Ambient air pollutants increase the risk of Immunoglobulin E-mediated allergic diseases: a systematic review and meta-analysis

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Abstract

Immunoglobulin E (IgE)-mediated allergic diseases, including eczema, atopic dermatitis (AD) and allergic rhinitis (AR), have increased prevalence in recent decades. Recent studies have proved that environmental pollution might have correlations with IgE-mediated allergic diseases, but existing research findings were controversial. Thus, we performed a comprehensive meta-analysis from published observational studies to evaluate the risk of long-term and short-term exposed to air pollutants on the eczema, AD and AR in the population (per 10 μg/m^3 increase in $PM_{2.5}$ and PM_{10}; per 1 ppb increase in SO_2, NO_2, CO and O_3). PubMed, Embase and Web of Science were searched to identify qualified literatures. Cochran Q test was used to assess heterogeneity and quantified with I^2 statistic. Pooled effects and the 95% confidence intervals (CIs) were used to evaluate outcome effects. A total of 55 articles were included in the study. The results showed that long-term and short-term exposed to PM_{10} increased the risk of eczema (PM_{10}, RR_{long}=1.583, 95% CI: 1.328, 1.888; RR_{short}=1.006, 95% CI: 1.003-1.008) and short-term exposed to NO_2 (RR_{short}=1.009, 95% CI: 1.008-1.011) was associated with eczema. Short-term exposed to SO_2 (RR_{short}: 1.008, 95% CI: 1.001-1.015) was associated with the risk of AD. For AR, $PM_{2.5}$ (RR_{long}=1.058, 95% CI: 1.014-1.222) was harmful in long-term, and short-term exposed to PM_{10} (RR_{short}: 1.028, 95% CI: 1.008-1.049;) and NO_2 (RR_{short}: 1.018, 95% CI: 1.007-1.029) were risk factors. The findings indicated that exposed to air pollutants might increase the risk of IgE-mediated allergic diseases. Further studies are warranted to illustrate potential mechanism for air pollutants and allergic diseases.

Introduction

Allergic diseases are inflammatory disorders that involve various types of cells and factors, including allergens, immunoglobulin (Ig)E, mast cells, basophils, cytokines, and soluble mediators. The etiological mechanisms of allergic diseases are complex. The incidence of allergic diseases has increased sharply with increasing industrialization and the accompanying changes to the environment and people's lifestyles. According to one study conducted by the World Allergy Organization and involved 30-nation/region, approximately 250 million (22%) of the 1.2 billion people in those regions suffered from allergic diseases (Hu et al., 2018). Because of their high prevalence, these diseases pose a serious financial threat to affected households and consume substantial resources in socialized healthcare systems.

Allergic diseases can be divided into two categories, which are IgE mediated and non-IgE mediated. IgE-mediated allergies reactions are typically of rapid onset and symptoms range from mild to severe. IgE, an antibody class found only in mammals, has unique properties, and plays a central role in the development of acute allergic reactions and IgE-mediated allergic diseases. IgE-mediated allergic diseases, involving eczema, atopic dermatitis (AD) and allergic rhinitis (AR). Major risk factors for IgE mediated allergic diseases studied widely were genetics and immune functions. However, these traditional risk factors were not changed dramatically in recent decades. Therefore, traditional risk factors alone may not be sufficient to explain the massive rise in IgE mediated allergic diseases prevalence.

Are long-term or short-term air pollution associated with the development and prevalence of IgE-mediated allergic conditions? Numerous studies have attempted to answer this question, but no consensus has reached. For instance, Schnass et al. conducted a cohort study and concluded that traffic-related air pollution would increase the prevalence of eczema for elder (Schnass et al., 2018). However, Lopez et al. found that long-term air pollution has no adverse effect on adult eczema (Lopez et al., 2021). The same dispute can also be found in AR's research. Huang et al reported the prevalence of AR in children would increase when exposed to $PM_{2.5}$ (Huang et al., 2019). But a cohort study established in Canada reported that PM2.5 did not increase the risk of AR for children (To et al., 2020). There are also meta-analyses tried to illustrate this question, and several important but inconsistent results have been received. In 2014, a meta-analysis on allergy and sensitization found an association between air pollution exposure and childhood eczema, whereas another meta-analysis found no association between air pollution and eczema (Fuertes et al., 2020).

These contrary results might reveal the impact of different inclusion criteria, regions, and other factors on the generalization of the results. Usually, clinicians tend to interchangeably use the terms eczema and atopic dermatitis (AD). However, the term eczema is considered an ambiguous term and its meaning should not be considered synonymous with AD. In International Classification of Diseases (ICD), AD was only classified into the ICD-10 code L20, ICD-9 code 691 catalogue, whereas eczema could be classified into ICD-10 code L30. A diagnosis of AD is thought to confer a worse prognosis in terms of disease severity and the potential risk for developing other comorbid diseases of an atopic nature compared with receiving a diagnosis of eczema alone. Most of the existing meta-analyses did not consider the inclusion criteria of AD and eczema and mixed these two diseases to conducted meta-analyses. Therefore, there is a need to divide these two diseases separately to conduct a meta-analysis to better understand the relationship between air pollution and IgE mediated allergic diseases.

To address the gap of inadequate knowledge of IgE-mediated allergic diseases and air pollutants, this systematic review and meta-analysis was conducted. Long-term and short-term effects of ambient six pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3) on risks for IgE-mediated allergic diseases are comprehensive analyzed in this study.

Material And Methods

Search strategy

Embase, PubMed and Web of science were searched to find relevant research concerning the association between air pollutants and diseases up to May 2021. Search terms included (1) "allergic rhinitis", "allergic respiratory diseases", "eczema", "eczematous dermatitides", "atopic dermatitis", "dermatitis atopic"; (2) "carbon monoxide", "sulfur dioxide", "particulate matter", "nitrogen dioxide", "ozone", "$PM_{2.5}$", "PM_{10}". Also, synonyms of diseases and particulate matters were searched using Medical Subjects Headings terms. The detailed search process was shown in supplementary Table S1.

