

RESEARCH ARTICLE

Association between Air Pollutants and Asthma Emergency Room Visits and Hospital Admissions in Time Series Studies: A Systematic Review and Meta-Analysis

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Abstract

Background

Air pollution constitutes a significant stimulus of asthma exacerbations; however, the impacts of exposure to major air pollutants on asthma-related hospital admissions and emergency room visits (ERVs) have not been fully determined.

Objective

We sought to quantify the associations between short-term exposure to air pollutants [ozone (O₃), carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), and particulate matter ≤10μm (PM₁₀) and PM_{2.5}] and the asthma-related emergency room visits (ERV) and hospitalizations.

Methods

Systematic computerized searches without language limitation were performed. Pooled relative risks (RRs) and 95% confidence intervals (95% CIs) were estimated using the random-effect models. Sensitivity analyses and subgroup analyses were also performed.

Results

After screening of 246 studies, 87 were included in our analyses. Air pollutants were associated with significantly increased risks of asthma ERVs and hospitalizations [O₃: RR(95%

CI), 1.009 (1.006, 1.011); $I^2 = 87.8\%$, population-attributable fraction (PAF) (95%CI): 0.8 (0.6, 1.1); CO: RR(95%CI), 1.045 (1.029, 1.061); $I^2 = 85.7\%$, PAF (95%CI): 4.3 (2.8, 5.7); NO₂: RR(95%CI), 1.018 (1.014, 1.022); $I^2 = 87.6\%$, PAF (95%CI): 1.8 (1.4, 2.2); SO₂: RR (95%CI), 1.011 (1.007, 1.015); $I^2 = 77.1\%$, PAF (95%CI): 1.1 (0.7, 1.5); PM₁₀: RR(95%CI), 1.010 (1.008, 1.013); $I^2 = 69.1\%$, PAF (95%CI): 1.1 (0.8, 1.3); PM_{2.5}: RR(95%CI), 1.023 (1.015, 1.031); $I^2 = 82.8\%$, PAF (95%CI): 2.3 (1.5, 3.1)]. Sensitivity analyses yielded compatible findings as compared with the overall analyses without publication bias. Stronger associations were found in hospitalized males, children and elderly patients in warm seasons with lag of 2 days or greater.

Conclusion

Short-term exposures to air pollutants account for increased risks of asthma-related ERVs and hospitalizations that constitute a considerable healthcare utilization and socioeconomic burden.

Introduction

Asthma is characterized by airway hyperresponsiveness and inflammation, the pivotal components leading to the cascades of pro-inflammatory mediator release and airflow limitation [1] that are associated with allergen exposures, air pollution, cigarette smoking and noxious particle insults [2].

The relationship between air pollution and asthma has been well-established [3–89], particularly in the countries with rapid urbanization and industrialization. Three multi-center studies conducted in Europe [14,51] and Australia [53] reported an overall insignificant association between major air pollutants and the asthma-related emergency room visits (ERVs), except for nitrogen dioxide (NO₂) [14,53] and particulate matter with a diameter of 10 µm or less (PM₁₀) [51]; whereas other multi-city studies conducted in Korea and Europe demonstrated different magnitudes of the associations between asthma exacerbation and ozone (O₃) [5] and sulfur dioxide (SO₂) [5,76] pollution. Moreover, exposure to environmental NO₂ and PM₁₀ has recently been associated with worsening of symptoms and lung function decline during asthma exacerbations [90–92].

Whilst the adverse impacts of air pollution on asthma exacerbations have been confirmed, the effect sizes and the extent to which any single pollutant acts as a surrogate of other pollutants are less clear. As epidemiologic evidence regarding the effects of air pollution on asthma accumulates, it is crucial to consider different concentration-response functions (CRFs, defined as the percentage change in any health outcome per unit change in concentration, to different air pollutants [93]), based on the concurrent evidence. Determination of the effect modification across studies may also be challenging because of the underlying geographic diversity, heterogeneous primary outcome indices, the differences in statistical algorithms, the complexity of multiple pollutants and other confounders [4].

Consequently, meticulous risk assessments exploring the influences of multiple air pollutants, calculated as the CRFs [93], are warranted. In view that the quantification between air pollution and asthma-related ERVs or hospitalizations has been well-established and that the majority of population is exposed to air pollution, the relative risks (RRs) and population attributable fractions (PAFs) of individual pollutants on asthma-related ERVs or

hospitalizations should be taken into account. Furthermore, investigations of the effect modification may provide further insights into these associations [94]. For instance, there have been the literature reports delineating stronger pollution effects during the warm seasons, despite the culmination of pediatric asthma attacks during cold seasons [1,4,5,17,18,24,52,54,85]. Sex [5,7,37,40,50,68] and age [16,24,30,38,57] differences might also confound the asthma outcomes to air pollutant exposure.

In this study, we sought to conduct a systematic review and meta-analysis on the association between short-term exposure to air pollutants and asthma-related ERVs and hospital admissions based on time-series and case-crossover studies, thus offering rationales to improve public health and environmental protection. We further assessed the impacts of age, sex, season, hospital variance and long lag patterns (lag >2days) on these associations.

Methods

Eligibility criteria and literature searches

Systematic searches were conducted to identify studies focusing on short-term exposures, defined as the duration of up to 7 days to one of the air pollutants associated with asthma exacerbation. These studies involved all age intervals without language limitation. We excluded: (1) animal studies, *ex vivo* and toxicological studies, summaries, commentaries and editorials, case reports and case series; (2) duplicate publications; (3) studies evaluating long-term exposure only; (4) non-peer reviewed articles (a potential source of bias); (5) study duration of less than one year; (6) no original data. Authors were contacted by e-mail in case data were incomplete. Studies were excluded if no reply was obtained despite repeated contacts with corresponding authors.

Time-series studies (including case-crossover studies) were searched comprehensively in EMBASE, PubMed, Cochrane Central Register of Controlled Trials and EBM Reviews—Cochrane Database of Systematic Reviews, Web of Science, Ovid and Highwire up to March 2015 (no start date specified). References were checked for additional data. When the same population was used in several publications, only the largest and the most complete study (i.e. multi-cities study) was included. In addition, single-city study with different time periods from multi-cities study was also accepted. We used a combination of keywords related to the types of exposure (air pollution, CO, PM₁₀, PM_{2.5}, SO₂, NO₂ and O₃) and the outcomes of asthma exacerbations (hospital admission and ER visit). (See **Search Strategies** in the online supplements for further details)

Quality score assessment

This study complies with the preferred reporting items of PRISMA [95]. Since no validated scales of time-series and case-crossover studies were recommended by New Castle Ottawa and Cochrane risk of bias tool, we evaluated the validity based on Mustafic's study [96]. Three components were assessed, including asthma diagnosis (0 to 1 point), air pollutant measures (0 to 1) and adjustment for confounders (0 to 3). We confirmed asthma exacerbation if coded by *International Classification of Diseases*, *American Thoracic Society*, *National Asthma Education or Prevention Program* or *International Classification of Primary Care 2* (0 for no valid criteria). The frequency of measurement and missing data were considered (1 point for measurements performed daily with <25% missing data, otherwise 0 point was assigned). Regarding the potential confounders, 1 point was scored if long-term trends, seasonality and temperature were all adjusted, otherwise 0 point was assigned. Any additional adjustment for the humidity or day-of-week was added for 1 point. Any adjustment made for influenza epidemics and holidays was added for 1 point. Studies fulfilling 5 points were analyzed in sensitivity analyses.

Study selection and data extraction

Two independent reviewers (S.C. and H.D.) screened the abstracts and titles. Full texts were reviewed to determine eligibility for inclusion. Disagreement was resolved by discussion. If consensus was not reached, another reviewer (X.Z.) was consulted to vote for final decisions.

A standardized form was used for data extraction including the main characteristics (author, year of publication, location and period, type of study, age and sex of populations, title and journal), outcome measures (general practitioner's house calls, primary care visits, asthma-related hospitalization and ERV), the quality of measurement methods and adjustments (long-term trend, seasonality, temperature, humidity, days of the week, holidays and influenza epidemics). Data extraction was done by two independent reviewers (W.G. and L.J.) for comparisons. Disagreements were resolved by consultation with the third reviewer (X.Z.).

Statistical analysis

As current evidence suggests a linear association between air pollutants and asthma-related ERVs and hospital admissions, the standardized effect estimates were expressed as the risk ratios (RRs) and 95% confidence intervals (95% CIs), derived from single-pollutant models reporting RRs (95% CIs) or percentage change (95% CIs), and further recalculated to reflect a 10 $\mu\text{g}/\text{m}^3$ increase in the pollutants by assuming a linear relationship of all pollutants, except for CO (1 mg/m^3 increase) [96]. There was a time lag (measured in days) between short-term air pollution and asthma exacerbations; however, each of the included study varied in lag selection patterns. Some authors recommended the use of the most significant estimate, irrespective of the direction. Given the lack of standardized methods of reporting, we adopted a *priori* lag selection scheme proposed by Atkinson et al [97]. If only one lag estimate for a given pollutant/outcome pair was demonstrated (either the only one was analyzed or reported), it would be included for analyses. If multiple lag estimates were reported, the selection algorithms were: 1) the most frequently used lag in all selected studies; 2) single lags, but not cumulative/distributed lags, were selected as a priority.

Random-effect model is the most conservative tool incorporating within- and between-study heterogeneity in 95%CI, and has been adopted for studies investigating different populations with anticipated significant heterogeneity which is calculated using the I^2 test. The I^2 values of 0 to 30, 30 to 50, and greater than 50 denoted low, moderate and high heterogeneity, respectively [98]. This algorithm is currently recommended by Cochrane collaboration (<http://www.cochrane.org>) despite concerns of underpowered statistics.

The prevalence of exposure to air pollution in the population was estimated to be 100%, which is imputed from the epidemiological studies reporting effect estimates [99]. Population attributable fractions (PAFs) were calculated from RRs (95%CI) in overall analyses, calculated as $\text{PAF} = (\text{RR} - 1) / \text{RR}$.

To explore the heterogeneity in our pooled analysis, sensitivity analyses of the lag patterns and study quality were applied, based on the studies with the same and most commonly used lag pattern or the studies with 5 scores.

Subgroup analyses of the study characteristics were conducted to combine the effects for evaluating the differences between strata-specific estimates (age, sex, seasons, hospitalization or ERVs). Additional subgroup analyses were performed for short- (≤ 2 days) and long-lag (> 2 days) patterns. The default for short-lag patterns was the most frequently used for individual pollutants; otherwise, lag1 or lag0 or lag 0–1 served as surrogates. For long-lag patterns, single lag was a priority selection compared with the cumulative lag.

Potential publication bias was assessed by using the asymmetric plot and confirmed by the Egger's test [100].

Statistical analyses were conducted using STATA 11.2 (Stata, College Station, TX, USA). All tests were two-sided and statistical significance was defined as $P < 0.05$, except for the heterogeneity assessment ($P < 0.10$).

