 885	One monitoring	One monitoring	Maximum	In overall population,

2017a (4)	crossover	(mean age 5.5 years)	population not reported; 2098 children included	and 33 hospitalizations in the three hospitals, respectively	site on one of the included hospitals (Burkard trap)	site in one of the cities, 20km from allergen measurement site	temperature and mean relative humidity	asthma hospitalizations weakly associated for certain lags of <i>Coprinus</i> , <i>Periconia</i> , and <i>Chaetomium</i> and total fungal spores counts. Some associations stronger among females and older adolescents (14-18 years).
Tham et al. 2017b (5)	Case-crossover	2-17 years (median age 5.2 years); also stratified into: 1) 2-5, 6-10, 11-15, 16-18 years and 2) 2-14, 15-18 years	Size of at-risk population not reported; 644 children included	644 children with asthma	One monitoring site 2km away from recruiting hospital (Burkard trap)	Several monitoring stations in study area [‡]	Maximum temperature and mean relative humidity, human rhinovirus infection. Sensitization status also tested but not found to be relevant covariate.	In overall population, asthma hospitalizations associated with same-day <i>Alternaria</i> , <i>Leptosphaeria</i> , <i>Coprinus</i> , <i>Drechslera</i> , and total spore counts. Some associations stronger for those with <i>Cladosporium</i> sensitization. Additional associations with other fungal taxa seen with lags up to 3 days.
Chen et al. 2016 (6)	Timeseries and case-crossover	All ages; also stratified into: < 17 vs ≥ 18 years	Size of at-risk population not reported; 3653 observation-days, of which 388 had missing exposure data.	Overall mean daily asthma hospital admissions: 9.9	One monitoring site (volumetric Hirst trap)	One monitoring site 5km west of city center	For timeseries: day of the week, weekend/public holidays vs not, mean temperature and humidity, long-term time trends, seasonality. For case-crossover: mean temperature and humidity	Asthma admissions associated with NO ₂ , PM _{2.5} , PM ₁₀ and pollen counts, with effects stronger in cold season. O ₃ effects stronger in warm season. Effect estimates strongest in children.

Gleason et al. 2014 (7)	Case-crossover	3-17 years	Size of at-risk population not reported; 21,854 asthma visits	Overall total asthma visits: 21,854	One monitoring site (in Springfield, volumetric trap)	Spatial and temporal model (12km x 12km resolution)	3-day average temperature and relative humidity, holiday indicator, school-in-session indicator (as marker of influenza)	Asthma visits associated with O ₃ , PM _{2.5} , and tree and weed pollen counts. Only minimal associations with grass pollen counts.
Konishi et al. 2014 (8)	Case-crossover	Age not specified; assumed whole population.	Size of at-risk population not reported; 11,713 consultations	Overall mean daily consultations: 10.6	9 monitoring sites (Durham method)	Several monitoring sites [‡]	Mean temperature and relative humidity (day of the week, long-term and seasonal effects adjusted by design, public holidays and weekends excluded)	Main effects of pollen counts or pollutants not reported.
Cakmak et al. 2012 (9)	Timeseries	All ages.	Over 12 million people.	Overall mean daily asthma hospital admissions: 28.7	One monitoring site per city (rotational impaction). Same method used in each city.	Monitoring sites in each city [‡]	Day of the week, mean temperature, barometric pressure and relative humidity.	Asthma admissions reported to be associated with all allergen counts (results not presented).
Darrow et al. 2012 (10)	Case-crossover	All ages; also stratified into: 1-4, 5-17, ≥18 years	Size of at-risk population not reported; 1408 to 1782 observation-days depending on pollen species.	Overall total visits for asthma and wheeze: 400,819	One monitoring site on rooftop (Rotorod sampler). Data measured five days/week, and estimated for Friday and Saturday	Monitoring sites [‡]	Month, year, maximum and minimum temperature, average dew point, hospital, day of week, holidays, upper respiratory infections	Associations with asthma- and wheeze-related visits strongest for Quercus and grass pollen counts.
Erbas et al.	Timeseries	< 15 years	Size of at-risk population not	Overall mean daily	One monitoring site on University	One monitoring site (~7km NE of	Maximum temperature, mean	Asthma visits associated with grass pollen counts,