Inclusion and exclusion criteria

The included criteria were based on the population, exposure, comparator, and outcomes (PECO) framework. A framework was used to explore the association of air pollutants exposure with health outcomes. P refers to people who have IgE-mediated allergic diseases. E refers to air pollutants. C refers to incremental effect of per unit increased in concentration of air pollutants for diseases risk. O refers to the outcome of eczema, AR and AD (Morgan et al., 2018; Marx et al., 2021).

The inclusive criteria were as follows. (1) Articles should be epidemiologic studies focusing on the associations between the IgE-mediated allergic diseases with air pollutants exposure. (2) Eczema diagnosis was made according to ICD-10 code L30. ICD-10 code L20, and ICD-9 code 691 were used to classify AD. ICD-10 code J30 and ICD-9 code 477 were principles to detect AR. The classification of these three diseases could also be based on questionnaires of eczema or AD or AR. (3) Studies reported effect estimates (RR, OR, HR, PC) or data that could calculate the effect size. Animal studies, mechanism studies, reviews and meta-analyses, case reports, treatment effect evaluations and studies without original data were excluded. Studies focusing on the association between indoor air pollution and prenatal and allergic diseases were also excluded.

Data extraction

Endnote software (X9 version) was used to screen eligible literature. All articles were evaluated by two investigators. First, duplicated studies were removed. Then, two investigators (Wang H and Li XB) independently screened remaining studies to select eligible studies. When controversy existed, a third investigator was asked to discuss and resolve the disagreement.

For each included study, basic characters were extracted, including disease, first author, publication year, region, study design, sample size, number of cases, age, ICD, data sources of pollutants, term of exposure (short-term or long-term) (Ibrahim et al., 2021), mean concentration of pollutants and impact effect estimates. Investigators extracted information based on the following principle. A single pollutant model was used to find the effect of a pollutant, and a multi-pollutant model was utilized to explore the interactions of multiple pollutants on disease risk. If the study contained single pollutant and multi-pollutant models, the former would be chosen (Yang et al., 2018).

Quality and risk bias assessment

The Newcastle-Ottawa Scale (NOS) and the office of health assessment and translation (OHAT) tool were used to evaluate the quality of included literature. Among them, NOS was used to assess the reported quality of cohort, case-control, and cross-sectional studies (Lin et al., 2021a). NOS has eight items, and its score ranged from 0 to 9. A study with a score higher than 7 was regarded as a high-quality study. A study with a score of 3 to 6 was intermediate quality. Otherwise, it was low quality. To the best of our knowledge, there is no effective scale to assess the quality of time series literature. Therefore, we adopted the quality scale used by Mustafic et al. This scale mainly evaluates three aspects: the validity of the outcome event, the assessment of air pollutant exposure and the adjustment of confounding factors. When the evaluated document score was 3-5 points, it could be considered high-quality (Mustafic et al., 2012). In a meta-analysis, OHAT tool was used to assess the risk of bias in each study (Zhang et al., 2021a).

Data synthesis

Due to inconsistent units of pollutant concentration in some literature, we standardized all effect sizes for every 10 ug/m^3 increase in $PM_{2.5}$ and PM_{10} and 1 ppb increase in NO_2, SO_2, CO and O_3 (Fan et al., 2020). The specific formulas were as follows: 1 ppm=1000 ppb, 1 ppb = M/22.4 (ug/m^3). M refers to the molecular weight of each air pollutant. Adjusted relative risk (RR), odds ratio (OR), risk ratio (HR) and percentage change (PC) were used to assess the risk of eczema, AR and AD (Ning et al., 2021). During data consolidation, PC was transformed into RR. The effect estimates (RR/OR/HR) were standardized. OR and HR were roughly regarded as RR, when outcome events were popular and the effect size was small (Chen et al., 2017). All the effect sizes were pooled by the standardized increment of environmental pollutant concentration. The standardized formulae of effect sizes were as follows:

$$RR_{(standardized)}=RR_{(original)}^{Increment(10)/Increment\ (original)}$$

$$OR_{(standardized)}=OR_{(original)}^{Increment(10)/Increment\ (original)}$$

$$HR_{(standardized)}=HR_{(original)}^{Increment(10)/Increment\ (original)}$$

Cochran's Q-test and I^2 statistic were used to evaluate the heterogeneity between studies. If I^2 is greater than 50%, the heterogeneity is high. Otherwise, the heterogeneity is low. If the *p*-value of the Q test is less than 0.05, a high heterogeneity is between the studies. Then the random effect model was chosen. The fixed effect model was applied if the heterogeneity was "medium or low". Funnel plots were used to represent the publication bias in studies (Bai et al., 2020). In addition, the pooled effect values were tested by performing subgroup analyses on ICD, age (<18 years old; ≥ 18 years old; all ages), regional and study types for each pollutant (Chevalier et al., 2015). Limited by the number of available studies, sensitivity analyses were performed for studies that could be combined in each pollutant. All data analyses were realized by R packages "metafor" and "forestplot" in version 4.0.3.

Results

Characteristics of included studies

A total of 2478 articles were searched. After screening title and abstract, 150 articles were identified. After thoroughly reading the full text, a total of fifty-five articles were finally included. The process of literature screening was detailed in Figure 1. In four articles, two diseases were simultaneously discussed (Kim et al., 2016; Wang et al., 2016; Min et al., 2020; To et al., 2020). Therefore, included studies were as follows. There were seventeen eczema studies (six time-

series, six cohorts, and five cross-sectional studies), thirty-one AR studies (nine time-series, nine cohorts, one case-control, and twelve cross-sectional studies), and eleven AD studies (four time-series, five cohorts, and two cross-sectional studies). The information extracted from the literature are shown in Table 1. According to the NOS scale and the OHAT tool, the qualities of the included articles were high. Scores of articles and details of risk bias assessment were listed in supplementary Table S2 (eczema), Table S3 (AD) and Table S4 (AR).