The PRISMA checklist for this meta-analysis could be found in [S1 File](#) in the supporting information.

Results

Eligible studies

We initially identified 1099 literature reports. After screening for the titles and abstracts, 246 full-text articles were assessed for eligibility, of which 87 were included (86 in English and 1 in Spanish, [Fig 1](#)).

Main characteristics of 87 eligible studies, consisting of 62 time-series and 25 case cross-over studies, are displayed in [S1 Table](#). Databases were extracted from 46 ERVs, 37 hospital admissions and 4 ERVs/hospital admissions. The study cohort consisted of the general population. Lag exposures varied from a specific day (single-lag) to 7 days or less before the onset of asthma exacerbations.

Of the 87 included studies, 50 focused on children, 21 on adults, 13 on elderly population, and 44 on general population. Only 12 studies have conducted sex modification analyses, with

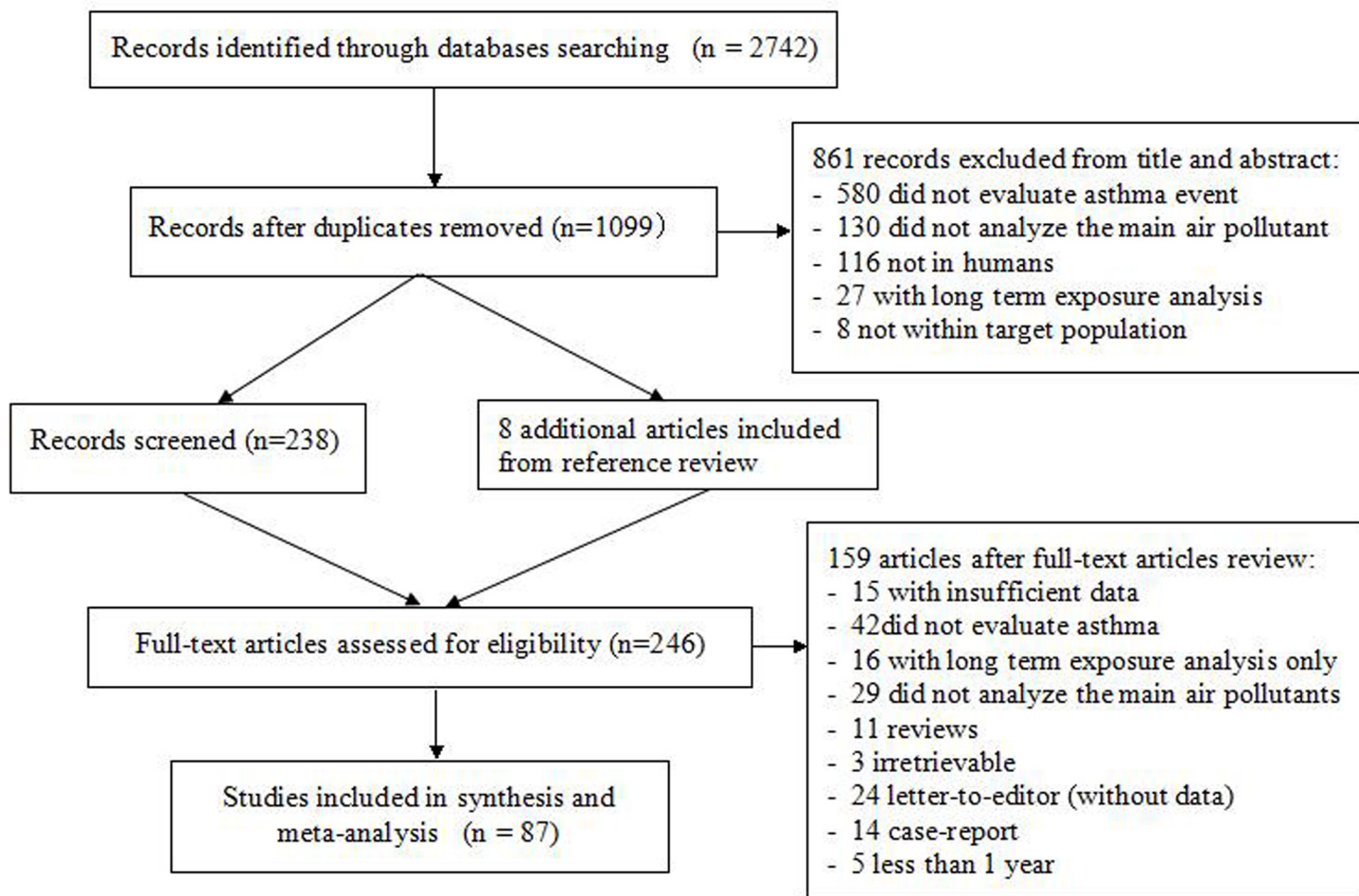


Fig 1. Study flow chart.

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Table 1. Association of six major air pollutants with ERVs and hospital admissions for asthma in overall and sensitivity analyses.

Characteristics	Air pollutant (incremental unit)					
	O ₃ (10 µg/m ³)	CO (1 mg/m ³)	NO ₂ (10 µg/m ³)	SO ₂ (10 µg/m ³)	PM ₁₀ (10 µg/m ³)	PM _{2.5} (10 µg/m ³)
Overall study analyses						
No. of the studies	71	42	66	65	51	37
I ² , %	87.8	85.7	87.6	77.1	69.1	82.8
RR (95%CI)	1.009 (1.006, 1.011)	1.045(1.029, 1.061)	1.018 (1.014, 1.022)	1.011 (1.007, 1.015)	1.010 (1.008, 1.013)	1.023(1.015, 1.031)
Egger's test, P value	<0.001	0.01	<0.001	<0.001	<0.001	0.06
PAF, %(95%CI) ^a	0.8 (0.6, 1.1)	4.3 (2.8, 5.7)	1.8 (1.4, 2.2)	1.1 (0.7, 1.5)	1.1 (0.8, 1.3)	2.3 (1.5, 3.1)
Study quality sensitivity analyses						
No. of the studies	12	7	11	13	7	3
I ² , %	55.7	13.6	55.7	57.9	0.0	0.0
RR (95%)	1.005 (1.002, 1.008)	1.013 (1.000, 1.028)	1.009 (1.004, 1.015)	1.009 (1.003, 1.015)	1.006 (1.003, 1.009)	1.004 (1.000, 1.009)
Egger's test, P value	0.15	0.16	0.16	0.28	0.53	0.71
Lag exposures sensitivity analyses						
No. of the studies	9	14	11	12	13	13
Lag exposure, d	0	1	0	0	1	1
I ² , %	22.4	0.0	65.9	41.8	0.0	6.6
RR (95%)	1.010 (1.005, 1.014)	1.013 (1.001, 1.025)	1.010 (1.002, 1.018)	1.004 (1.000, 1.008)	1.005 (1.003, 1.008)	1.008 (1.003, 1.013)
Egger's test, P value	0.99	0.08	0.93	0.96	0.42	0.49

Abbreviations: PAF, population attributable fraction; PM₁₀, particulate matter of ≤10 µm; PM_{2.5}, particulate matter of ≤2.5 µm; RR, relative risk
The PAF was calculated by {PAF = P[(RR–1)/P(RR–1)+1]}, where P indicates prevalence of exposure to air pollution in the population which was estimated as 100%.

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12 male and 11 female sub-datasets. 31 studies were performed in warm seasons and 25 in cold seasons.

Mean 24-hr or 8-hr maximum concentrations of six pollutants are demonstrated in [S1 Table](#).

Overall analyses

Associations between the six major air pollutants and asthma-related ERVs/hospitalizations were statistically significant [O₃: 71 studies; RR (95%CI), 1.009 (1.006, 1.011); I² = 87.8%, PAF (95%CI): 0.8 (0.6, 1.1); CO: 42 studies; RR (95%CI), 1.045 (1.029, 1.061); I² = 85.7%, PAF (95%CI): 4.3 (2.8, 5.7); NO₂: 66 studies; RR (95%CI), 1.018 (1.014, 1.022); I² = 87.6%, PAF (95%CI): 1.8 (1.4, 2.2); SO₂: 65 studies; RR (95%CI), 1.011 (1.007, 1.015); I² = 77.1%, PAF (95%CI): 1.1 (0.7, 1.5); PM₁₀: 51 studies; RR (95%CI), 1.010 (1.008, 1.013); I² = 69.1%, PAF (95%CI): 1.1 (0.8, 1.3); PM_{2.5}: 37 studies; RR (95%CI), 1.023 (1.015, 1.031); I² = 82.8%, PAF (95%CI): 2.3 (1.5, 3.1)]. ([Table 1](#), [Figs 2–7](#)).

Publication bias was detected in all analyses evaluating all pollutants except for PM_{2.5} (P = 0.06). See [S1 Fig](#) in the online supplement for the funnel plots of the relative risks of emergency/hospital admissions for asthma in relation to six air pollutants in the overall analyses. The Excel form of our database ([S2 File](#)) is also available in the supporting information.