2012 (11)			provided; 2559 asthma visits recorded	asthma visits: 21	of Melbourne	Melbourne CBD)	relative humidity, rainfall, time trend, day of the week	even at low levels.
Ghosh et al. 2012 (12)	Timeseries	Age not specified; assumed whole population.	16.6. million people in Kolkata (health data from two state-run teaching hospitals included); 180 10-day observation-slots available	Mean daily asthma-related admissions were highest in March (21.8) and September (22.3) and lowest in January (2.8) and July (2.9)	One monitoring site (Burkard trap) located 16-20 miles from the two hospitals	One monitoring site	None mentioned	Asthma admissions associated with <i>Cheno-Amaranthaceae</i> and <i>Cyperaceae</i> pollen counts, SO ₂ and respirable particulate matter.
Krmpotic et al. 2011 (13)	Timeseries	>18 years	> 779,000; 808 asthma admissions recorded	Overall mean daily asthma visits: 0.7	Measurement method not stated. Data from the Institute of Public Health.	Data from 4 monitoring stations [‡]	Temperature, humidity, day of the week, season, weekly influenza cases	Asthma admissions associated with CO, NO ₂ and hornbeam pollen counts.
Babin et al. 2008 (14)	Timeseries	All ages; also stratified into: 5-12, 21-49 years	Size of at-risk population not reported; 61,218 visits recorded	Overall total asthma-related visits: 61,218	Measurement method not stated. Data from the US Army Centralized Allergen Extract Laboratory. Pollen collected ≥ 3 days/week.	Monitoring sites in DC, ~3 per pollutant	Long-term trend, day of the week, temperature and dew point	Overall asthma visits associated with PM _{2.5} . In warm season, visits associated with O ₃ , grass and tree pollen (all ages), O ₃ and grass (5-12 year-olds), and O ₃ (21-49 year-olds).
Babin et al. 2007 (15)	Timeseries	0-17 years; also stratified into: 1-4; 5-12; 12-17 years	Size of at-risk population not reported.	Annual rate of asthma emergency department visits for 1-17 year-olds: 0.029	Measurement method not stated. Data from the US Army Centralized Allergen Extract Laboratory. Pollen	Monitoring sites in DC, 3 per pollutant	Maximum temperature, month and season (day of week not found to be relevant)	Asthma visits associated with tree pollen counts for 5-12 year-olds, weed pollen counts for 5-12 and 1-17 year-olds, and O ₃ for 1-17 year-olds. Latter associations strong for 5-12

					collected ~ 3 days/week (more frequently in Spring/Fall)			year-olds.
Carracedo-Martinez et al. 2008 (16)	Case-crossover	All ages	Approximately 300,000	Overall mean daily calls for cardiovascular and respiratory causes were ~4 and 3.	One monitoring site on top of city hall (volumetric trap)	Average of 8 monitoring sites	Mean temperature, atmospheric pressure and relative humidity, Sunday/public holiday vs not, weekly cases of influenza	Calls for respiratory causes associated with several types of pollen counts. Calls for cardiovascular, respiratory and cardiorespiratory causes associated with black smoke and SO ₂ .
Villeneuve et al. 2006 (17)	Timeseries	≥ 65 years	Size of at-risk population not reported.	Total primary care visits for allergic rhinitis: 52,691	One monitoring site (rotational impaction)	Monitoring sites (ranging from 4-10 sites depending on pollutant)	Long-term time trends (adjusted for day of the week and public holidays), influenza visits, mean daily temperature and relative humidity	Allergic rhinitis visits associated with 10-day average ragweed counts but none of the pollutants tested.
Dales et al. 2004 (18)	Timeseries	All ages; also stratified into: ≤ 13 vs >13 years (median)	7.83 million; 60,066 asthma admissions recorded	Total asthma hospital admissions: 60,066	One monitoring site per city. Same method used in each city.	Monitoring sites in each city (rotational impaction)*	Day of the week, long-term time trends, weather variables (maximum and minimum temperatures, mean barometric pressure, dew point temperature, and relative humidity)	In combined analyses, asthma admissions associated with weed and grass pollen counts and all three fungal spores counts. City-specific associations consistently positive and majority significant.
Lierl and Hornung	Timeseries	Children; age	Size of at-risk population not	Monthly daily means ranged from 5.5 to	One monitoring site (Rotorod	One monitoring	None listed	Asthma visits associated