Table 1
Characteristics of included studies

Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
Eczema	Brauer et al (2007)	Netherlands	Cohort	2571/—	4	questionnaire	monitoring campaign	long-term	$PM_{2.5}$:16.9ug/m NO_2:25.2ug/m^3
	Krämer et al (2009)	Germany	Cohort	2753/1741	0-6	questionnaire	monitoring stations	long-term	NO_2:23.7ug/m^3
	Gehring et al. (2010)	Netherlands	Cohort	3184/—	8	questionnaire	land-use regression model	long-term	$PM_{2.5}$: 16.9(μg/m
	Aguilera et al (2013)	Spanish	Cohort	2199/460	1-1.5	questionnaire	Monitoring stations	long-term	—
	Schnass et.al. (2018)	Germany	Cohort	760/60	73.5	questionnaire	monitoring campaign	long-term	$PM_{2.5}$,32.11ug/m PM10,48.37ug/m
	Lopez et.al (2021)	Australian	Cohort	3152/115	53	questionnaire	monitoring sites	long-term	$PM_{2.5}$:6.4ug/m^3;
	Anderson et al. (2010)	Internationa-l	Cross-sectional	—/3086 /per center	13-14	questionnaire	monitoring stations	short-term	PM_{10}:34ug/m^3
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Liu et al. (2016)	China	Cross-sectional	3358/—	4-6	questionnaire	Shanghai Environmental Monitoring Center	long-term	PM_{10}:79.4ug/m^3 NO_2:53.6ug/m^3;S
	Kathuria et al. (2016)	U. S	Cross-sectional	91642/11895	0-17	questionnaire	Environ mental Protection Agency	short-term	$PM_{2.5}$:6.187ug/m PM_{10}:24.996ug/ NO_2,12.851ppm; CO:1.161ppm; O_3
	Deng et al. (2019)	China	Cross-sectional	3167/848	3-6	questionnaire	monitoring stations	short-term	$PM_{2.5}$:72.11ug/m PM_{10}:115.58ug/
	Min et al. (2020)	Korea	Cross-sectional	14614/2323	1-12	questionnaire	monitoring station	short-term	$PM_{2.5}$:25.13μg/m PM_{10}:49.36μg/m NO_2:35.6μg/m^3
	Li et al. (2016)	China	Time-series	—/510158 (outpatient visits)	—	ICD-10: L30.9	monitoring station	short-term	PM_{10}:83μg/m^3; NO_2:60μg/m^3; SO

Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Li et al. (2018)	China	Time-series	—/2305 (outpatient visits)	—	ICD-10: L30.9	monitoring station	short-term	PM_{10},119.6μg/m NO_2:55.2μg/m^3;
	Wang et al. (2019)	China	Time-series	—/2585 (outpatient visits)	≥18	ICD-10: L30.9	monitoring station	short-term	$PM_{2.5}$:101.2μg/m
	Guo et.al (2019)	China	Time-series	—/157595 (outpatient visits)	—	ICD-10: L20-L30	Beijing Municipal Environmental Monitoring Center	short-term	$PM_{2.5}$:87.4ug/m^3 PM_{10}:116.6ug/m NO_2:53.1ug/m^3; SO_2:27.1ug/m^3
	Karagün et al. (2021)	Turkish	Time-series	—/27549 (outpatient visits)	—	ICD-10:L-20, L-25, and L-30	monitoring station	short-term	PM_{10}:82.8μg/m^3 SO_2,7.6μg/m^3
	Zhang et al. (2021)	China	Time-series	—/293340 (outpatie-nt visits)	—	ICD-10: L30.902	monitoring station	short-term	—
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
AD	Wang et al. (2015)	Taipei	Cohort	2661/383	5.5	questionnaire	monitoring station	long-term	$PM_{2.5}$,29.07ug/m PM_{10}:48.32ug/m SO_2:6.46 ppb; CO:0.63ppm O_3:27.62ppb;
	Hüls et al. (2018)	Canada	Cohort	5132/440	7-8	questionnaire	land-use regression models	long-term	NO_2
	Belugina et al (2018)	Minsk	Cohort	—/12-335 cases per 100,000 person-year	0-2	ICD-10:L20.80	National Academy of Science of Belarus	long-term	PM_{10}:27.94%; NO CO:584.4ug/m^3; O_3:31.19ppb.
	To et.al (2020)	Canada	Cohort	1286/958	3	ICD-9: 691.8 ICD-10: L20	monitors	long-term	$PM_{2.5}$:10.88ug/m NO_2:26.14ug/m^3

Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Park et al. (2021)	Korea	Cohort	209168/3203	—	ICD-10:L20	Korean Department of Environmental Protection	long-term	—
	Kim et al. (2016)	Korea	Cross-sectional	1828/669	6-7	questionnaire	monitoring sites	long-term	PM_{10}:58.8μg/m^3 NO_2:29.7ppb; SO_2:5.2ppb; CO:6 O_3:30.7ppb.
	Tang et al. (2017)	China	Cross-sectional	6115/1023	≥20	ICD-9: 691	Environmental Protection Agency monitoring stations	long-term	$PM_{2.5}$:33.6μg/m^3 PM_{10}:56.3μg/m^3 NO_2:18.6ppb; SO_2:4ppb; CO:0.5ppb; O_3:27.9ppb
	Lee et al. (2010)	Korea	Time-series	—/183+29 (daily hospitaladmission)	<15	ICD-10:L20	monitoring station	short-term	seoul :O_3,26.09p ulsan:O_3,32.05p
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Kim et al. (2017)	Korea	Time-series	—/117	2.0 ± 1.6	questionnaire	National Institute of Environmental Research	short-term	PM_{10}:45.2ug/m^3 NO_2:32.4ppb; O_3:38.1ppb
	Guo et al. (2019)	China	Time-series	64987 (outpatie-nt visits)	—	ICD-10: L20.	Monitoring stations	short-term	PM_{10}:110.5ug/m $PM_{2.5}$:79.7ug/m^3 SO_2:16.9ug/m^3
	Baek et al. (2021)	Korea	Time-series	—/513870(medical care visits)	—	ICD-10:L20.8, L20.9	monitoring station	short-term	—
AR	Kim et al. (2011)	Korea	Cohort	1340/—	6.84	questionnaire	monitoring station	long-term	O_3:37.93μg/m^3

Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Fuertes et al. (2013)	Canada	Cohort	10027/4736	7 or 8	questionnaire	land-use regres sion modeling	long-term	$PM_{2.5}$,NO_2,O_3
	Fuertes et al. (2013)	Germany	Cohort	4623/460	10	questionnaire	land-use regression models	long-term	$PM_{2.5}$:15.3μg/m^3 NO_2:22.4μg/m^3; O_3:42.5μg/m^3
	Wang et al. (2015)	Taipei	Cohort	2661/798	5.5	questionnaire	monitoring station	long-term	$PM_{2.5}$,29.07ug/m PM_{10}:48.32ug/m SO_2:6.46 ppb; CO:0.63ppm O_3:27.62ppb;
	Chung et al. (2016)	China	Cohort	9960/1088	0-6	ICD-9-CM:477.0, 477.1, 477.2, 477.8, 477.9	Environmental monitoring sites	long-term	PM_{10},56.8μg/m^3 SO_2,4.81ppb; CO,561ppb; O_3,27.9ppb
	Burte et al. (2018)	Europe	Cohort	1533/394	42.7	questionnaire	monitoring station	long-term	—
	To et al. (2020)	Canada	Cohort	1286/511	3	ICD-9: 477;ICD-10: J301-J304	monitors	long-term	$PM_{2.5}$:10.88mg/ NO_2:26.14ppb; O_3:43.72ppb
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Lin et al. (2021)	China	Cohort	140911/47276	1	ICD-9: 477.0,477.1, 477.2, 477.8, 477.9	novel satellite-based hybrid model	long-term	$PM_{2.5}$:33.84μg/m
	Kim et al. (2021)	Korea	Cohort	3592/995	9.08	questionnaire	national monitoring sites	long-term	PM_{10}:40.3ug/m^3 SO_2:5.4ppb; CO:5 O_3:42.5ppb
	de Marco et al. (2002)	Italy	Cross-sectional	18873/3529	33.1	questionnaire	monitoring sites	long-term	NO_2:31.46μg/m^3

Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Hwang et al. (2006)	China	Cross-sectional	32143/8202	6-15	questionnaire	Environmental Protection Agency air-monitoring station.	long-term	PM_{10}:55.58ug/m SO_2:3.53ppb; CO:664ppb; O_3:23.14ppb
	Arnedo-Pena et al. (2009)	Spain	Cross-sectional	20455/—	6-7	questionnaire	Pollutant detection systems of centers	long-term	NO_2:40.4ug/m^3; CO:0.8ug/m^3;
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Lu et al. (2013)	China	Cross-sectional	2159/182	3-6	questionnaire	Environmental Protection Agency	long-term	PM_{10};SO_2;NO_2
	Wood et al. (2015)	London	Cross-sectional	1808/242	8-9	questionnaire	dispersion models	short-term	$PM_{2.5}$:13.7μg/m PM_{10}:23.4μg/m^3 NO_2:43.5μg/m^3;
	Kim et al. (2016)	Korea	Cross-sectional	1828/673	6-7	questionnaire	monitoring sites	long-term	PM_{10}:58.8μg/m3 SO_2:5.2ppb; CO:6.5(100ppb); O_3:30.7ppb.
	Chen et al. (2016)	China	Time-series	—/19370	2-15	experienced physicians diagnosed	Shanghai Environmental Bureau	short-term	SO_2:39.63μg/m^3 O_3:43.22μg/m^3;
	Jo et al. (2017)	Korea	Cross-sectional	—/4.4(daily admission)	—	ICD-10: J30	monitoring stations	short-term	$PM_{2.5}$:24.2μg/m
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Chen et al. (2018)	China	Cross-sectional	30756/204	4.6	questionnaire	Global Burden of Disease	long-term	$PM_{2.5}$:64μg/m^3
	Liu et al. (2019)	China	Cross-sectional	56137/5395	10	questionnaire	monitoring stations	short-term	$PM_{2.5}$:55.08μg/m PM_{10}:98.75μg/m NO_2:35.43μg/m^3
	Min et al. (2020)	Korea	Cross-sectional	14614/5286	1-12	questionnaire	monitoring station	dispersion models	$PM_{2.5}$:25.13μg/m PM_{10}:49.36μg/m NO_2:35.6μg/m^3

Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Wang et al. (2020)	China	Cross-sectional	40279/2658	—	questionnaire	National Bureau of Statistics	short-term	PM_{10}, NO_2
	Hao et al. (2021)	China	Case-Control	3047/194	2-4	questionnaire	monitoring statio	long-term	PM_{10}:88ug/m^3; N SO_2: 26ug/m^3; C O_3:92ug/m^3
	Zhou et al. (2021)	China	Cross-sectional	59754/3186	10	questionnaire	satellite-based random forest approach	long-term	O_3: 89.39μg/m^3
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Tecer et al. (2008)	Zonguldak	Time-series	—/424 admissions	0-14	ICD-9: 470–478	Anderson automatic dichotomous sampler	short-term	$PM_{2.5}$:29.1μg/m
	Zhang et al. (2011)	China	Time-series	—/1506(outpatien)	≥20	questionnaire	Beijing Municipal Environmental Protection Monitoring Center	short-term	PM_{10}:116.092μg SO_2:44.052μg/m
	Chen et al. (2016)	China	Time-series	—/124773(clinicvisits)	—	ICD-9:477	monitoring stations	short-term	PM_{10}:45.79μg/m SO_2:3.51ppb; CO:0.62ppm; O_3:23.77ppb
	Teng et al. (2017)	China	Time-series	—/23344(outpatien)	—	ICD-9:477	Changchun Municipal Environmental Protection Monitoring Center.	short-term	$PM_{2.5}$:66.5μg/m NO_2:43.6μg/m^3; CO: 0.93μg/m^3; O3: 71.1μg/m^3
Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Hu et al. (2019)	China	Time-series	2410392/646975	<18	ICD-10:J30	Shanghai Environmental Protection Agency	short-term	NO_2:49.1μg/m^3; O_3:68.5 μg/m^3
	Chu et al. (2019)	China	Time-series	—/33063	—	medical history, clinical symptoms, and the relevant test	Environmental Monitoring Centre	short-term	$PM_{2.5}$:57.3μg/m PM_{10}:98.9μg/m^3