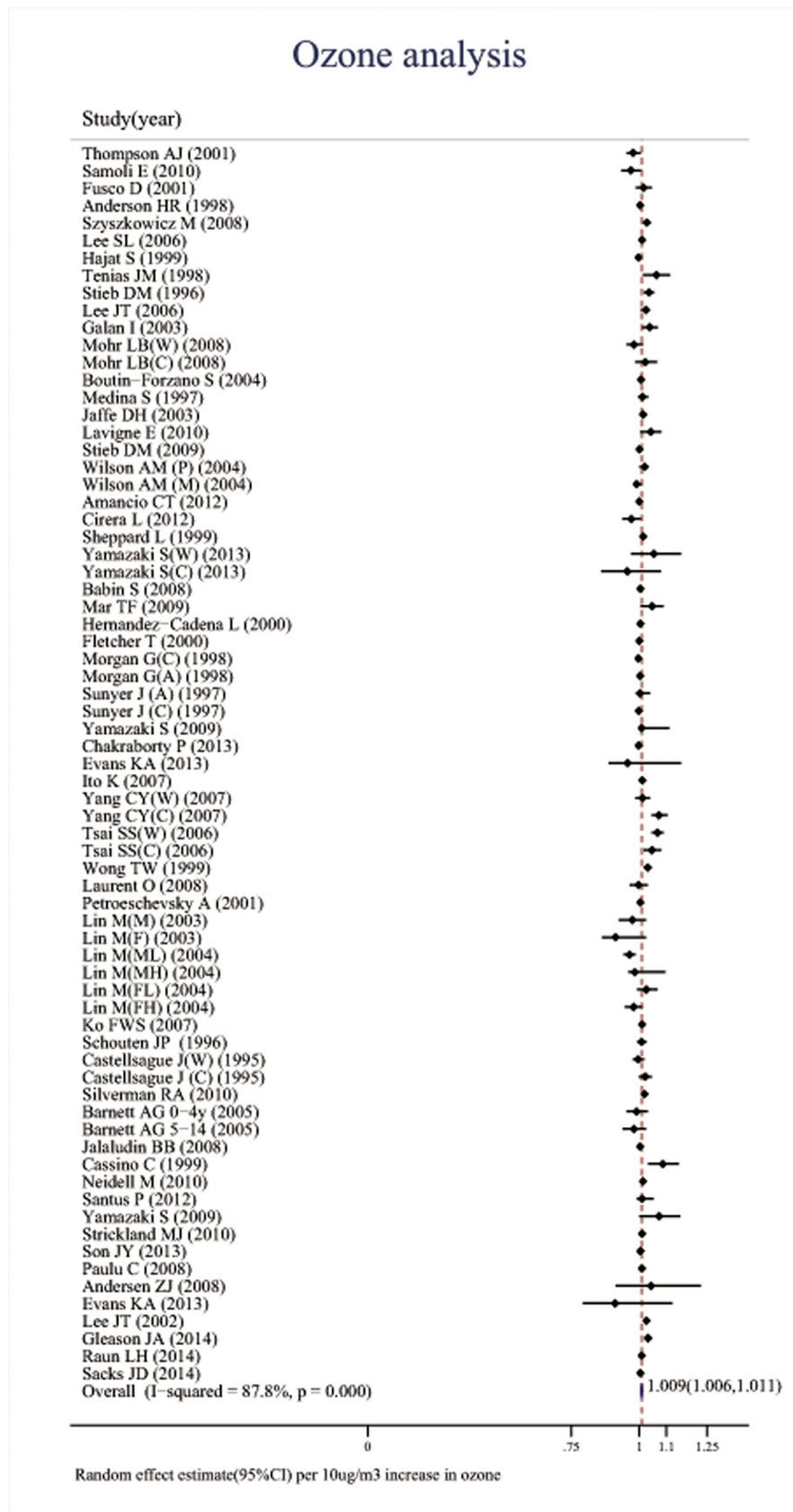


Fig 2. Association between ozone and ERVs/hospital admissions for asthma in the overall analyses.

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Carbon monoxide analysis

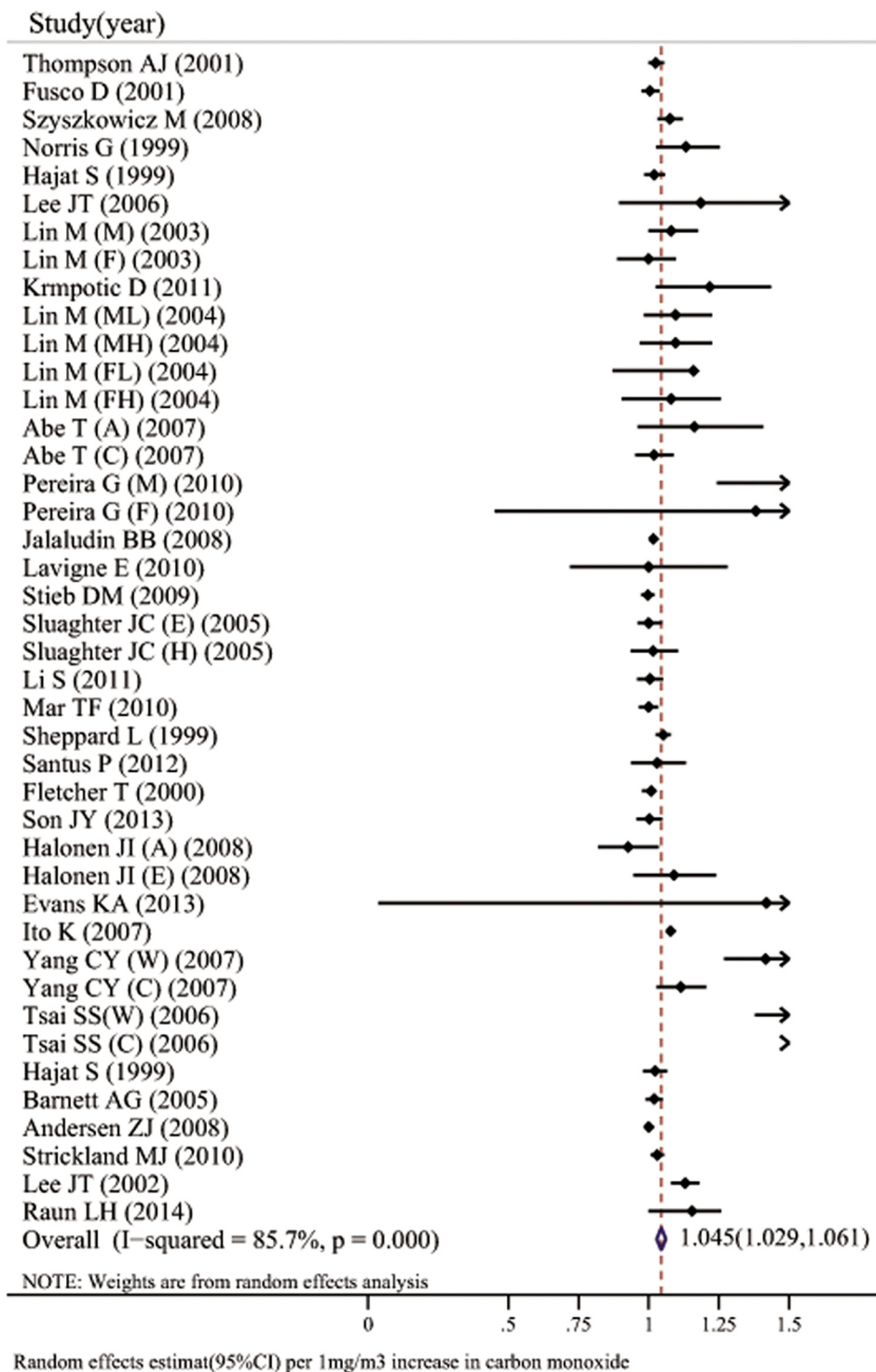


Fig 3. Association between carbon monoxide and ERVs/hospital admissions for asthma in the overall analyses.

doi:10.1371/journal.pone.0138146.g003

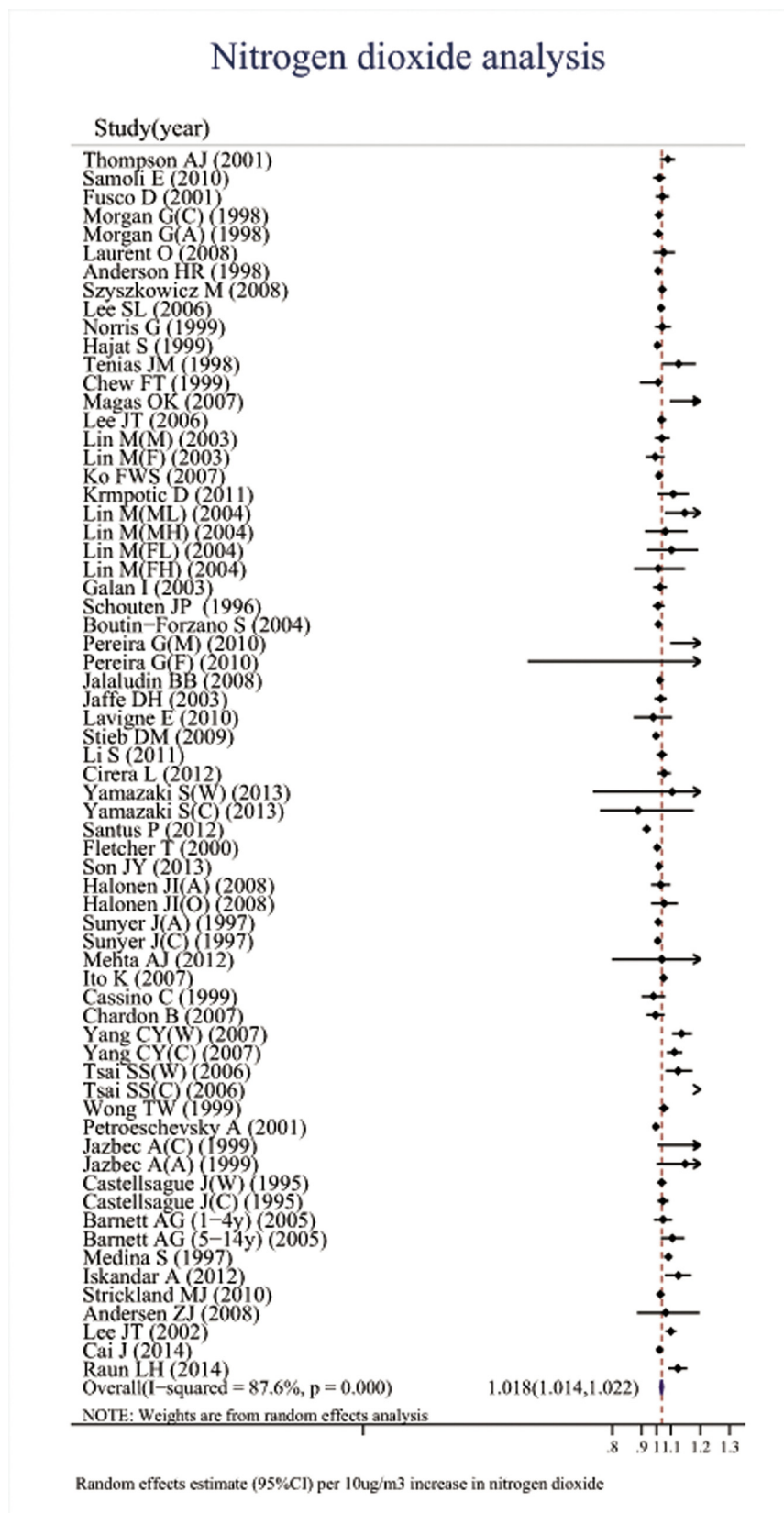


Fig 4. Association between nitrogen dioxide and ERVs/hospital admissions for asthma in the overall analyses.

