

The impact of PM_{2.5} on asthma emergency department visits: a systematic review and meta-analysis

Jingchun Fan^{1,2,3} · Shulan Li⁴ · Chunling Fan⁵ · Zhenggang Bai^{1,2} · Kehu Yang^{1,2}

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Abstract Although the relationship between asthma and exposure to fine particulate matter (PM_{2.5}) has been frequently measured, reported conclusions have not been consistent. As emergency department (ED) visits are an effective way to estimate health outcomes for people with asthma and short-

term exposure to PM_{2.5}, this review systematically searched five databases without language or geographical restrictions from inception to January 13, 2015 to study the impact of PM_{2.5} on asthma ED visits. A random-effects model was used to calculate the pooled risk ratio (RR) and 95 % confidence intervals (CI). With respect to short-term effects, asthma ED visits increased at higher PM_{2.5} concentrations (RR 1.5 % per 10 µg/m³; 95 % CI 1.2–1.7 %), and children were more susceptible (3.6 % per 10 µg/m³; 95 % CI 1.8, 5.3 %) than adults (1.7, 95 % CI 0.7 %, 2.8 %) to increased PM_{2.5}; the ED visits increased during the warm season by 3.7 % (95 % CI 0.5, 6.9 %) per 10 µg/m³ increase in PM_{2.5}, which was higher than the corresponding increase during the cold season (2.6, 95 % CI 0.7–4.6 %). This demonstrates that ambient PM_{2.5} has an adverse impact on asthma ED visits after short-term exposure and that children are a high-risk population when PM_{2.5} concentrations are high, particularly in warm seasons, during which measures should be taken to prevent PM_{2.5}.

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Shulan Li contributed equally to this work.

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✉ Kehu Yang
yangkh2006@163.com

Jingchun Fan
fan_jc@126.com

Shulan Li
vivian138lan@163.com

Chunling Fan
fanchl8@sina.com

Zhenggang Bai
baizhenggang@126.com

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Introduction

Fine particulate matter (PM_{2.5}) describes air pollutants with tiny airborne particles or droplets two and one half microns or less in width. Their small size makes them readily inhalable and capable of penetrating deep into airways. Penetration of particles is not wholly dependent on their size; shape and chemical composition also play a role. A wide range of morbidity indicators has been investigated in epidemiological studies, and exposure to PM_{2.5} has been associated with adverse human health impacts such as asthma symptoms, missed school days, hospitalization and the frequency of asthma episodes (Jacquemin et al. 2015; O'Connor et al. 2008; Zora

- ¹ Key Laboratory of Evidence Based Medicine and Knowledge Translation of Gansu Province, No. 199 Donggang West Road, Chengguan District, Lanzhou, Gansu 730000, China
- ² Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, No. 222 Tianshui South Road, Chengguan District, Lanzhou, Gansu 730000, China
- ³ First Clinical Medical College, Lanzhou University, No. 1 Donggang West Road, Chengguan District, Lanzhou, Gansu 730000, China
- ⁴ Department of Ultrasound, People's Hospital of Gansu Province, No. 204 Donggang West Road, Chengguan District, Lanzhou, Gansu 730000, China
- ⁵ Department of Clinical Pharmacy, Gansu Provincial Cancer Hospital, No. 2 Xiaoxihu East Street, Qilihe District, Lanzhou, Gansu 730050, China

et al. 2013). Asthma is a common condition affecting approximately 5–10 % of the population (Eder et al. 2006). In 2010, asthma had the 28th highest disease burden globally in terms of disability-adjusted life years (Murray et al. 2012).