Disease	First author/ publication year	Region	Study design	Sample size/Cases	Age (years)	ICD	Data sources of pollutants	Duration	Mean Concentration
	Wang et al. (2020)	China	Time-series	—/14965(outpatient)	—	ICD10:J30	China's National Urban Air Quality Real-time Publishing Platform	short-term	$PM_{2.5}$:75.7μg/m^3; PM_{10}:132.1μg/m^3; SO_2:33.2μg/m^3; NO_2:48.4μg/m^3; O_3:59.4μg/m^3; CO:1377μg/m^3.
	Wang et al. (2020)	China	Time-series	—/229685(outpatient visits)	—	ICD-10:J30.401	monitoring station	short-term	$PM_{2.5}$:99.5μg/m^3

Relationship between air pollution and eczema

Effect of long-term air pollution exposure on eczema

As shown in Table 2 and Figure S1, long-term exposed to PM_{10} was found to increase the risk of eczema (PM_{10}: RR=1.583, 95% CI: 1.328-1.888) with per (10 μg/m^3 increase in $PM_{2.5}$ and PM_{10}; 1 ppb increase in SO_2, NO_2, CO and O_3) unit increase in concentration. However, exposed to $PM_{2.5}$, NO_2 and SO_2 was not associated with the risk of eczema ($PM_{2.5,}$ RR=1.171, 95% CI: 0.944-1.45; NO_2, RR=1.033, 95% CI: 0.970-1.101; SO_2, RR=1.101, 95% CI: 0.897-1.351). The heterogeneity of pooled studies was high in studies that exposed to $PM_{2.5}$ ($PM_{2.5}$: I^2=77.97%), whereas low in studies of PM_{10}, NO_2 and SO_2 (PM_{10}: I^2=0.00%; NO_2: I^2=0.00%; SO_2: I^2=0.00%). There was no publication bias in the combined studies for $PM_{2.5}$ and NO_2 (P>0.05) (Fig. S2a, Fig.S2b).

Table 2
Pooled estimates of the effect on the risk of diseases

Prevalence/incidence Disease	Duration	Pollutants	Number of studies	RR [95%CI]	I^2	*P*-value for heterogeneity	Publication bias(*p*)
Eczema	Long-term	$PM_{2.5}$	4	1.171[0.944,1.453]	77.97%	0.0044	>0.05
		PM_{10}	2	1.583[1.328,1.888]*	0.00%	0.9654	—
		NO_2	6	1.033[0.970,1.101]	0.00%	0.9050	>0.05
		SO_2	1	1.101[0.897,1.351]	0.00%	1.0000	—
	Short-term	$PM_{2.5}$	5	1.001[0.994,1.007]	72.91%	0.0033	>0.05
		PM_{10}	8	1.006[1.003,1.008]*	63.25%	<0.0001	>0.05
		NO_2	7	1.009[1.008,1.011]*	10.84%	0.2555	>0.05
		SO_2	5	1.004[0.999,1.009]	12.41%	0.4648	>0.05
		CO	1	1.000[0.956,1.046]	0.00%	1.0000	—
		O_3	1	0.628[0.342,1.152]	0.00%	1.0000	—
AD	Long-term	$PM_{2.5}$	4	1.153[0.962,1.381]	98.65%	<0.0001	>0.05
		PM_{10}	5	1.101[0.947,1.280]	99.29%	<0.0001	>0.05
		NO_2	7	1.048[0.984,1.116]	97.80%	<0.0001	>0.05
		SO_2	4	1.223[0.954,1.568]	97.34%	<0.0001	>0.05
		CO	5	1.006[0.998,1.013]	73.30%	0.0033	>0.05
		O_3	5	1.010[0.978,1.043]	0.44%	0.1920	>0.05
	Short-term	$PM_{2.5}$	1	1.004[1.002,1.007]	0.00%	1.0000	—
		PM_{10}	3	1.011[0.995,1.028]	98.35%	0.0036	>0.05
		NO_2	3	1.000[0.997,1.004]	0.00%	0.8268	>0.05
		SO_2	2	1.008[1.001,1.015]*	62.27%	0.1035	—
		CO	1	1.004[0.999,1.009]	0.00%	1.0000	—
		O_3	3	1.033[0.990,1.078]	82.22%	0.0035	>0.05
AR	Long-term	$PM_{2.5}$	7	1.058[1.014,1.222]*	90.81%	<0.0001	<0.05
Prevalence/incidence Disease	Duration	Pollutants	Number of studies	RR [95%CI]	I^2	*P*-value for heterogeneity	Publication bias(*p*)
		PM_{10}	8	1.004[0.988,1.020]	27.66%	0.1230	>0.05
		NO_2	11	1.003[0.995,1.011]	0.78%	0.6720	<0.05
		SO_2	8	1.014[0.996,1.033]	0.00%	0.9395	>0.05
		CO	7	1.127[0.893,1.422]	99.68%	<0.0001	>0.05
		O_3	11	1.004[0.992,1.016]	0.00%	0.7592	>0.05
	Short-term	$PM_{2.5}$	9	1.049[0.995,1.107]	99.27%	<0.0001	>0.05
		PM_{10}	11	1.028[1.008,1.049]*	98.69%	<0.0001	<0.05
		NO_2	9	1.018[1.007,1.029]*	87.91%	<0.0001	>0.05
		SO_2	5	1.009[1.000,1.018]	83.78%	<0.0001	>0.05
		CO	3	1.000[1.000,1.001]	0.00%	0.6335	>0.05

Prevalence/incidence Disease	Duration	Pollutants	Number of studies	RR [95%CI]	I^2	*P*-value for heterogeneity	Publication bias(*p*)
		O_3	4	1.010[0.998,1.022]	68.28%	0.0138	>0.05

RRs were shown per 10 μg/m^3 increase in $PM_{2.5}$ or PM_{10} and 1 ppb increase in SO_2, NO_2, CO and O_3. * Indicates that air pollutants increase the risk of IgE mediated allergic disease.