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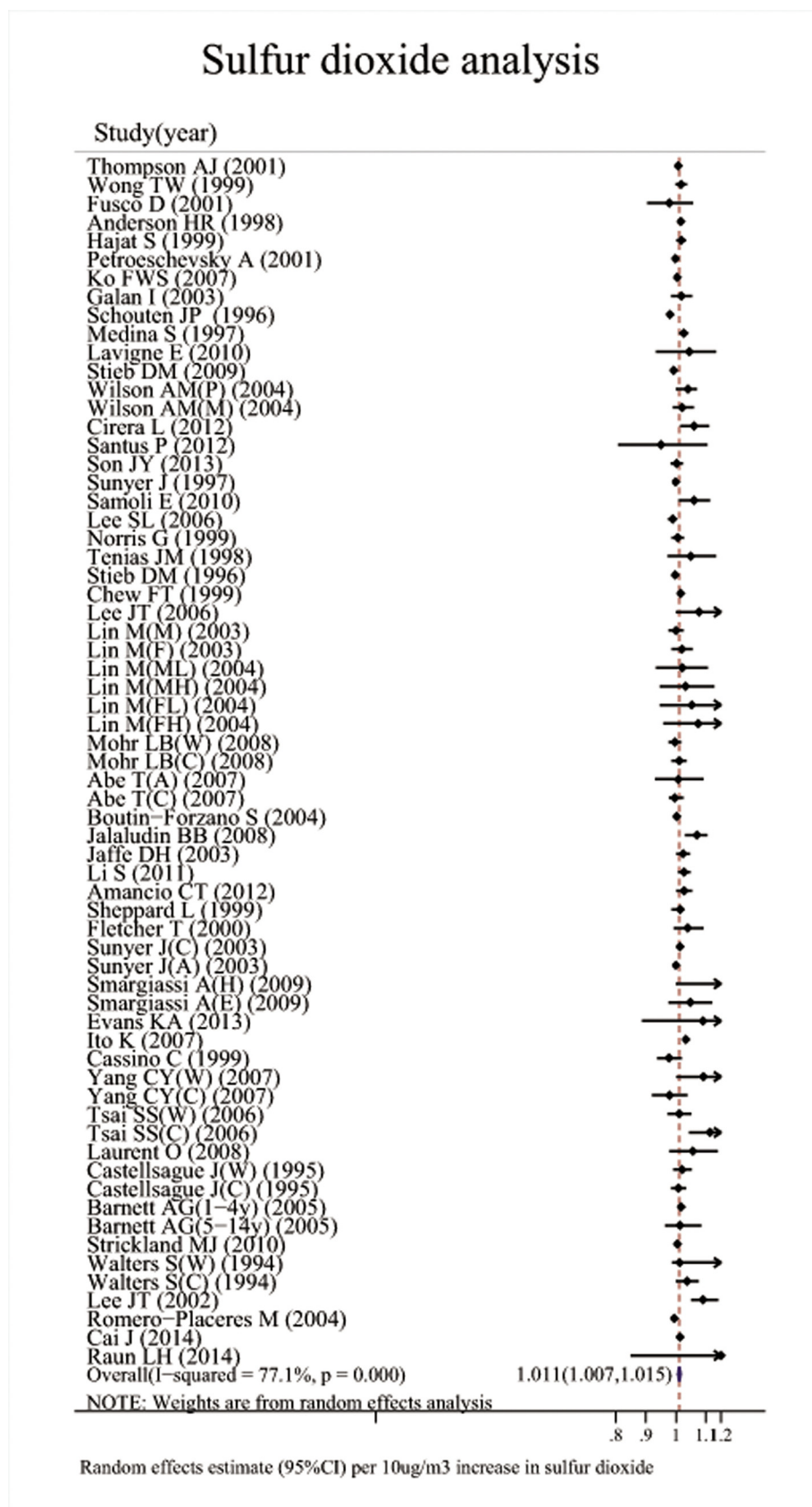


Fig 5. Association between sulfur dioxide and ERVs/hospital admissions for asthma in the overall analyses.

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PM10 analysis

Study(year)



Fig 6. Association between PM₁₀ and ERVs/hospital admissions for asthma in the overall analyses.

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PM_{2.5} analysis

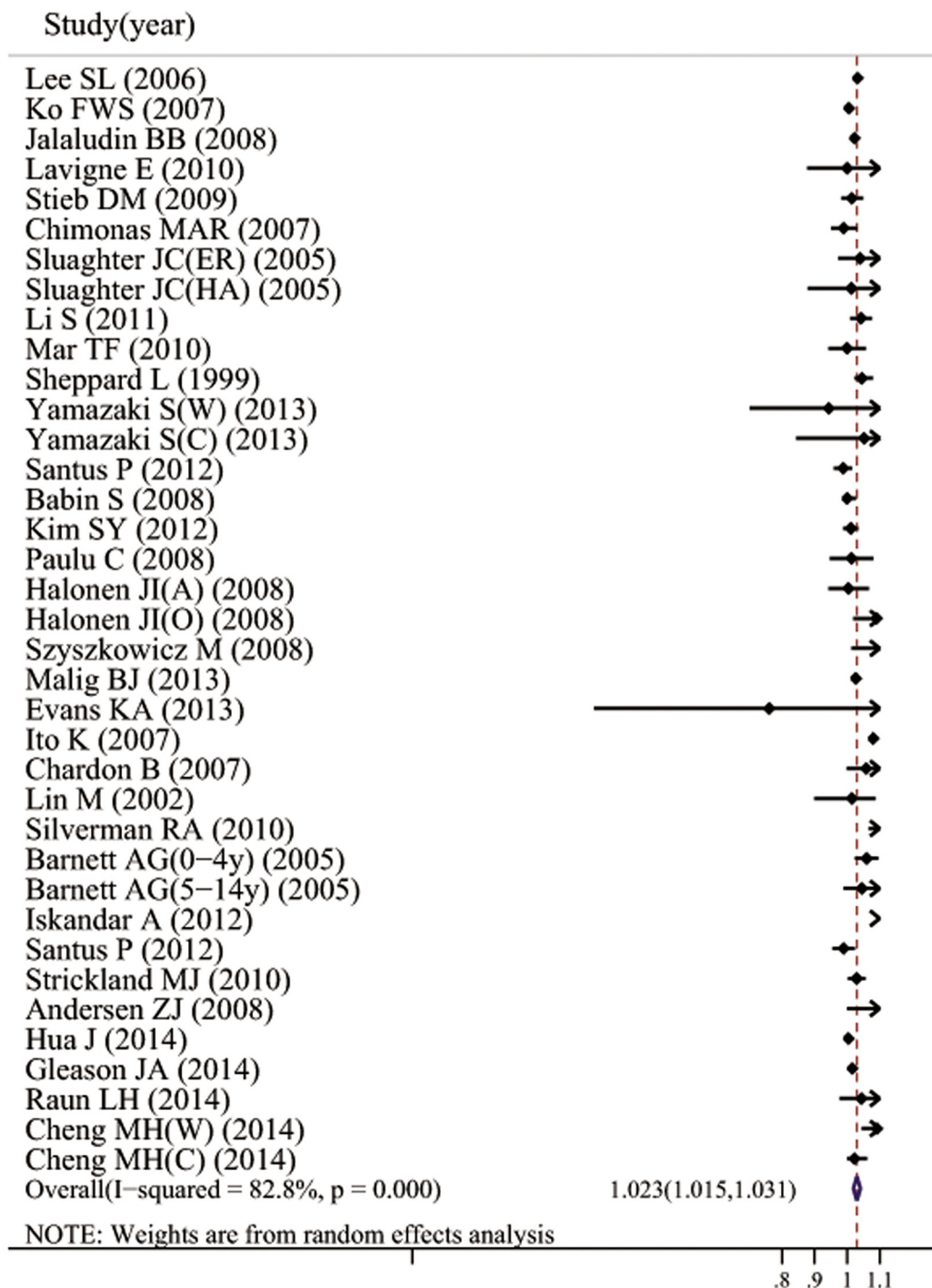


Fig 7. Association between PM_{2.5} and ERVs/hospital admissions for asthma in the overall analyses.

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Sensitivity analyses

Study quality. There were significant associations between air pollutants and asthma-related ERVs/hospitalizations in the sensitivity analyses, based on 29 studies fulfilling the quality score of 5 points without significant publication bias [O_3 : 12 studies; RR (95%CI), 1.005 (1.002, 1.008); $I^2 = 55.7\%$; Egger's test, $P = 0.15$; CO: 7 studies; RR (95%CI), 1.013 (1.000, 1.028); $I^2 = 13.6\%$; Egger's test, $P = 0.16$; NO_2 : 11 studies; RR (95%CI), 1.009 (1.004, 1.015); $I^2 = 55.7\%$; Egger's test, $P = 0.16$; SO_2 : 13 studies; RR (95%CI), 1.009 (1.003, 1.015); $I^2 = 57.9\%$; Egger's test, $P = 0.28$; PM_{10} : 7 studies; RR (95%CI), 1.006 (1.003, 1.009); $I^2 = 0.0\%$; Egger's test, $P = 0.53$; $PM_{2.5}$: 3 studies; RR (95%CI), 1.004 (1.000, 1.009); $I^2 = 0.0\%$; Egger's test, $P = 0.71$] ([Table 1](#), and [S1 Fig](#) in the online supplement for the funnel plots of the relative risks of emergency/hospital admissions for asthma in relation to six air pollutants regarding studies with a score of 5.)

Lag exposure. Lag exposure was 0 day for O_3 , NO_2 and SO_2 , and 1 day for CO, PM_{10} and $PM_{2.5}$. Likewise, associations between the six air pollutants and asthma-related ERVs/hospitalizations were statistically significant [O_3 : 9 studies; RR (95%CI), 1.010 (1.005, 1.014); $I^2 = 22.4\%$; Egger's test, $P = 0.99$; CO: 14 studies; RR (95%CI), 1.033 (1.001, 1.025); $I^2 = 0.0\%$; Egger's test, $P = 0.37$; NO_2 : 11 studies; RR (95%CI), 1.010 (1.002, 1.018); $I^2 = 65.9\%$; Egger's test, $P = 0.93$; SO_2 : 12 studies; RR (95%CI), 1.004 (1.000, 1.008); $I^2 = 41.8\%$; Egger's test, $P = 0.96$; PM_{10} : 12 studies; RR (95%CI), 1.005 (1.003, 1.008); $I^2 = 0.0\%$; Egger's test, $P = 0.42$; $PM_{2.5}$: 13 studies; RR (95%CI), 1.008 (1.003, 1.013); $I^2 = 6.6\%$; Egger's test, $P = 0.49$]. No publication bias was detected. ([Table 1](#), [Fig 8](#))

Subgroup analyses

Effect modification of O_3 , CO, NO_2 , PM_{10} and $PM_{2.5}$ on asthma-related hospital admission and ERVs (stronger association for hospital admissions) was found.

In subgroup analysis of sex, more pronounced associations were demonstrated in males [CO: 1.080 (1.047, 1.113), NO_2 : 1.028 (1.008, 1.038); PM_{10} : 1.025 (1.011, 1.039); $PM_{2.5}$: 1.013 (1.000, 1.018)]. No significant association was found in females, except for exposure to O_3 [1.023 (1.006, 1.040)].

There was a tendency towards stronger associations between ERVs/hospital admissions and the six air pollutants in children [CO: 1.018 (1.013, 1.023); NO_2 : 1.018 (1.013, 1.023); SO_2 : 1.016 (1.011, 1.022); PM_{10} : 1.013 (1.008, 1.018); $PM_{2.5}$: 1.025 (1.013, 1.037)] and the elderly [CO: 1.094 (1.002, 1.185); NO_2 : 1.019 (1.013, 1.024); SO_2 : 1.024 (1.005, 1.044)] as compared with the adults.