Some researches have indicated that PM_{2.5} plays a role in triggering asthma in children and adults, but that finding has not been universal. Yu et al. observed an 18 % increase in asthma symptoms for each 10 µg/m³ increase in PM_{2.5} in 133 children in Seattle (2000) and a 1.2-fold increase in the odds of a severe asthma attack for each 10 µg/m³ increase in PM_{2.5} lagged 1 day (Slaughter et al. 2003). Anderson et al. also concluded that outdoor PM_{2.5} concentration was consistent with asthma incidence using a meta-analysis of cohort studies (2013). However, many studies have found no significant associations between asthma prevalence and PM_{2.5} exposure, including a meta-analysis of motor vehicle air pollution and asthma in children (Gasana et al. 2012) and the ESCAPE multicentre study of air pollution exposure and childhood asthma (Molter et al. 2015).

Changes in morbidity have been associated with exposure to PM_{2.5} in asthmatic people, including increases in symptoms, medication use and visits to hospital emergency departments (ED) (Evans et al. 2014). ED visits are one measure of health outcomes for asthma patients with short-term exposure to PM_{2.5}. The aim of this analysis was to better understand the association between PM_{2.5} and asthma ED visits and to identify influencing factors through a comprehensive systematic review and meta-analysis.

Materials and methods

Search strategy and selection criteria

We systematically searched Embase, PubMed, the Cochrane library, Web of Science and China biomedical literature database using the following keywords: “particulate matter”, “particle matter”, “particle matters”, “PM”, “asthma”, “asthmas”, “emergency department”, “emergency departments”, “emergency service”, “emergency ward”, “emergency room”, “emergency unit” and “ED” to identify the studies describing associations between PM_{2.5} and ED visits globally. We considered studies that reported relationships between short-term PM_{2.5} exposure and asthma ED visits, and only peer-reviewed original articles were included (the full search criteria are shown in Appendix S1). Bibliographies of relevant studies retrieved using the inclusion criteria were manually checked. We limited our database searches to the period between inception and January 13, 2015 with no geographical or language restrictions.

Data extraction

Two investigators independently retrieved titles and abstracts, then screened relevant full-text articles and independently extracted study characteristics and unadjusted effect sizes with 95 % CI; conflicts were adjudicated by a third investigator (Chunling Fan). Data were compiled using a standardized data collection form in duplicate. We contacted authors of included studies for additional data or clarification as needed. The study characteristics included the following items: first author, publication year, location studied, period studied, patient age, number of events, design type, statistical method, PM_{2.5} description index (mean, SD, maximum, minimum, median, percentiles, interquartile range (IQR)), lag day and season (see Appendix S2). We were only interested in continuous analyses of PM_{2.5}.

Quality assessment

Two investigators independently performed quality assessment and the quality of the selected studies was assessed using the combined criteria (Fan et al. 2015; Shah et al. 2013). As a result, the quality of each study included in the meta-analysis was determined across eleven metrics: generalizability, description of PM_{2.5}, source of data, >10,000 events (whether total asthma ED visits was greater than 10,000), reporting bias, limitations (whether the authors considered the limitations of their research), multiple lag, adjustment for confounding factors (the confounding factors included: meteorological variables, demographic variables, pollen and holiday or week-end effects), adjustment for time trend, adjustment for seasonality and funding support.

Statistical analysis

We calculated standardized risk estimates according to unadjusted or adjusted risk ratios (RRs) with 95 % CIs for each study included in the meta-analysis. We used the following formula (Shah et al. 2013) for a standardized increment of 10 µg/m³; if PM_{2.5} increases/decreases by 10 µg/m³, the degree of the RR and 95 % CIs will increase/decrease:

$$RR_{(\text{standardised})} = RR_{(\text{original})}^{\frac{\text{increment} \left(10 \mu\text{g} / \text{m}^3 \right)}{\text{increment (original)}}}$$

The I–V heterogeneity method and a random-effects model were used to calculate the pooled RRs and 95 % CIs. We described inter-study heterogeneity due to study type, different lag exposures, season and patient ages by meta-regression and subgroup and ran a Monte Carlo permutation test with 10,000 permutations. I^2 metric and τ^2 were used to account for both intra- and inter-study heterogeneity. Based on the

included articles, season was divided into two groups: warm and cold seasons; patient age was divided into three groups: children < 18 years, 18 years ≤ adults < 64 years and aged ≥ 65 years. We further performed a subgroup analysis to clarify within groups the reported seasons and the ages of patients; if studies included information from the full year or the whole population, we analysed them separately.