In subgroup analyses according to age, study types and regions, long-term exposed to $PM_{2.5}$ and NO_2 had no impact on the risk of eczema. Details were shown in Figure 2a. After we conducting subgroup analyses, heterogeneity was still high in $PM_{2.5}$ subgroups (I^2>50%), other undiscovered factors might have impact on the heterogeneity. Furthermore, the studies of CO and O_3 were not enough for subgroup analyses at present.

Effect of short-term air pollution exposure on eczema

By pooled effect size, we found that short-term exposed to PM_{10} and NO_2 were associated with the risk of eczema (PM_{10}, RR=1.006, 95% CI: 1.003-1.008; NO_2: RR=1.009, 95% CI: 1.008-1.011), while exposed to $PM_{2.5}$, SO_2 did not increase the risk of eczema ($PM_{2.5}$, RR=1.001, 95% CI: 0.994-1.007; SO_2, RR=1.004, 95% CI: 0.999-1.009) (Table 2, Fig. S1). The pooled studies in $PM_{2.5}$ and PM_{10} were still high in heterogeneities (I^2>50%). There was no publication bias in $PM_{2.5}$, PM_{10} and SO_2 (Fig. S2 c, Fig. S2d, Fig. S2f). Moreover, the heterogeneity of pooled studies was low in NO_2 and there was no publication bias by funnel plot (*P*>0.05) (Fig. S2e). Studies on pollutants CO and O_3 were not enough for combining analyses at present.

In Figure 2a, the results of analysis on ICD were consistent with no ICD grouping, the combined effects of pollutants PM_{10} and NO_2 were also associated with the risk of eczema (PM_{10}, RR=1.005, 95% CI:1.003-1.008; NO_2: RR=1.009, 95% CI: 1.007-1.011). In age<18 group, $PM_{2.5}$, PM_{10} and NO_2 were associated with eczema. Nevertheless, PM_{10} and NO_2 increased the risk of eczema in the all age groups (PM_{10}, RR=1.007, 95% CI: 1.004-1.009; NO_2: RR=1.008, 95% CI: 1.005-1.010), with low heterogeneity (I^2<50%). Combined effect by cross-sectional studies showed no association between short-term exposed to pollutants $PM_{2.5}$, PM_{10}, NO_2 and the risk of eczema. The combination of the time-series studies suggested that these three pollutants increased the risk of eczema ($PM_{2.5}$, RR=1.003, 95% CI: 1.002-1.004; PM_{10}, RR=1.007, 95% CI: 1.004-1.009; NO_2, RR=1.008, 95% CI: 1.005-1.010). Furthermore, $PM_{2.5}$, PM_{10}, and NO_2 exposure were related to eczema in Asia with low heterogeneity (I^2<50%).

Relationship between air pollution and AD

Effect of long-term air pollution exposure on AD

A total of eleven studies for AD were included in this study. However, significant results were not found in long-term air pollutants exposure ($PM_{2.5}$, RR=1.153, 95 CI%:0.962, 1.381; PM_{10}, RR=1.101, 95 CI%:0.947, 1.280; NO_2, RR=1.048, 95 CI%:0.984, 1.116; SO_2, RR=1.223, 95 CI%:0.954, 1.568; CO, RR=1.006, 95 CI%:0.998, 1.013; O_3, RR=1.010, 95 CI%:0.978, 1.043) (Table 2, Fig.S3). The heterogeneities of the combined study were high in $PM_{2.5}$, PM_{10}, NO_2, SO_2 and CO (I^2>50%). The funnel plots showed that there were no publication bias (*P*>0.05) in $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO and O_3 (Figure S4a-4f).

From the Figure 2b, ICD subgroup analyses showed that long-term exposure to six pollutants were not harmful to AD. The results were consistent with the effect of no ICD grouping for AD. However, the results of combined effects through subgroup analyses indicated that PM_{10} and CO were harmful to the occurrence of AD (PM_{10}, RR=1.049, 95% CI: 1.010-1.089; CO: RR=1.009, 95% CI: 1.006-1.012) with low heterogeneity (I^2<50%) in age<18, while $PM_{2.5}$, NO_2, SO_2 and O_3 were irrelevant. Subgroup analyses of study type was found a significant association between AD and SO_2 (RR=1.622, 95% CI: 1.556-1.690, I^2=0.00%) in cohort studies. No positive results were discovered for the combination of cross-sectional studies effects. In addition, the subgroup analyses showed no association between AD and the pollutants in Asian.

Effect of short-term air pollution exposure on AD

As we can see from Table 2 and Figure S3, short-term exposure to SO_2 increased the risk of AD by 1.008 per unit of concentration (RR: 1.008, 95% CI: 1.001-1.015, I^2=62.27%). PM_{10}, NO_2 and O_3 had no adverse effect on AD with per unit increase in concentration (PM_{10}, RR: 1.011, 95% CI: 0.995-1.028; NO_2, RR: 1.000, 95% CI: 0.997-1.004; O_3, RR: 1.033, 95% CI: 0.990-1.078). Since only one research article studied on $PM_{2.5}$, CO and AD, they cannot be combined for a further analysis.

In Figure 2b, the sensitivity analyses of ICD groups showed that PM_{10} (RR: 1.003, 95% CI: 1.002-1.005, I^2=0.00%), SO_2 (RR: 1.008, 95% CI: 1.001-1.015, I^2=0.00%) and O_3 (RR: 1.012, 95% CI: 1.007-1.017, I^2=0.00%) were correlation with AD in short time. Analyses of SO_2 and O_3 by ICD showed that increased the risk of AD with per unit increase in concentration (SO_2: RR: 1.008, 95% CI: 1.001-1.015; O_3, RR: 1.012, 95% CI: 1.007-1.017). In different age groups, PM_{10} increased the risk of AD in the general population. Furthermore, NO_2 and O_3 did not increase AD's risk for the population aged<18. What's more, air pollutants were not associated with AD risk in subgroup analyses of study types and regions.