Stronger associations can also be observed in warm seasons [CO: 1.166 (1.099, 1.232), NO_2 : 1.029 (1.018, 1.040); SO_2 : 1.018 (1.010, 1.026); PM_{10} : 1.021 (1.007, 1.023); $PM_{2.5}$: 1.028 (1.011, 1.044)], except for ozone exposure.

Additional subgroup analyses demonstrated that long-lag patterns that were associated with significant heterogeneity yielded a stronger association than short-lag patterns ([Table 2](#)).

Discussion

Principal findings

We have systematically evaluated and confirmed the associations between short-term exposure to six air pollutants which are closely regulated by the environmental protection agencies and asthma-related ERV/hospitalizations, based on all available time-series and case-crossover studies. Low heterogeneity and no publication bias was observed in the sensitivity analyses.

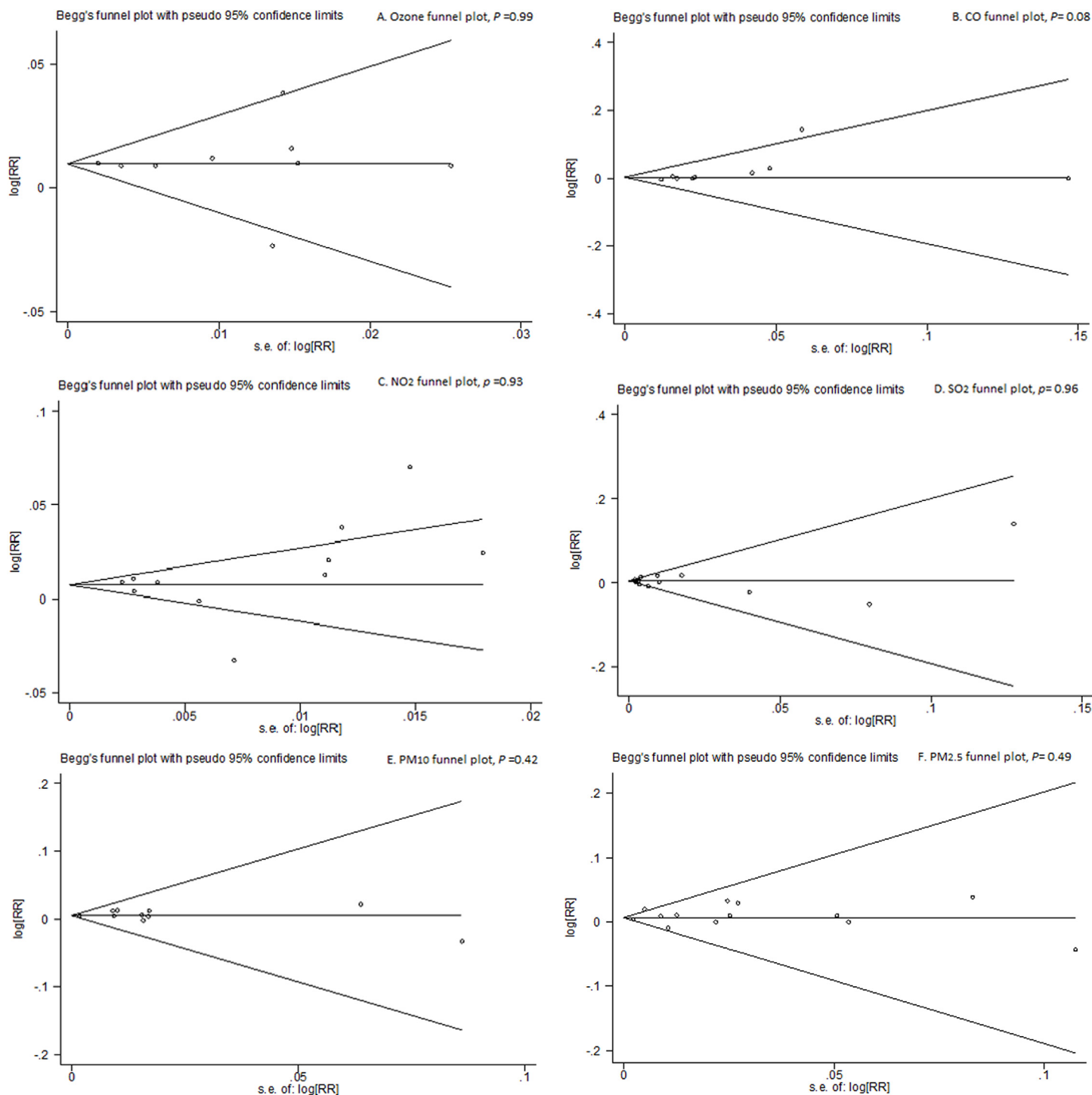


Fig 8. Funnel plots for relative risks of ERVs/hospital admissions for asthma in relation to the six air pollutants in lag pattern sensitivity analyses. A) Funnel plot for ozone; B) Funnel plot for CO; C) Funnel plot for NO₂; D) Funnel plot for SO₂; E) Funnel plot for PM₁₀; F) Funnel plot for PM_{2.5}.

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Our findings remained robust, despite potential publication bias resulting from the relatively small sample sizes in sensitivity analyses.

Table 2. Stratum-specific combined estimates of the association of six major air pollutants with ERVs and hospital admissions for asthma.

Stratum	Air pollutant (incremental unit)																							
	O ₃ (10 µg/m ³)				CO (1 mg/m ³)				NO ₂ (10 µg/m ³)				SO ₂ (10 µg/m ³)				PM ₁₀ (10 µg/m ³)				PM _{2.5} (10 µg/m ³)			
	No.	RR (95%CI)	I ²	No.	RR (95%CI)	I ²	No.	RR (95%CI)	I ²	No.	RR (95%CI)	I ²	No.	RR (95%CI)	I ²	No.	RR (95%CI)	I ²	No.	RR (95%CI)	I ²	No.	RR (95%CI)	I ²
Sex																								
Males	9	1.009 (0.993,1.025)	77	7	1.080 (1.047,1.113)	0	10	1.028 (1.008,1.038)	68	7	1.018 (0.996,1.040)	40	8	1.025 (1.011,1.039)	80	5	1.013 (1.000,1.018)	79						
Females	9	1.023 (1.006,1.040)	79	7	1.045 (0.966,1.124)	33	10	1.008 (0.987,1.029)	71	7	1.014 (0.996,1.021)	0	6	1.005 (1.000,1.009)	0	4	1.012 (1.000,1.020)	7						
Age																								
Children	42	1.008 (1.005,1.012)	89	29	1.018 (1.013,1.023)	70	39	1.018 (1.013,1.023)	87	37	1.016 (1.011,1.022)	53	25	1.013 (1.008,1.018)	83	20	1.025 (1.013,1.037)	82						
Adults	23	1.013 (1.008,1.018)	79	7	1.004 (0.963,1.045)	13	14	1.008 (1.003,1.014)	68	15	1.002 (0.997,1.007)	26	7	1.009 (1.003,1.014)	29	6	1.027 (1.007,1.047)	56						
Elderly	10	1.010 (1.002,1.017)	61	5	1.094 (1.002,1.185)	40	9	1.019 (1.013,1.024)	0	9	1.024 (1.005,1.044)	25	6	1.009 (1.004,1.015)	52	5	1.022 (1.014,1.031)	0						
Season																								
Cold	22	1.017 (1.007,1.028)	82	10	1.087 (1.020,1.154)	94	21	1.026 (1.016,1.038)	85	19	1.012 (1.002,1.022)	71	11	1.014 (1.006,1.023)	71	13	1.004 (0.997,1.011)	61						
Warm	29	1.016 (1.010,1.021)	87	12	1.166 (1.099,1.232)	85	23	1.029 (1.018,1.040)	84	22	1.018 (1.010,1.026)	43	14	1.021 (1.007,1.023)	74	15	1.028 (1.011,1.044)	91						
Type of admission																								
ERV	40	1.007 (1.004,1.010)	85	22	1.030 (1.011,1.049)	81	33	1.013 (1.008,1.018)	73	34	1.013 (1.007,1.019)	74	23	1.010 (1.006,1.014)	65	23	1.017 (1.006,1.029)	77						
HA	31	1.010 (1.006,1.014)	84	20	1.080 (1.048,1.112)	87	33	1.023 (1.017,1.029)	91	31	1.008 (1.002,1.014)	71	28	1.011 (1.008,1.015)	70	14	1.028 (1.017,1.040)	85						
Lag pattern																								
Lag ≤2days	49	1.007 (1.004,1.011)	82	32	1.036 (1.018,1.055)	78	44	1.013 (1.009,1.014)	70	48	1.008 (1.004,1.013)	73	35	1.008 (1.005,1.010)	67	27	1.021 (1.011,1.031)	83						
Lag >2days	23	1.010 (1.006,1.013)	90	11	1.082 (1.042,1.122)	92	22	1.028 (1.019,1.036)	92	17	1.022 (1.012,1.032)	79	16	1.016 (1.012,1.020)	4	10	1.031 (1.012,1.050)	78						

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Mechanisms of air pollutants on eliciting asthma exacerbations

The observed effects of the six major air pollutants on asthma ERVs/hospitalization are biologically plausible. The major mechanisms of individual air pollutants responsible for triggering asthma exacerbations are as follows:

** NO₂ and ozone have been implicated in eliciting lipid peroxidation of the cell membranes and the generation of various free radicals which collectively impair the structure and function of the asthmatic airways [101]. Furthermore, exposure to ozone and (or) NO₂ can also promote the release of inflammatory mediators (i.e. interleukin-8, granulocyte macrophage-colony stimulating factor [102],

** SO₂, a well-known inorganic chemical irritant, has been demonstrated to promote airway inflammation (increased levels of tumor growth factor- β in bronchoalveolar fluids) and eosinophilia, induce bronchospasm and airway fibrosis (a factor potentially leading to increased airway responsiveness) in asthma [103].

** Particulate matters harbor a more complex impact on asthmatic airways, since their deposition in the airways directly elicited airway inflammation, mucosal edema and cytotoxicity [104]. The convergence of regulatory signals generated by particulate matter-induced oxidative stress in dendritic cells and their interactions may also be responsible for asthma exacerbations [105]. Furthermore, the defective airway macrophage phagocytosis, resulting from increased prostaglandin E₂ levels, could have augmented the adverse effects of inhaled carbonaceous particulate matters on eliciting exacerbations [106].

** The direct association between CO and asthma is unfortunately less clearer [29,107]. It is plausible that CO might act as a surrogate of other noxious gases which are derived from incompletely combusted products. Moreover, CO seemed to confer greater adverse impacts on asthmatic children because of their immature lung development.

Interpretation

Most studies were limited at all age intervals, which constituted an important effect modifier [52]. In keeping with literature reports [16,24,30,38,57], we further confirmed that children and elderly people were more susceptible to asthma exacerbations. A plausible interpretation could be that children harbor immature lung growth and host-defense capacity and that, in elderly individuals, air pollution amplifies inflammatory responses of remodeled airways.