Publication bias was assessed using funnel plot which was tested using Egger's linear regression method. We considered heterogeneity at a 10 % level of significance and I^2 exceeding 50 %. All analyses were performed using Stata Software (Version 12.0, StataCorp, TX, USA). Statistical significance was considered nominally as two-sided and $p < 0.05$.

Results

Sixteen studies were included

The initial search yielded 466 records, of which 426 remained after duplicate removal and screening of titles and abstracts; 16 records published between 2005 and 2014 strictly met the inclusion criteria (Babin et al. 2008; Chen et al. 2013; Delfino et al. 2014; Glad et al. 2012; Gleason et al. 2014; Halonen et al. 2008; Li et al. 2011; Mar and Koenig 2009; Mar et al. 2010; Meng et al. 2010; Paulu and Smith 2008; Peel et al. 2005; Slaughter et al. 2005; Stieb et al. 2009; Strickland et al. 2010; Winquist et al. 2012) (the reference list is shown in Appendix S3). All studies were from developed countries or areas, with 13 studies from the USA and the other three from Canada, Finland and Taiwan. Conditional logistic regression, Poisson regression and generalized additive models were mainly used to statistically analyse the association between PM_{2.5} and asthma ED visits. There were a total of 777,563 asthma ED visits in the included studies, and the reported mean and maximum concentrations of 24-h PM_{2.5} were 8.2–27.6 and 37–115.5 $\mu\text{g}/\text{m}^3$, respectively, which exceed WHO air quality guidelines of 25 $\mu\text{g}/\text{m}^3$ (WHO & Europe 2006). The quality of included studies was assessed by the two authors, and studies scored between 6 and 9 points; the mean score was 8 points (see Appendix S4).

Season and age were the two factors to influence the asthma ED visits

To analyse the relationship between exposure to PM_{2.5} and asthma ED visits, we extracted RR data and 95 % CI. The adjusted RR and 95 % CI of asthma ED visits and PM_{2.5} for the included studies is shown in Table 1. According to the meta-analysis, there was a positive association between PM_{2.5} and asthma ED visits; for each 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration, the risk of asthma ED visits increased by 1.5 % (95 % CI 1.2, 1.7 %).

Though we used a random-effects model to analyse heterogeneity between the studies and substantial overlap between CI for the results, we still found that there was substantial heterogeneity between studies because of the high I^2 values and $p < 0.05$. Study type, different lag exposures, season and patient age were the potential factors of heterogeneity in our meta-analysis. We conducted a meta-regression using a Monte Carlo permutation test to explore those factors. The results suggested that season and age of patients in the included articles were the factors that contributed to heterogeneity; study type and lag periods did not (Table 2).

A subgroup analysis of the season's effect on ED visits demonstrated that the warm season increased asthma ED visits by 3.7 % (95 % CI 0.5, 6.9 %); the effect during the cold season was weaker (2.6, 95 % CI 0.7–4.6 %). After we divided the patients into three groups based on age, only one set of data included the aged group (≥ 65 years). The risk of asthma ED visits in the adult group increased 1.7 % (95 % CI 0.7, 2.8 %) per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}, but the risk for the child group increased 3.6 % (95 % CI 1.8, 5.3 %) per 10 $\mu\text{g}/\text{m}^3$ increase (Table 3).

Publication bias

Egger's linear regression was used to test publication bias in the included articles, but we did not find any publication bias ($p = 0.201$, 95 % CI −1.35–6.52) (see Table 4 and Fig. 1).

Discussion

For this quantitative review, we systematically collected and summarized all published evidence of the association between asthma ED visits and PM_{2.5}. The results showed a positive correlation between PM_{2.5} and asthma ED visits; children were more sensitive than adults to PM_{2.5} increase of 10 $\mu\text{g}/\text{m}^3$, and the risk of asthma ED visits to exposure PM_{2.5} in warm seasons was higher than in cold seasons. All studies included in this review were conducted in developed countries or areas, which might be due to a lack of monitoring data in developing countries (van Donkelaar et al. 2010).