Relationship between air pollution and AR

Effect of long-term air pollution exposure on AR

The results showed that only long-term exposure to $PM_{2.5}$ had a harmful effect to the occurrence of AR (RR=1.058, 95% CI: 1.014-1.222; Table 2, Fig.S5). But the heterogeneity of the combined articles was high (I^2=90.81%), and the included articles had publication bias (*P*<0.05) (Fig. S6a). PM_{10}, NO_2, SO_2, CO, O_3

had no effect on the risk of AR, and the details were shown in supplementary material Figure S5. In addition, the articles studying PM_{10}, SO_2, CO and O_3 had no publication bias (P>0.05) (Fig. S6b, S6d-S6f), while that studying NO_2 had publication bias (P<0.05) (Fig. S6c).

According to subgroup analyses in Figure 2c, combined analyses of articles classified by ICD showed no association between $PM_{2.5}$, O_3 and AR ($PM_{2.5}$, RR=1.145, 95% CI: 0.885-1.480; O_3, RR=1.040, 95% CI: 0.949-1.140. Additionally, only $PM_{2.5}$ increased the risk of AR in the age<18 group ($PM_{2.5}$: RR=1.133, 95% CI: 1.017-1.262). The pooled RR of PM_{10} was significant in cross-sectional studies (PM_{10}: RR=1.021, 95% CI: 1.003-1.038, I^2=0.00%). In addition, $PM_{2.5}$ was also found to be strengthened the risk of AR in Asia ($PM_{2.5}$: RR=1.222, 95% CI: 1.098-1.361), while other pollutants did not have a positive relationship with AR for Europe.

Effect of short-term air pollution exposure on AR

As shown in Table 2 and Figure S5, short-term exposure to PM_{10} and NO_2 were associated with the risk of AR (PM_{10}: RR=1.028, 95% CI: 1.008-1.049; NO_2: RR=1.018, 95% CI: 1.007-1.029). However, $PM_{2.5}$, SO_2, CO and O_3 were not associated with the risk of AR ($PM_{2.5}$: RR=1.049, 95% CI: 0.995-1.107; SO_2: RR=1.009, 95% CI: 1.000-1.018; CO: RR=1.000, 95% CI: 1.000-1.001; O_3: RR=1.010, 95% CI: 0.998-1.022). Except for CO, the heterogeneity was higher ($PM_{2.5}$: I^2= 99.27%, PM_{10}: I^2= 98.69%, NO_2: I^2= 87.91%, SO_2: I^2=83.78%, O_3: I^2= 68.28%). There was no publication bias for the pollutant studies (P>0.05) besides PM_{10} (Fig. S6g-S6i).

As shown in Figure 2c, the subgroups of ICD, PM_{10}, NO_2 and SO_2 were harmful factors for AR (PM_{10}, RR=1.030, 95% CI: 1.004-1.056; NO_2, RR=1.022, 95% CI: 1.009-1.035; SO_2, RR=1.016, 95% CI: 1.003-1.030), but the heterogeneity of included articles were high (I^2>50%). Through the ICD subgroup, we found that SO_2 increases AR's risk. In analysis of age, PM_{10} was harmful to age<18. For all age group, $PM_{2.5}$, PM_{10}, NO_2 and SO_2 increased the risk of AR ($PM_{2.5}$, RR=1.005, 95% CI: 1.003-1.007; PM_{10}, RR=1.012, 95% CI: 1.003- 1.021; NO_2, RR=1.016, 95% CI: 1.008-1.024; SO_2, RR=1.016, 95% CI: 1.003-1.030) with low heterogeneity (I^2<50%). In addition, PM_{10} and NO_2 were potential risk factors for AR (PM_{10}, RR: 1.022, 95% CI: 1.003-1.041; NO_2, RR: 1.018, 95% CI: 1.007-1.028) in time-series studies with high heterogeneity (PM_{10}: I^2= 98.88%, NO_2: I^2= 91.23%,). In subgroup analyses on region, the impacts of PM_{10} and NO_2 for AR were detrimental in Asia (PM_{10}, RR: 1.023, 95% CI: 1.005-1.041; NO_2, RR: 1.017, 95% CI: 1.004-1.029). But the heterogeneity of both were still high (PM_{10}: I^2=98.34%; NO_2: I^2=90.31%), which may be affected other factors.

Discussion

This meta-analysis has several main findings. (1) Long-term exposure to PM_{10} increased the risk of eczema. (2) Long-term exposure $PM_{2.5}$ was associated with AR. (3) Short-term exposure to PM_{10} and NO_2 increased the risk for eczema and AR. (4) Short-term exposure to SO_2 was associated with the development of AD. In addition, significant results were found in subgroup analyses. (1) By ICD classification analyses, long-term exposure to PM_{10} increased the risk of eczema, AD and AR. (2) In age<18 years old group, long-term exposure to PM_{10}, $PM_{2.5}$ increased the risk of AD and AR respectively. For all age group, short-term exposure to PM_{10} and NO_2 were associated with eczema and AR. (3) SO_2 has been found to increase the risk of AD in cohort studies and PM_{10} and NO_2 were correlated with eczema and AR in time series studies types. (4) Long-term exposure to $PM_{2.5}$ increased the risk of Asia's AR patients and short-term exposure to PM_{10} and NO_2 were associated with the development of eczema and AR.