To date, effect modification by sex has not been well established [5,7,37–38,40,50,68]. The higher rate of asthma-related hospitalizations and ERVs in males could not justify the sex-related susceptibility, since the exposures (outdoor occupations, social activities) and biologic characteristics (i.e. hormonal levels, lung size and growth and airway inflammation) are different. Furthermore, greater effects of ozone on females were consistent with those in a previous report [108].

If the additive effects of air pollution were season-independent, then the PAFs and RRs would be higher during warm seasons because of fewer competing pollutants. However, unlike other pollutants, the association of ozone (a component of “photochemical cocktail” which is typically a warm-season pollutant [24,27,31–32,52,54,76,78,82,87]) and asthma exacerbations was similar between the warm and cold seasons. Unfortunately, the variability of temperature adjustment approaches and the lack of information regarding solar radiation and brightness have constrained our analyses in determining the seasonal modifications. Furthermore, limiting the analysis to the above-mentioned confounders might have minimized the number of eligible studies, possibly resulting in inaccurate conclusions.

Clinical significance

Despite the weak associations between air pollution and asthma exacerbations, the effects of air pollution were globally considerable because the RRs and percentage increase were derived from large cohorts in time-series studies, reflecting significant healthcare utilization, immense social and economical burden. Despite that the high PAFs for outdoor air pollution was essentially imputed from the prevalence of exposure of 100%, this assumption may still be reasonable, since epidemiological studies generally assigned outdoor average level to all individuals. Furthermore, we quantified asthma risk according to the changes in air pollution, since asthma-related ERVs/hospitalizations and the changes in air pollutant concentrations would assume a linear correlation, and hence, no positive threshold [109] could be established.

Limitations

First, the differences between ERVs and hospitalizations did have certain impacts on their utility for quantifying the observed associations with air pollution in subgroup analysis. However, a high degree of heterogeneity could be observed in analyses of all strata, including hospital admissions and ERVs. This might be linked to the various study design quality, inclusion criteria, analytic strategies and lag patterns. Heterogeneities were reduced dramatically among studies with a common analytic strategy (most commonly used lag patterns) or standardized protocol (study quality >5), highlighting the importance of standardized study protocol with the most appropriate lag.

Second, we did not analyze the association between air pollutants and other systemic diseases, therefore the multi-faceted adverse effects of air pollution could have been markedly diluted. Lower levels of air pollutants reportedly led to attenuated asthma symptoms [110–111], airway inflammation [112], lung function improvement [112] and less healthcare utilization and access to medications [113], confirming the roles of air pollution on eliciting asthma exacerbations.

Third, the coefficients from “single-pollutant” model were utilized despite potential interactions among different air pollutants. Regarding that the lack of crystal-clear exposure-asthma relationships hampered selection of additive or multiplicative model, and that a large number of complex parameters rendered the ideal ‘multivariate’ meta-analysis computationally impractical [114], we therefore independently analyzed the effects of individual pollutants [15, 17–18, 115].

Finally, the methodologies of lag selection remain controversial. Any particular lag selection would have excluded a considerable number of studies. In this study, we chose the most frequently used short lags (lag0, lag1 or lag0-1), since longer lags have been less consistently reported in previous literature and harbored a significant heterogeneity in our pooled analysis.

Practical implications

Our findings has called for the implementation of more stringent regulations on the traffic and industry, including the utilization of environmental-friendly fuels (i.e. liquid natural gas, diesel derived from biomass fuels, hydrogen gas), engines or techniques (such as hybrid vehicles, purely electric motors), and the utilization of filters or absorbers of noxious gases before release into the atmosphere, and the upgrading of traditional industrial facilities (i.e. cement production). The development of fine particle separating facial masks or intranasal gel might be useful for the patients who have difficulty in avoiding direct exposure to exposure, particularly at the workplace. The levels of air pollutants should also be incorporated into weather forecasts so as to issue alerts to population at risk, thus facilitating administration of preventative medications.

Conclusion

Short-term exposure to air pollutants confers an increased risk of asthma-related ERVs and hospital admissions. Our findings call for greater awareness of environmental protection and the implementation of effective measures to improve the quality of air, which may reduce the risks of adverse effects on the population's health. However, the effects need to be interpreted cautiously since longer lags are essential in time-series studies to better determine the effects of outdoor air pollution on asthma outcomes.

Supporting Information

S1 Fig. Funnel plots of the relative risks of ERVs/hospital admissions for asthma in relation to six air pollutants in the overall analyses and sensitivity analyses (studies with a score of 5). Fig A. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to CO in the overall analyses; Fig B. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to NO₂ in the overall analyses; Fig C. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to ozone in the overall analyses; Fig D. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM_{2.5} in the overall analyses; Fig E. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM₁₀ in the overall analyses; Fig F. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to SO₂ in the overall analyses; Fig G. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to CO in the sensitivity analyses regarding studies with a score of 5; Fig H. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to NO₂ in the sensitivity analyses regarding studies with a score of 5; Fig I. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to ozone in the sensitivity analyses regarding studies with a score of 5; Fig J. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM_{2.5} in the sensitivity analyses regarding studies with a score of 5; Fig K. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM₁₀ in the sensitivity analyses regarding studies with a score of 5; Fig L. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to SO₂ in the sensitivity analyses regarding studies with a score of 5.

(EPS)

S1 File. PRISMA checklist.

(DOC)

S2 File. The database of the association between six air pollutants and ERVs/hospital admissions for asthma in overall analyses (in Excel form).

(XLS)

S1 Table. Search strategies and main characteristics of all included studies.

(DOC)

Author Contributions

Conceived and designed the experiments: XYZ WJG JPZ QC. Performed the experiments: XYZ HD LNJ SWC. Analyzed the data: XYZ MQ YXZ. Wrote the paper: XYZ WJG. Provided critical review of the manuscript and approved the final submission: WJG QC.

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<div><p>Fig A. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to CO in the overall analyses; Fig B. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to NO₂ in the overall analyses; Fig C. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to ozone in the overall analyses; Fig D. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM_{2.5} in the overall analyses; Fig E. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM₁₀ in the overall analyses; Fig F. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to SO₂ in the overall analyses; Fig G. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to CO in the sensitivity analyses regarding studies with a score of 5; Fig H. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to NO₂ in the sensitivity analyses regarding studies with a score of 5; Fig I. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to ozone in the sensitivity analyses regarding studies with a score of 5; Fig J. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM_{2.5} in the sensitivity analyses regarding studies with a score of 5; Fig K. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to PM₁₀ in the sensitivity analyses regarding studies with a score of 5; Fig L. Funnel plot of the relative risks of ERVs/hospital admissions for asthma in relation to SO₂ in the sensitivity analyses regarding studies with a score of 5.</p></div>

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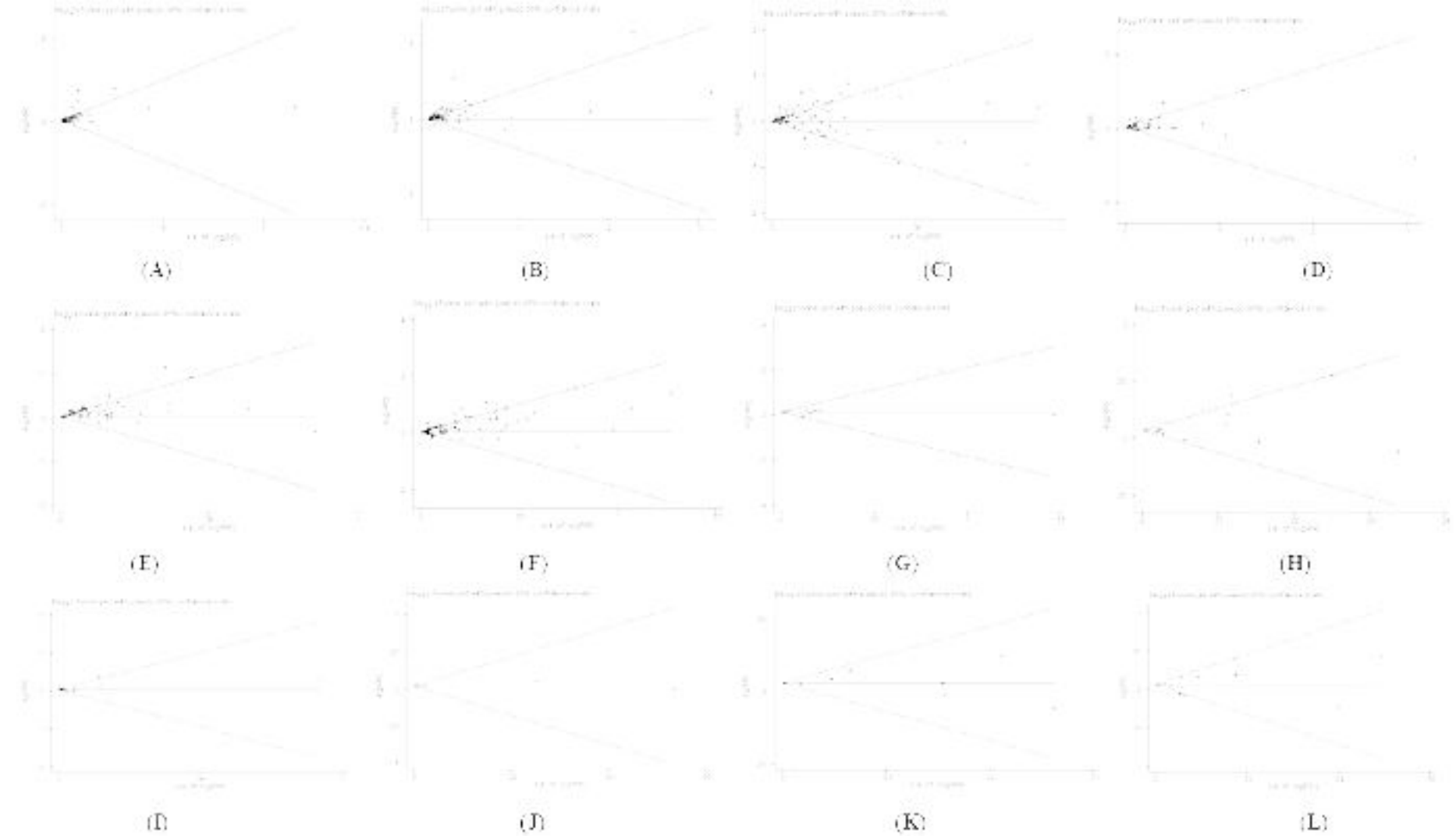
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5,6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6,7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7,8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7,8



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8,9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9,10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10,11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

E-Appendix: Search strategies

Database(s): EMBASE 1988 to May 2014, Ovid MEDLINE In-process & Other Non-indexed Citations and Ovid MEDLINE 1948 to present, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane Database of Systematic Reviews 2005 to May 2014.