2003 (19)		not specified	reported.	17.2	sampler)	site		with total pollen counts.
Sunyer et al. 2002 (20)	Case-crossover	>14 years	Size of at-risk population not reported; 1078 participants died	1078 participants died of the 5610 captured in study sample. Main causes of death were cardiovascular in women and respiratory in men admitted once, and respiratory in both sexes among those admitted more than once.	One monitoring site in NE of city (Cour method)	Mean of 3 monitoring sites, except black smoke which was assessed using network of 15 samplers.	Temperature, humidity, hot days, influenza epidemics and soybean asthma epidemics. Day of the week controlled for by design.	Among severe asthmatics, risk of mortality associated with NO ₂ . Similar associations observed with O ₃ but only in warm season.
Weisel et al. 2002 (21)	Timeseries	Age not specified; assumed whole population.	Size of at-risk population not reported.	Summary of outcomes not provided	Measurement method not stated. Data obtained from the University Hospital, Newark.	Mean of several monitoring stations in study area [†]	Temperature, relative humidity	Asthma visits and admissions associated with pollen counts and O ₃ .
Lewis et al. 2000 (22)	Timeseries	≥14 years	400,000	Overall mean daily asthma admissions and visits were 0.81 and 1.24, respectively	One monitoring site (Burkard trap) 4 km SW of city centre	One monitoring site for O ₃ and NO ₂ , and another for black smoke (1 mile away)	Two time trend variables, temperature, humidity, thunderstorms, influenza epidemics and day of the week	Asthma admissions associated with <i>Cladosporium</i> counts (weaker associations also seen with asthma visits). Asthma visits associated with grass pollen counts, especially on days with light rainfall.
Anderson et al. 1998	Timeseries	All ages; also stratified into: 0-14, 15-64, ≥	Size of at-risk population not reported; 1796	Overall mean daily asthma admissions:	One monitoring site in North London (Burkard	Monitoring sites in London (ranging from 1-4 sites	Time trend, seasonal cycles, day of the week, public	Asthma admissions associated with O ₃ for 15-64 year-olds, NO ₂ for 0-14 and

(23)		65 years	observation-days but pollen only measured on 915 days in warm season.	35.1	trap)	depending on pollutant)	holidays, influenza epidemics, temperature and humidity	65+ year-olds, SO ₂ for 0-14 year-olds and black smoke for ≥ 65 year-olds.
DellaValle et al. 2012 (24)	Panel	4-12 years	430 participants	Median percent of days with any symptom during pollen season: 4.9 (medication users) and 0.90 (medication non-users).	Temporal and spatial model generating daily estimates for each subject based on home residence.	Monitoring sites (range of 8 to 18 depending on pollutant). Values from closest monitor assigned to each participant (living within ~10-21 kms depending on pollutant)	Maximum temperature, season and antibiotic use.	Several asthma symptoms associated with weed pollen count among those sensitized and taking medication. Several asthma symptoms associated with grass pollen counts among those sensitized and not taking medication.
Chen et al. 2011 (25)	Panel	Mean age: 10.6 years	33 asthmatics, 30 with allergic rhinitis, and 37 healthy controls ; 682 observation-days	Average FVC, FEV ₁ , FEF ₂₅ , FEF ₅₀ , FEF ₇₅ , FEF ₂₅₇₅ were 1.98 l, 1.79 l, 3.70 l/s, 2.67 l/s, 1.38 l/s and 2.4 l/s	One monitoring site (Burkard 7-day recording trap).	One monitoring site within 2.5km of schools	Age, height, respiratory infection, asthma/allergic rhinitis symptoms, medicinal use, temperature, relative humidity, day of week, gender, school, parental education, parental atopy, secondhand smoke	Lower FVC and FEV ₁ associated with total fungal spore counts. Lower FVC associated with PM _{2.5} and lower FEF ₂₅ , FEF ₅₀ , FEF ₇₅ , FEF ₂₅₇₅ associated with O ₃ .
Jalaludin et al. 2004 (26)	Panel	Mean age: 9.6 years	125 children; 36,956 observation days	Overall prevalences were 9.7% 10.1, 11.2 for wheeze, wet cough, and dry cough. 14.2% and 16.3% of days had	Average of 2 monitoring sites used (Burkard spore trap)	Children assigned value from closest of 6 monitoring sites to their school	Time trend, mean temperature and humidity, number of hours spent outdoors, season.	Wet cough associated with NO ₂ . Doctor visits for asthma associated with PM ₁₀ .