To our knowledge, this is up-to-date meta-analysis and review of current evidence between air pollutants and IgE mediated allergic disease. There were meta-analyses on IgE mediated allergic diseases. About eczema, one meta-analysis has been studied by Fuertes et al. found no association between $PM_{2.5}$, NO_2 and children's eczema (Fuertes et al., 2020). Our results also suggested that long-term exposure to $PM_{2.5}$ and NO_2 were not associated with eczema in children. In addition, our results complemented that long-term exposure to PM_{10} and NO_2 increased the risk of eczema in all age group. Subgroup analyses of study design and regions were also performed and the results were innovative. In 2014, a meta-analysis on allergy and sensitization of traffic-related air pollution showed that two of birth cohorts reported adverse effects of NO_2 on the prevalence of eczema (Bowatte et al., 2015). Our meta-analysis updated the risk assessment of NO_2 on children's eczema. Besides AD has not been studied for a meta-analysis. AR, Zou et al. included thirteen studies for meta-analysis and found that when exposed to NO_2, SO_2, PM_{10} and $PM_{2.5}$, the prevalence of childhood AR might increase (Zou et al., 2018). In a meta-analysis of particulate matter (PM) and the prevalence of AR in children published in 2021, Lin et al. had reported the relation between $PM_{2.5}$, PM_{10} and childhood AR. In our study, we considered the effects of long-term and short-term exposure to pollutants, the results shown that long-term exposure to $PM_{2.5}$ increased the risk of children's AR and short-term exposure to PM_{10} increased the risk of children's AR. Moreover, we performed subgroup analyses of ICD, study types, and age.

Air pollution has become a public health problem, and was the most important cause of premature death in 2015 (Combes and Franchineau, 2019). Air pollution is widely considered as a detrimental factor for the lungs, respiratory tract and most organ systems. At the same time, air pollution affects the human immune system, that might be related to allergic sensitization and the occurrence of autoimmune diseases (Schraufnagel et al., 2019). Li et al. found that $PM_{2.5}$ could cause dermatitis by promoting the expression of thymic stromal lymphopoietin in keratinocytes (Li et al., 2020). In a BALB/c mouse model of $PM_{2.5}$ exposure mechanism study, nucleotide-binding oligomerization domain-containing protein 1(Nod 1) and nuclear factor (NF)-κB signaling pathway would be activated after exposing to $PM_{2.5}$, then cause pro-inflammatory reactions (Manzo et al., 2012). PM_{10} might induce NF-κB activation in human airway epithelial cells, and this process is mediated by oxidation mechanisms (Salvi, 2001). Exposure to air pollution increases the increase of eosinophils (EOS) in the nasal mucosa. A mechanism study in female mouse reported that NO_2 was an endogenous mediator of inflammation. After exposure, mixed Th2/Th17 adaptive immune response and neutrophils would appear. EOS and neutrophils were recruited to the airway, causing inflammation (Martin et al., 2013) (Fig. 3).

Air pollutants could be absorbed into subcutaneous tissues by hair follicles and sweat/sebaceous glands of the skin. When the defense capability is exceeded, the function of the skin will be impaired and may lead to the occurrence of skin diseases (Puri et al., 2017). A study conducted by Park et al. found that PM_{10} could increase the expression of NF-κB, IL-1, IL-6, IL-8 and IL-33 genes in dermal fibroblasts, thereby transcribing pro-inflammatory genes and inducing skin inflammation (Park et al., 2018). Piao et al. conducted experiments in mice, the result showed that $PM_{2.5}$ could produce reactive oxygen species ROS and participates in oxidative stress, this can cause DNA damage, lipid peroxidation and protein carbonylation (Piao et al., 2018). When normal human epidermal keratinocytes are exposed to PM, the aromatic hydrocarbon receptor (AHR) is activated. AHR pathway and ROS induce pro-inflammatory factors. The activation of AHR is related to human atopic dermatitis (Araviiskaia et al., 2019). In short, PM exposure increased pro-inflammatory mediators and the expression of AHR, then increased ROS. Finally, skin damage is mainly caused by PM-induced oxidative stress. Moreover, it has been reported that NO_2 might damage the barrier function of the skin (Eberlein-König et al., 1998). The above is related to the pathology of dermatitis (Fig. 3). At present, the mechanism between air pollution and IgE immune-mediated diseases is not yet clear. and it might also be related to human susceptibility (Kimata, 2004; Schmitz et al., 2012). Therefore, more mechanisms in this area need to be studied. Only in this way can we prevent the occurrence of the disease from the root cause.

The advantages of this analysis were including update studies of short-term and long-term exposure to air pollutants. There were six pollutants and a larger sample size to analyze the pooled effects and the results were more comprehensive. Then, based on the widely accepted NOS and OHAT inclusion of the study tools, the quality and risk of deviations were carefully assessed. All included studies had high quality. At last, all effect values were standardized for further analyses. However, the study limitations should be considered. The existing articles on air pollutants are not sufficient for analysis, more studies related to the effects of air pollution on IgE mediated allergic disease are still needed.

In conclusion, this comprehensive meta-analysis found that particulate pollutants ($PM_{2.5}$ and PM_{10}), NO_2, and SO_2 were potentially harmful to IgE-mediated immune diseases. Air pollutants may be emerging risk factors for allergic diseases. Therefore, the underlying factors shouldn't be ignored. More attention should be paid to vulnerable population, especially for children. Moreover, strengthen protective measures should be conducted to reduce the incidence of allergic diseases, alleviate people from diseases and save medical resources.

Declarations

Ethical Approval Not applicable.

Consent to Participate: Not applicable (This study does not contain any individual person's data in any form).

Consent to Publish: The authors declare that they agree with the publication of this paper in this journal.

Author Contributions

Hua Wang: performed the data analysis, writing-original draft. Xian-Bao Li: performed the data analysis. Xiu-Jie Chu: investigation, data curation. Nv-Wei Cao: formal analysis, helped revise the manuscript. Hong Wu: investigation. Rong-Gui Huang: investigation. Bao-Zhu Li (lbz88730@163.com) and Dong-Qing Ye (anhuiydq@126.com): conceptualization, project administration, funding acquisition, writing-original draft.

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Figures

Figure 1

The process of articles selection

Figure 2

Forest plot of subgroup analysis for diseases

Figure 3

Mechanistic insight into air pollutants and IgE mediated allergic diseases

Nod 1: nucleotide-binding oligomerization domain-containing protein 1; NF-κB: nuclear factor (NF)-κB; EOS: eosinophils; AHR: aromatic hydrocarbon receptor.

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