#	Search strategies	Results
1	exp Asthma/	182357
2	exp Wheeze	13635
3	exp 'respiratory tract allergy'	213770
4	Or 1-3	219475
5	exp air pollution/	114335
6	exp Particulate Matter/	23190
7	((air or atmosphere or atmospheric) adj (pollution * or polluted or pollutant* or contamination or contaminated)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui, kw, tx, ct]	156170
8	('particulate matter' or PM2.5 or PM10).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui, kw, tx, ct]	32864
9	exp ozone/	20388
10	exp Carbon Monoxide/	27567
11	exp Carbon Monoxide intoxication /	5042
12	exp nitrogen dioxide/	7833
13	exp Sulfur Dioxide/	12095
14	(ozone or 'O ₃ ' or 'carbon monoxide' or carbon monoxide or 'CO' or 'nitrogen dioxide' or 'NO ₂ ' or 'N ₂ O ₄ ' or 'dinitrogen tetraoxide' or 'nitrogen peroxide' or 'nitrogen tetraoxide' or nitrogen oxide or 'nitrous dioxide' or 'sulphur dioxide' or 'sulphur dioxide' or 'sulfurous anhydride' or 'SO ₂ ').mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui, kw, tx, ct]	1078084
15	Or 5-14	1214094
16	#4 and #15	6274
17	limit 16 to human [Limit not valid in CCTR,CDSR; records were retained]	2742
18	remove duplicates from 17	1091

Table S1. Main characteristics of the included studies

Study	Location/Period	Quality score	Sample size	Population	Diagnosis standard	Type of study	Pollutants and concentration						Measurement quality score (0-1 point)	Lag pattern(single day/ mean days)	Adjustments (long-term trend, seasonality, temperature, humidity, pressure, day for the week, holiday and influenza epidemics)
							CO	PM ₁₀	PM _{2.5}	SO ₂	NO ₂	Ozone			
Studies with emergency room visit indices															
Thompson AJ ³ 2001	Belfast, Northern Ireland/ 3 yr	5	-	Children	-	TS	0.65	28.4	-	47.1	43.6	38.4	1	Both	long-term trend, seasonality, temperature, humidity, day of week, public holiday
Sunyer J ¹⁴ 1997	Barcelona, Helsinki, Paris, London, 6yr	5	75190	Children + adults	ICD-9: 493	TS				27.8	49.8	43.8	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemics
Chardon B ¹⁵ 2007	Paris, 3yr	5/4 ^b	8027	General	ICPC2.R96	TS		23.0	14.7		44.4		1/0 ^b	Cumulative	long-term trends, seasonality, temperature, humidity, day-of-week, influenza epidemic, pollen
Halonen JI ¹⁶ 2008	Helsinki, Finland, 6 yr	5	4807	General	ICD-9: 493	TS	0.5 ^a		9.5		28.2		1	Single	long-term trends, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemics
Hajat S ³⁰	London,UK, 3yr	5	38653	General	ICD-9 J493	TS	1.0	28.5		21.2	69.0	37.5	1	Both	Long term trend, seasonality,

1999															temperature, humidity, day-of-week, influenza epidemic
Galan I ⁴¹ 2003	Madrid, Spain, 3yr	5	4827	General	ICD-9 J493	TS		32.1		23.6	67.1	45. 8	1	Single	Long-term trend, seasonality, temperature, humidity, pressure, day-of-week, public holiday, influenza epidemics
Atkinson RW ⁵¹ 2001	Barcelona, Birmingham, London, Milan, the Netherlands, Paris, Rome, and Stockholm, 4yr	5	-	General	ICD-9 J493	TS		29.3					1	Single	long-term trend, seasonality, temperature, humidity, day for the week, holiday and influenza epidemics
Medina S ⁵⁵ 1997	Paris, France, 4yr	5	-	General	SOS-Medecins R01	TS				19.0	56.0	34. 0	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemics
Stieb DM ⁵⁸ 2009	Canada(Montr eal, Ottawa, Edmonton, Saint John, Halifax, Toronto, Vancouver), 10yr	5/4 ^b	83563	General	ICD-9/10 493; J45	TS	0.8	8.3	20.6	14.6	37.6	40. 0	0/1 ^a	Single	long-term trend, seasonality, temperature, humidity, day-of-week, holiday

Wilson AM ⁶⁰ 2005	Portland, Maine, Manchester, New Hampshire, 2yr	5	7300	General	ICD-9 J493	TS				39.4 ^b		41. 0	1/0(ozone)	Single	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
Sunyer J ⁷⁷ 2003	Birmingham, London, Milan, the Netherlands, Paris, Rome, Stockholm, 2-8 yr	5	-	Children + adults	ICD-9 J493	TS				17.6			1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, influenza epidemic
Szyszkowicz M ²⁷ 2008	Edmonton, Canada, 10yr	4	62563	General	ICD-9 J493	TS	0.9	22.6	8.5		45.0	39. 9	1	Single	Long term trend, temperature, seasonality humidity, day-of-week
Norris G ²⁹ 1999	Seattle, US, 27mon	4	1458	Children	ICD-9 J493	TS		21.7		17.1	41.5		1	Single	Long term trend, seasonality temperature, humidity, day-of-week
Tenias JM ³¹ 1998	Valencia, Spain, 3 yr	4	734	Adults + elderly	-	TS				26.6	57.7	62. 8	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemics
Stieb DM ³⁴ 1996	Saint John, New Brunswick, Canada, 8yr	3	1163	General	-	TS						89. 1	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week,

Mohr LB ⁴³ 2008	St. Louis, US, 2yr	3	12836	Children	ICD-9 J493	TS			-		-	-	1	Single	Long-term trend, seasonality, temperature,
Castellsague J ⁴⁶ 1995	Barcelona, Spain, 5yr	3	6019	Adults+ elderly	-	TS				45.5	58.0	70.5	1	Cumulative	Long term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
Chakraborty p ⁴⁷ 2013	Kolkata city, India, 2yr	4	2703	Children	ICD-9 J493+ICD-10 J45/4d	TS		3.8				1.3 ^c	1	-	Long term trend, seasonality, temperature, humidity
Jaffe DH ⁵⁶ 2003	Cincinnati, Cleveland, and Columbus, US, 5yr	4	4416	Children+ adults	ICD-9 J493	TS		49.5		28.8	10.1	35. 8	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Mar TF ⁶⁴ 2010	Tacoma, Washington, 3.5 yr	3	10091	General	-	TS	1.2		12.3				1	Single	long-term trend, seasonality, temperature, humidity
Cirera L ⁶⁵ 2012	Cartagena, Spain, 4yr	4	1617	General	-	TS				32	51	81	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemic
Cassino C ⁶⁶ 1999	New York, US, 3.5yr	4	285	Adults	NAEPP/ ICD-9 J493-493.9	TS	1.2			29.4	92.4	37.5 ^c	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Babin S ⁷⁷ 2008	Washington DC, US, 11yr	4	61218	General	ICD-9 J493	TS		-	-			-	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Mar TF ⁷⁹	Seattle,	3	3217	Children	ICD-9 J493-493.9	TS						84.	0	Single	long-term trend, seasonality,

2009	Washington, US, 4yr			+ adults								0			temperature, humidity, day-of-week
Hernandez-C adena L ⁸¹ 2000	Ciudad Juárez, Chihuahua, Mexico, 1yr	4	2459	General	ICD-9 J493	TS		34.4 6				110 .6	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
Ito K ⁸⁷ 2007	New York, US, 4yr	3		General	-	TS	1.6 ^a	15.7		22.3	31.1	65. 1	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
Cadelis G ⁸² 2014	Guadeloupe, France, 1yr	3	836	Children	ICD10: J45-J46	TS		19.2					1	Both	long-term trend, seasonality, temperature
Jazbec A ⁴² 1999	Zagreb, Croatia, 1.5yr	0	1372	Children +adults	-	TS					45.1		0	Cumulative	long-term trend, seasonality,
Abe T ⁴⁸ 2007	Tokyo, Japan, 1 yr	2	6447	General	-	TS	1.4			15.1			1	Single	seasonality, temperature, humidity
Chimonas MAR ⁶¹ 2007	Anchorage, Alaska, 3.5yr	2	11037	Children	ICD-9 J493	TS		27.6	6.1				0	Single	long-term trend, seasonality, temperature
Strickland MJ ⁴ 2010	Atlanta, US, 11 yr	5	91386	Children	ICD-9 J493	CC	1.1 ^b	23.8	16.4	30.9 ^b	47.8 ^b	97.3	1	Both	long-term trend, seasonality, temperature, humidity, day of week and influenza epidemics
Paulu C ¹¹ 2008	Maine, US, 4yr	5	8020	General	ICD-9: 493	CC			8.5			83. 6	1	Both	long-term trend, seasonality, temperature, humidity, day of week, holiday
Jalaludin BB ⁵⁴	Sydney ,Austral ia, 5 yr	5	317724	Children	ICD-9 J493	CC	1.0	16.8	9.4	3.1	47.6	67. 7	1	Both	long-term trend, seasonality, temperature, humidity,

2008															day-of-week, public holiday
Lavigne E ⁵⁷ 2010	Windsor, Canada, 7 yr	5	3728	General	ICD-10: J45, J46, T486, Y556, Z825	CC	0.4		7.3	5.3	17.4	41. 5	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
Malig BJ ²² 2013	California, 4yr	4	74978	General	ICD-9 J493	CC		35.0	12.1				1	Single	long-term trends, seasonality, temperature, humidity, day of week
Boutin-Forza no S ⁴⁸ 2004	Marseille, France, 1yr	3	549	Children + adults	-	CC				22.5	34.9	50. 1	1	Single	long-term trend, seasonality, temperature, humidity
Yamazaki S ⁷² 2013	Himeji, Japan, 2yr	3	956	Children	-	CC		34.3	21.2		22.9	55. 3	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Santus P ⁷⁵ 2012	Milan, Italy, 2yr	3	3569	General	-	CC	1.5	47.1	32.8	4.13	102. 6	74.3	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
Yamazaki S ⁷⁷ 2009	Tokyo, Japan, 1yr	4	403	Children+ adults	-	CC			19.1		45.3	60. 2	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week, holiday
Mehta AJ ⁶ 2012	Switzerland, 2yr	1	147	adults	-	CC					33.9		1	Single	Long-term trend, influenza epidemics
Laurent O ²³ 2008	SMA, France 5yr	2	4677	General	-	CC		22.6		8.9	36.0	57.7	1	Both	temperature, pressure, humidity, influenza epidemic and pollen count
Pereira G ⁵⁰ 2010	Perth, Australia, 5 yr	2	603	Children	ICD-10J46	CC	0.3				12.9		1	Single	-