				reported use inhaled b2-agonist and inhaled corticosteroids, and 0.5% of days had doctor visits for asthma				
Delfino et al. 2002 (27)	Panel	9-19 years	22 participants; 1248 observation-days	Average symptom score was 0.9 and 1.24 (range is 0-6) for those taking and not taking anti-inflammatory medication, respectively.	One monitoring site (Burkard trap)	One monitoring site	Temperature, relative humidity, day of the week, linear time trend, lower and upper respiratory infections	Asthma symptoms associated with air pollutants, pollen and fungal spore counts, although restricted to small group (N=12) not taking anti-inflammatory medications.
Just et al. 2002 (28)	Panel	Mean age: 10.9 years	82 children	Frequency of incident and prevalent episodes of asthmatic attacks were 1.0 and 1.9, respectively.	Measurement method not stated. Data obtained from French surveillance system.	Average of monitoring sites (5 to 22 sites depending on pollutant).	Time trends, day of the week, pollen temperature and relative humidity. Respiratory infections tested in sensitivity analysis.	In overall population, black smoke and NO ₂ associated with nocturnal cough and respiratory infections, O ₃ with asthma attacks, respiratory infections and eye irritation and changes in PEFr, and PM ₁₀ with eye irritation.
Ross et al. 2002 (29)	Panel	5-49 years	40 participants; follow-up period is 155 days	Summary of outcomes not provided	3 monitoring sites placed in study area (Rotorod sampler). Unknown how data combined across sites.	Several monitoring stations in study area.* Participants lived within 8 km of monitors.	Maximum temperature (relative humidity also adjusted for in models for evening PEFr only)	Total pollen counts and O ₃ associated with increased morning and evening symptom scores, decreased evening PEFr and increased asthma medication use. <i>Curvularia</i> counts associated with increased morning and evening symptom scores,

								decreased morning PEFR and increased asthma medication use. Ragweed pollen counts associated with decreased evening PEFR and increased medication use. Grass pollen counts associated with increased morning and evening symptom scores. Atopic subgroup not found to be at increased risk.
Higgins et al. 2000 (30)	Panel	20-71 years (mean age: 46 years)	35 patients with asthma or chronic obstructive pulmonary disease	Mean and range of baseline FEV ₁ : 2.44 (1.40 – 4.05)	One monitoring site (Burkard spore trap)	Two monitoring sites in each of the two towns. Unclear how exposures assigned to participants.	None listed	O ₃ associated with decreasing mean PEFR, increasing variability in PEFR and wheeze symptoms. Fungal spore counts associated with increasing variability in PEFR and wheeze symptoms. NO ₂ associated with increasing wheeze symptoms. Atopic subgroup not at increased risk.
Jalaludin et al. 2000 (31)	Panel	Mean age: 9.6 years	125 children; 31,209 observation-days	Overall mean PEFR was 323.5 L/min (for individual children ranged from 212 to 446)	Average of 2 monitoring sites used (Burkard spore trap)	Average of 6 monitoring sites (population regression model) and value from closest of 6 monitoring sites to school (GEE model)	Time trend, mean temperature and humidity, number of hours spent outdoors, season.	Daily mean deviation in PEFR negatively associated with mean daytime O ₃ . Effects stronger in those with bronchial hyperreactivity and asthma.