Particle pollution—especially PM_{2.5}—can get deep into the lungs and cause serious health problems including aggravated asthma, according to US EPA (2014). However, the reported associations between asthma attacks and PM_{2.5} have been different, and even contradictory, because typical local or regional situations affected the emission, composition and kinetics of aerosols (Tecer et al. 2008). In the present study, we pooled data on the association between PM_{2.5} and asthma ED visits globally and found that asthma ED visits increased with increasing concentrations of PM_{2.5}. Similar results have been reported showing an association between asthma hospital admissions and PM_{2.5} in children in Zonguldak, Turkey (Tecer

Table 1 Adjusted OR and 95 % CI between PM2.5 and asthma ED visits in meta-analysis (random-effects model)

Study	Study type	Lag	Season	Population	Adjusted OR	Adjusted 95 % CI	
Peel et al.	Time series	N/A	All	All	1.005	0.977	1.033
Slaughter et al.	Time series	1	All	All	1.03	0.98	1.09
Slaughter et al.	Time series	2	All	All	1.00	0.95	1.05
Slaughter et al.	Time series	3	All	All	1.01	0.96	1.06
Babin et al.	Time series	N/A	All	All	1.02	1.00	1.03
Babin et al.	Time series	N/A	All	5–12	1.05	1.01	1.10
Babin et al.	Time series	N/A	All	21–49	1.02	1.00	1.04
Babin et al.	Time series	N/A	Warm	All	1.00	0.99	1.20
Babin et al.	Time series	N/A	Warm	5–12	1.03	0.96	1.09
Babin et al.	Time series	N/A	Warm	21–49	1.02	1.00	1.05
Halonen et al.	N/A	0	All	<15	1.006	0.958	1.056
Halonen et al.	N/A	1	All	<15	0.999	0.953	1.047
Halonen et al.	N/A	2	All	<15	1.007	0.961	1.054
Halonen et al.	N/A	3	All	<15	1.041	0.995	1.087
Halonen et al.	N/A	4	All	<15	1.041	0.997	1.086
Halonen et al.	N/A	5	All	<15	1.019	0.976	1.063
Paulu et al.	Time series and case-crossover	0	All	>2	1.03	0.99	1.08
Paulu et al.	Time series and case-crossover	1	All	>2	1.01	0.96	1.06
Paulu et al.	Time series and case-crossover	2	All	>2	0.98	0.93	1.02
Paulu et al.	Time series and case-crossover	3	All	>2	0.95	0.91	1.00
Paulu et al.	Time series and case-crossover	4	All	>2	0.94	0.91	0.98
Paulu et al.	Time series and case-crossover	Average 0–1	All	>2	1.07	1.03	1.11
Mar et al.	Time series	0–3	All	All	No significance		
Stieb et al.	Time series	N/A	Warm	All	1.093	1.062	1.123
Stieb et al.	Time series	0	All	All	1.021	0.970	1.074
Stieb et al.	Time series	1	All	All	1.011	0.987	1.037
Stieb et al.	Time series	2	All	All	1.005	0.980	1.029
Stieb et al.	Time series	0 h	All	All	1.070	1.036	1.104
Stieb et al.	Time series	3 h	All	All	1.034	1.013	1.055
Stieb et al.	Time series	6 h	All	All	1.018	1.011	1.024
Stieb et al.	Time series	9 h	All	All	1.010	1.010	1.011
Stieb et al.	Time series	12 h	All	All	1.011	1.009	1.021
Stieb et al.	Time series	15 h	All	All	1.011	1.011	1.011
Mar et al.	N/A	0	All	All	1.000	0.957	1.043
Mar et al.	N/A	1	All	All	1.000	0.957	1.043
Mar et al.	N/A	2	All	All	1.058	1.014	1.102
Mar et al.	N/A	3	All	All	1.043	1.000	1.087
Mar et al.	N/A	4	All	All	1.029	0.986	1.072
Mar et al.	N/A	5	All	All	1.014	0.986	1.058
Meng et al.	N/A	N/A	All	1–17	1.480	0.620	3.500
Meng et al.	N/A	N/A	All	18+	1.580	0.560	4.430
Strickland et al.	Time series and case-crossover	N/A	All	5–17	1.022	1.002	1.042
Strickland et al.	Time series and case-crossover	N/A	Warm	5–17	1.047	1.017	1.076
Strickland et al.	Time series and case-crossover	N/A	Cold	5–17	1.005	0.976	1.034
Li et al.	Time series and case-crossover	3	All	2–18	1.032	1.007	1.057
Li et al.	Time series and case-crossover	5	All	2–18	1.039	1.015	1.065
Glad et al.	Time series and case-crossover	0	All	All	1.005	0.970	1.040
Glad et al.	Time series and case-crossover	1	All	All	1.036	1.001	1.073
Glad et al.	Time series and case-crossover	2	All	All	1.032	0.999	1.068