Evans KA ⁶⁸ 2013	New York, US, 3yr	0	71	Children	-	CC	0.5		8.6	15.4		55. 9	0	Both	Temperature, humidity
Gleason JA ⁸⁷ 2014	New Jersey, US 4yr	5	21,854	Children	ICD-9 J493	CC			-			-	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, viral upper respiratory infections
Sacks JD ⁸⁸ 2014	North Carolina, US, 3yr	5	121,621	General	ICD-9 J493	CC						93. 4	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, viral upper respiratory infections
Raun LH ⁸⁹ 2014	Houston, Texas, US, 7yr	3	11,754	General	-	CC	0.3		10.7	4.3	21.6	76.7	0	Both	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, viral upper respiratory infections

Study	Location /Period	Quality score	Sample size	Population	Diagnosis standard	Type of study	Pollutants and concentration						Measurement quality score (0-1 point)	Lag pattern(single day/ mean days)	Adjustments (long-term trend, seasonality, temperature, humidity, pressure, day for the week, holiday and influenza epidemics)
							CO	PM ₁₀	PM _{2.5}	SO ₂	NO ₂	Ozone			
Studies with hospital admission indices															
Samoli E ⁷ 2010	metropolitan area of Athens, 3yr	5	3601	Children	ICD-9: 493	TS		43.9		16.8	84.8	70.9	1	Single	long-term trends, seasonality, temperature, humidity, day of week, public holidays and influenza epidemics
Wong TW ¹⁹ 1999	Hong Kong, 1yr	5	-	General	ICD-9 J493	TS		45.0		17.1	51.4	24.2	1	Both	long-term trends, seasonality, temperature, humidity, days-of-week, public holiday
Fusco D ²⁰ 2001	Rome, Italy 2yr	5	4635	General	ICD-9 J493	TS	3.6			9.1	86.7	27.0	1	Single	long-term trends, seasonality, temperature, humidity, day- of-week, public holiday, influenza
Morgan G ²¹ 1998	Sydney, Australia 5yr	5	-	General	ICD-9 J493	TS		19.2			30.8	53.6	1	Single	long-term trends, seasonality, temperature, humidity, day-of-week, holiday
Anderson HR ²⁴ 1998	London, UK 5yr	5	63039	General	ICD-9 J493	TS				32	76.4	33.2	1	Both	Long time trends, temperature, humidity, seasonality, days of the week, public holidays and influenza epidemics

Lee SL ²⁸ 2006	Hong Kong, 5yr	5	26663	Children	ICD-9 J49	TS		56.1	45.3	17.7	64.7	28.6	1	Single	Long term trend, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemic
Petroeschewsky A ³⁴ 2001	Brisbane, Australia, 8yr	5	13246	Children + adults	ICD-9 J493	TS				11.7	28.5	40.7	1	Both	Long term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
Ko FWS ³⁸ 2007	Hong Kong, China, 6yr	5	69176	General	ICD-9 J493	TS		52.5	36.4	18.8	53.2	43.4	1	Both	Long term trend, seasonality, temperature, humidity, day-of-week, public holiday
Krmpotic D ³⁹ 2011	Zagreb, Croatia, 3yr	5	808	Adults	ICD-10 J493	TS	0.8	39.0			30.3		1	Single	Long term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
Romero-Placeres M ⁵⁹ 2004	Habana, Cuba, 2yr	5	44 029	General	ICD-9 J45	TS		59.2		21.1			1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, public holiday
Morgan G ⁷¹ 2010	Sydney, Australia, 8.5yr	5	65448	Children + adults	ICD-9 J493	TS		62.0					1	Single	long-term trend, seasonality, temperature, humidity, day of week, influenza epidemic
Fletcher T ⁸⁰ 2000	San Paulo, Brazil, 2yr	4/5	-	Children	ICD-9 J493	TS	5.8	64.9		18.3	174.3	63.4 ^c	1	Single	long-term trend, seasonality, temperature, humidity, day of week, holiday
Son JY ⁵ 2013	Seoul, Busan, Incheon, Daegu, Daejeon,	4	-	General	ICD-9 J493	TS	1.0 ^a	52.4		15.7	48.0	71.7	1	Both	long-term trend, seasonality, temperature, humidity, pressure, day-of-week

	gwangju, and Ulsan, Korea, 6yr														
Andersen ZJ ⁸ 2008	Copenhagen, Denmark, 3yr	4	-	Children	ICD-9: 493	TS	0.36	24.0	10.0		22.6	51.4	0	Cumulative	long-term trends, seasonality, temperature, humidity, day-of-week, public holidays, influenza epidemics
Kim SY ¹⁰ 2012	Denver, US, 4yr	4	10590	General	ICD-9: 493	TS			8.0				1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Lee JT ¹¹ 2002	Seoul, Korea, 2 yr	4	6436	General	ICD-10 J45-J46	TS	2.3	64.0		22	64.7	77.1	1	Cumulative	long-term trend, seasonality, temperature, and humidity, day-of-week
Delfino RJ ¹³ 1994	Montreal, Canada, 4yr	3	10385	General	ICD-9: 493	TS		29.5					0	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Ye F25 2001	Tokyo, Japan, 15yr	3	2200	Elderly	ICD-9 J493	TS		46.0					1	Single	Long time trends, seasonality, temperature
Lee JT36 2006	Seoul, Korea, 1 yr	4	2952	Children	ICD-9 J493	TS	8.0 ^a	135. 2		25.0	156.2	63.9	1	Single	Long term trend, seasonality, temperature, humidity, day-of-week,
Lin M ⁴⁰ 2004	Vancouver, British Columbia, Canada, 12yr	4	3754	Children	ICD-9 J493	TS	1.2			13.6	38.4	60.0 ^c	1	Both	Long term trend, seasonality, temperature, humidity, day-of-week
Schouten	Amsterdam,	4	-	General	ICD-9 J493	TS				28.0	50.0	69.0	0	Both	long-term trend, seasonality,

JP ⁴⁵ 1996	the Netherlands, 12yr														temperature, humidity, day-of-week, public holiday, influenza epidemics
Silverman RA ⁵² 2010	New York, US, 7yr	4	75383	General	ICD-9 J493	TS			13.0			87.9	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of- week
Amancio CT ⁶⁵ 2012	San Paulo, Brazil, 2yr	4	841	Children	ICD10: J45	TS		25.2		4.6		74.3	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Sheppard L ⁷⁰ 1999	Seattle, Washington, 8yr	3/4 ^b	7837	Children + adults	ICD-9 J493	TS	2.3	31.5	16.7	22.9		65.1	1/0 ^a	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Neidell M ⁷⁵ 2010	Southern California, 8yr	4	-	General	ICD-9 J493	TS						175.7	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week
Fung KY ⁸¹ 2005	London, Ontario, Canada, 5yr	4	?	Children + adults	ICD-9 J493	TS		38.0					1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
Hua J ⁸³ 2014	Shanghai, China, 7yr	4		Children	ICD10: J45	TS			34.0				1	cumulative	long-term trend, seasonality, temperature, humidity
Walters S ⁹ 1994	Birmingham, UK, 2yr	2	-	General	ICD-9: 493	TS				39.1			1	Cumulative	Non declared
Magas OK ³⁵ 2007	Oklahoma city metropolitan area, US, 3yr	1	1270	Children	ICD-9 J493	TS					-		0	Single	Temperature, day-of-week, humidity, holiday

Barnett AG ⁵³ 2005	Australia (Brisbane, Canberra, Melbourne, Perth, and Sydney), New Zealand (Auckland, Christchurch), 3yr	5	-	Children	ICD-9 J493	CC	1.1	17.6	9.4	7.0	17.6	49.6	1	Cumulative	long-term trend, seasonality, temperature, humidity, day for the week, holiday and influenza epidemics
Yang CY ¹⁷ 2007	Taipei, 8yr	4	25602	General	ICD-9 J493	CC	1.7	49.0		12.3	63.0	44.0	1	Cumulative	Long-term trend, seasonality, temperature, humidity
Tsai SS ¹⁹ 2006	Kaohsiung, 8yr	4	17682	General	ICD-9 J493	CC	1.00	76.7		27.1	55.9	56.3	1	Cumulative	long-term trends, seasonality, temperature, humidity
Lin M ³⁷ 2003	Toronto, Ontario, Canada. 13yr	4	7319	Children	ICD-9 J493	CC	1.5			15.3	51.8	65.1 ^c	1	Both	Long term trend, seasonality, temperature, humidity, day-of-week,
Lin M ⁴⁴ 2002	Toronto, Canada, 14yr	4	7319	Children	ICD-9 J493	CC		30.2	18.0				1	Both	Long-term trend, seasonality, temperature, humidity, day-of-week
Iskandar A ⁶⁸ 2012	Copenhagen, Denmark, 8yr	4	8226	Children	ICD-10 J45-46	CC		26.2	10.3		23.3		1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week
Cheng MH ⁸⁵ 2014	Taipei, China, 5yr	3	10,440	General	ICD-9 J493	CC			30.0				1	Cumulative	long-term trend, seasonality, temperature, humidity

Cai J ⁸⁶ 2014	Shanghai, China 7yr	4	15,678	General	ICD-10 J45	TS		88.0		45. 0	60. 0		1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
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Study	Location/Period	Quality score	Sample size	Population	Diagnosis standard	Type of study	Pollutants and concentration						Measurement quality score (0-1 point)	Lag pattern(single day/ mean days)	Adjustments (long-term trend, seasonality, temperature, humidity, pressure, day for the week, holiday and influenza epidemics)
							CO	PM ₁₀	PM _{2.5}	SO ₂	NO ₂	Ozone			
Studies with both emergency room visit and hospital admission indices															
Chew FT ³³ 1999	Singapore, 5yr	4	6000(HA), 23000(ER)	Children	ICD-9 J493	TS				38.1	18.9		1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Sluaghter JC ⁶² 2005	Spokane, Washington DC, US, 7yr	4	2191/2373	General	ICD-9 J493	TS	1.6-3 .8	7.9-4 1.9	4.2-2 0.2				1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
Smargiassi A ²⁶ 2009	0.5–7.5 km of the refinery stacks, Montreal Canada, 8yr	4	1579/263	Children	ICD-9 J493	CC				12.3			1	Both	Long time trends, seasonality, temperature, humidity, day-of-week
Li S ⁶³ 2001	Detroit, Michigan, 2yr	4	7063	Children	ICD-9 J493	CC	0.5		15.0	10.8	34.4 ^c		1	Both	long-term trend, seasonality, temperature, humidity, day-of-week

a: 8-hr maximum concentration; c: daily averaged concentration; ICD: International Classification of Diseases; ICPC2: International Classification of Primary Care 2; GP: GP's house calls; NAEPP: National Asthma Education and Prevention Program; PC: primary care visits; TS: time-series study; CC: case cross over studies.
The default concentration for CO, NO₂, SO₂, PM₁₀ and PM_{2.5} is 24-h averaged concentration, while 8-hr maximum concentration for ozone