Delfino et al. 1997 (32)	Panel	9-46 years	22 participants (9 adults and 13 children); 1218 observation-days	Summary data for overall participants not reported	One monitoring site (Burkard trap)	Personal O ₃ measured using passive sampler. Outdoor O ₃ and other pollutants measured with one monitoring site	Maximum temperature, mean relative humidity, day of the week, respiratory infections. Age, gender, and height controlled for by design.	All 3 outcomes associated with total fungal spores counts. Associations larger for counts of certain fungal types and among those sensitized to the types of fungi measured. Inhaler use associated with PM ₁₀ .
Delfino et al. 1996 (33)	Panel	9-16 years	12 participants; 462 observation-days (only 7 participants and 276 observation-days available for inhaler use analyses)	Summary data for overall participants not reported	One monitoring site (Burkard trap)	Personal O ₃ measured using passive sampler. Outdoor O ₃ and other pollutants measured with one monitoring site	Maximum temperature, mean relative humidity, day of the week, respiratory infections. Age, gender, and height controlled for by design.	Symptom scores and inhaler use associated with personal measurements of O ₃ and total fungal spore counts. Inhaler use also associated with outdoor 12-hr O ₃ . No clear pattern for those sensitized to fungi.
Jones et al. 1994 (34)	Panel	Mean age: 10.6 years	20 children; follow-up period is 109 days	Daily mean values were 324.8 L for PEFR, 0.4 symptoms per day, 0.5 on symptom scale (range 0-6) and 2 medications used	One monitoring site (Rotorod sampler)	Average of 3 monitoring sites	Maximum temperature, humidity	PEFR, activity time and outside time negatively associated with mold.
Kanatani et al. 2016 (35)	Longitudinal cohort	Mean age: 32.2, 31.0, and 30.9 years in Kyoto, Toyama and Tottori,	3328 pregnant women	Symptoms reported in 48.2% of responses (56.1% and 46.9% of responses on dust and control days,	Daily mean of closest monitoring station from home (5 stations using beta-ray attenuation	Measured using a light detection and ranging system (LIDAR).	Smoking status of participants and their partners, house income, age, body mass index, air pressure, temperature and	Risk of allergen symptoms higher on desert-dust days. Effects greater among those sensitized to Japanese cedar pollen when pollen was present in the air. Allergen symptoms associated with

		respectively		respectively)	method and 3 stations using Durham method).		humidity	high pollen count days.
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[†]other than terms included for allergens and air pollutants; , [‡]unclear how many monitors or how data were combined/used

PEFR: peak expiratory flow rate

Table S4: Summary of quality assessment, ordered by study design (timeseries and case-crossover studies, panel studies, cohort study) and year

		Sampling			Valid measurement			Data analysis			Result interpretation		
Author, year	Study population well described	Sampling frame described	Eligibility criteria listed	Entire eligible population included	Allergens	Air pollutants	Outcomes	Data analysis clear	Interactions tested explicitly listed [†]	Control for study design	≥ 80% of completed study [†]	Good confounder control	Comments
Guilbert et al. 2018 (1)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Phosri et al. 2017 (2)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	No information on ages included.
Sakata et al. 2017 (3)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	No information on ages included.
Tham et al. 2017a (4)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Tham et al. 2017b (5)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Chen et al. 2016 (6)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	Text implies allergen-pollutant interactions tested but unclear which combinations examined.
Gleason et al. 2014 (7)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Konishi et al. 2014 (8)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	No information on ages included.
Cakmak et al. 2012 (9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Darrow et al. 2012 (10)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Erbas et al. 2012 (11)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Ghosh et al. 2012 (12)	No	Yes	Yes	Yes	Yes	Yes	Unsure	No	No	Yes	NA	No	No information on ages included or outcome definition, other than recorded in 10-day timeslots. Unclear how daily allergen and pollutant data combined into 10-day timeslots. Text implies allergen-pollutant interactions tested but unclear which combinations examined. No confounders listed.
Krmpotic et al. 2011 (13)	Yes	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	NA	Yes	No information regarding pollen collection method, other than provided by "Institute of Public Health".
Babin et al. 2008 (14)	Yes	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	No	Yes	NA	Yes	No information regarding pollen collection method, other than provided by US Army Centralized Allergen Extract Laboratory. Text implies allergen-pollutant interactions