Table 1 (continued)

Study	Study type	Lag	Season	Population	Adjusted OR	Adjusted 95 % CI	
Glad et al.	Time series and case-crossover	3	All	All	1.017	0.984	1.051
Glad et al.	Time series and case-crossover	4	All	All	1.006	0.974	1.038
Glad et al.	Time series and case-crossover	5	All	All	0.994	0.963	1.027
Glad et al.	Time series and case-crossover	0	All	18–64	0.993	0.955	1.034
Glad et al.	Time series and case-crossover	1	All	18–64	1.023	0.982	1.064
Glad et al.	Time series and case-crossover	2	All	18–64	1.039	1.000	1.079
Glad et al.	Time series and case-crossover	3	All	18–64	1.031	0.994	1.071
Glad et al.	Time series and case-crossover	4	All	18–64	1.019	0.982	1.057
Glad et al.	Time series and case-crossover	5	All	18–64	1.007	0.971	1.045
Winqvist et al.	Time series	N/A	All	All	1.029	1.008	1.050
Winqvist et al.	Time series	N/A	All	0–1	1.051	0.999	1.105
Winqvist et al.	Time series	N/A	All	2–18	1.054	1.023	1.086
Winqvist et al.	Time series	N/A	All	19–64	1.002	0.974	1.031
Winqvist et al.	Time series	N/A	All	65+	0.998	0.916	1.085
Chen et al.	Case-crossover	N/A	All	5–15	0.939	0.901	1.042
Delfino et al.	Case-crossover	1	Warm	0–18	1.054	1.003	1.108
Delfino et al.	Case-crossover	1	Cold	0–18	1.007	0.975	1.040
Delfino et al.	Case-crossover	3	Warm	0–18	1.071	1.011	1.134
Delfino et al.	Case-crossover	3	Cold	0–18	1.031	0.993	1.072
Delfino et al.	Case-crossover	5	Warm	0–18	1.091	1.015	1.171
Delfino et al.	Case-crossover	5	Cold	0–18	1.063	1.016	1.113
Delfino et al.	Case-crossover	7	Warm	0–18	1.101	1.011	1.198
Delfino et al.	Case-crossover	7	Cold	0–18	1.105	1.049	1.165
Gleason et al.	Case-crossover	0	Warm	3–17	1.035	1.023	1.047
Gleason et al.	Case-crossover	1	Warm	3–17	1.012	1.000	1.024
Gleason et al.	Case-crossover	2	Warm	3–17	0.977	0.965	0.988
Gleason et al.	Case-crossover	3	Warm	3–17	1.015	0.985	1.029
Gleason et al.	Case-crossover	5	Warm	3–17	0.952	0.921	0.968
Overall					1.015	1.012	1.017

N/A not applicable

et al. 2008) and Seville, Spain (de Pablo-Romero et al. 2015); these studies demonstrate that PM_{2.5} has an adverse effect on asthma.

It has been reported that children are particularly susceptible to ambient air pollutants. One study identified age as an essential factor affecting hospital admission, with children

aged 6–18 years having the highest risk (Silverman and Ito 2010). We performed a meta-regression to analyse the impact of PM_{2.5} impact on different age groups based on data from included articles. The results indicate that children under 18 were far more susceptible to PM_{2.5} than adults; this is consistent with previous studies. This might be because children's lungs and immune systems are not completely developed and require high baseline ventilation rates; moreover, children breathe more air per unit body weight, and they spent more time than adults outdoors (Selgrade et al. 2008). The prevalence of asthma has been reported as 12.7 % in those age 65 or higher, representing the highest rate among adults according to Kim et al. (Kim et al. 2002). However, we did not find sufficient available data on the elderly, so the impact of PM_{2.5} on that population could not be measured. This also suggests that researchers should pay close attention to the elderly, who suffer from chronic diseases and decreased

Table 2 Meta-regression analysis on the factors and RR of asthma ED visits and PM_{2.5}

<i>p</i>	Unadjusted <i>p</i>	Adjusted <i>p</i>
Study type	0.168	0.501
Lag exposures	0.585	0.963
Seasons	0.019	0.036
Ages of patients	0.025	0.049
Largest Monte Carlo SE (<i>p</i>)	0.0050	

Table 3 Subgroup analysis for the heterogeneity factors in the included articles

Subgroup	Included study	RR	95 % CI	
Seasons				
Warm	(Babin et al. 2008; Delfino et al. 2014; Gleason et al. 2014; Stieb et al. 2009; Strickland et al. 2010)	1.037	1.005	1.069
Cold	(Delfino et al. 2014; Strickland et al. 2010)	1.026	1.007	1.046
Pooled		1.029	1.013	1.069
Age of patients (years)				
<18	(Babin et al. 2008; Delfino et al. 2014; Halonen et al. 2008; Li et al. 2011; Meng et al. 2010; Strickland et al. 2010; Winquist et al. 2012)	1.036	1.018	1.053
18~64	(Babin et al. 2008; Meng et al. 2010; Slaughter et al. 2005; Winquist et al. 2012)	1.017	1.007	1.028
Pooled		1.031	1.017	1.044

immune function and would be more affected by PM_{2.5}. However, their asthma was reported overlooked when visiting the ED because of other more serious diseases, despite asthma being the chief culprit (Stieb et al. 2000). It is unclear if the respiratory effects of PM_{2.5} are greater than those of PM₁₀–2.5. In a Toronto study (Burnett et al. 1999), the authors found PM₁₀–2.5 concentrations to be a more reliable predictor of asthma admissions than PM_{2.5} and PM₁₀ in subjects of all ages.

- We performed a subgroup analysis of seasons because all pollutants had some seasonal variability, and asthma ED visits were associated with PM_{2.5} concentration. The mean concentrations of PM_{2.5} varied in different areas across warm and cold seasons, for example, the mean concentrations of PM_{2.5} elemental carbon were similar during the warm and cold seasons in metropolitan, Atlanta (Strickland et al. 2010), but PM_{2.5} concentrations were higher during the winter than during spring in Seattle (Mar et al. 2005). The results of the present study indicate that the risk of asthma ED visits increases much more as PM_{2.5} increases during warm seasons than that in the cold season. It has been reported that there is a strong associations between asthma and air pollution during warm months, and some study periods have been limited to warm seasons because peak pollen (tree, grass, weed and ragweed) count occurs between March and October (Port et al. 2006). Some researchers have defined mid-January to mid-October as the pollen season and mid-October to mid-January of the next year as the pollen-free season (Makra et al. 2014) and found that pollen levels was