													tested but unclear which combinations examined.
Babin et al. 2007 (15)	Yes	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	NA	Yes	No information regarding pollen collection method, other than provided by US Army Centralized Allergen Extract Laboratory.
Carracedo-Martinez et al. 2008 (16)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	Text implies allergen-pollutant interactions tested but unclear which combinations examined.
Villeneuve et al. 2006 (17)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Dales et al. 2004 (18)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes (city-specific analyses) / No (overall analyses)	NA	Yes	Text implies allergen-ozone interactions tested but unclear if other pollutants examined. City specific results presented in addition to overall analyses, the latter of which are not adjusted for differences between cities.
Lierl and Hornung 2003 (19)	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	No	Analysis restricted to children but no age-cut-off specified. No covariates other than air pollution mentioned.
Sunyer et al. 2002 (20)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	Stated that all allergen – pollutant interactions tested but results only mentioned for NO ₂ and O ₃ (and not for SO ₂ and CO), possibly because main effects only found for NO ₂ and O ₃ .
Weisel et al. 2002 (21)	No	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	No	Yes	NA	No	No information on ages included or pollen collection method, other than provided by the “University Hospital”. Text implies allergen-pollutant interactions tested but unclear which combinations examined. Time trends in data not accounted for.
Lewis et al. 2000 (22)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
Anderson et al. 1998 (23)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	
DellaValle et al. 2012 (24)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Length of follow-up not specified in article (information provided by corresponding author upon request).
Chen et al. 2011 (25)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Of 3937 who answered study questionnaire, only 100 participated in lung function testing. Random sample taken but unclear who was eligible or why restricted to 100. Text

													implies allergen-pollutant interactions tested but unclear which combinations examined.
Jalaludin et al. 2004 (26)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	148 recruited but only 125 included due to study withdrawal and non-compliance.
Delfino et al. 2002 (27)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	25 recruited but only 22 included due to study inclusion criteria and study withdrawal.
Just et al. 2002 (28)	Yes	Yes	Yes	No	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100 recruited but only 82 included due to study withdrawal and non-compliance. No information regarding pollen collection method, other than provided by two French surveillance systems.
Ross et al. 2002 (29)	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Eligibility criteria unclear. 59 recruited but only 40 included due to study withdrawal and non-compliance. Unclear how data from 3 allergen monitoring sites (placed in 3 areas in study area) were used to assign exposures.
Higgins et al. 2000 (30)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	36 recruited but only 35 included in PEFR analysis (30 in wheeze analysis). No covariates mentioned.
Jalaludin et al. 2000 (31)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	148 recruited but only 125 included due to study withdrawal and non-compliance. Text implies allergen-pollutant interactions tested but unclear which combinations examined.
Delfino et al. 1997 (32)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	24 recruited but only 22 included due to non-compliance.
Delfino et al. 1996 (33)	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear how participants recruited. 15 recruited but only 12 included in asthma symptom severity analysis due to non-compliance. Only 7 included for analysis on inhaler use as rest did not use inhaler.
Jones et al. 1994 (34)	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Eligibility criteria unclear. 24 volunteered but only 20 included due to study withdrawal and living outside study area.

Kanatani et al. 2016 (35)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Of 4178 eligible pregnant women in cohort, 3327 included. Of those excluded, unclear how many did not return questionnaire and how many did not experience an Asian dust season before delivery. Potential clustering by city not considered.
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[†] Not included in (36) but added by authors due to nature of systematic review

[‡] Not applicable for timeseries and case-crossover studies.

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