positively associated with respiratory disease as measured by medical emergency calls (Carracedo-Martinez et al. 2008). Pollen is a fine to coarse powder; it always causes allergic asthma. Therefore, pollen should be analysed as a confounding factor when studying the relationship between particulate matter and asthma. The chemical composition of PM_{2.5} would vary with seasonal trends, and different compositions have different functions on the respiratory system. Killer Fog of 1952 and 1955 in London led to over 4000 and 1000 more deaths, respectively, than usual for that time of year. A New York smog incident killed between 170 and 260 people in 1953. In Beijing China, severe PM_{2.5} episodes have occurred during winter but no extra deaths have been reported due to it. During winter, PM_{2.5} mass concentration peak is more likely due to a combination of increased emissions from heating sources (Song et al. 2015). In further studies, we suggest that researchers clarify the association between chemical composition and asthma so that the government can take appropriated action to influence pollution sources.

Several strengths and limitations of our study should be noted. A major limitation of our meta-analysis is that the limited sample size affected heterogeneity analysis. We found significant heterogeneity across patient age-group and seasons and performed subgroup and meta-regression analyses. However, only three of the articles studied included in the study reported the impact of PM_{2.5} on adults and only one article included the elderly; additionally, five articles made a distinction between warm and cold seasons and are unlikely to have

Table 4 Egger's test for publication bias

Asthma	Statistic	Coef.	Std. err.	<i>t</i>	<i>p</i>	95 % CI	
ED visits	Slope	0.010940	0.000199	15.11	0.0001	0.105442	0.011335
	Bias	0.505632	0.205972	1.54	0.13	−0.052093	0.915860

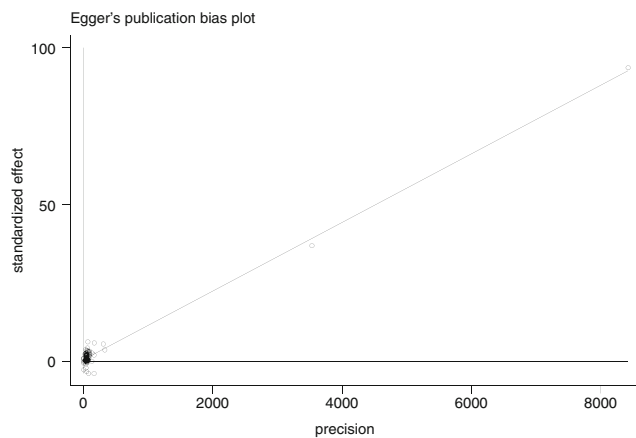


Fig. 1 Egger's publication bias plot of the included articles

fully accounted for heterogeneity. Another important limitation is that the estimated impact of PM_{2.5} was reported, but we did not consider the potential interaction of multiple air pollutants and meteorological factors or adjust for collinearity, such potential interactions would be examined in a future study. Third, we did not evaluate the impact of PM_{2.5} on asthma ED visits in developing and underdeveloped countries, which would bias the results and conclusion.

In summary, the evidence reviewed here indicates that PM_{2.5} concentration is associated with increases in asthma ED visits, that children were more susceptible than adults and that asthma ED visits rise during the warm season as PM_{2.5} increase. Though we drew the above conclusions, we also suggest researchers should pay close heed to the following points in the future study. First, the association between the chemical composition of PM_{2.5} and asthma ED visits is the key point that should be emphasized; it would provide the scientific basis for the government to control pollution sources. Second, we only analysed asthma conditioned visits related to PM_{2.5} and did not examine the long-term effect of PM_{2.5} exposure, though we believed PM_{2.5} would have an effect on chronic asthma and its severity. Third, the impact of PM_{2.5} in developing and undeveloped countries is more and more serious, but it is difficult to conduct studies because of the absence of PM_{2.5} monitoring. We suggest that governments establish a surveillance system with as far a range as possible. Fourth, the effects of meteorological and demographic factors should be thoroughly analysed in forthcoming research. Fifth, we extracted original data related to PM_{2.5} concentration and the RR between PM_{2.5} and asthma ED visits; dose–response effects could not be analysed but are meaningful for setting pollution standard.

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Conflict of interest The authors declare that they have no conflict of interest.

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