

Effect of Acute PM_{2.5} Exposure on Lung Function in Children: A Systematic Review and Meta-Analysis

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Objective: The objective of this study was to conduct a systematic review and meta-analysis to identify the adverse effects of acute PM_{2.5} exposure on lung function in children.

Design: Systematic review and meta-analysis. Setting, participants and measures: Eligible studies analyzing PM_{2.5} level and lung function in children were screened out. Effect estimates of PM_{2.5} measurements were quantified using random effect models. Heterogeneity was investigated with Q-test and I² statistics. We also conducted meta-regression and sensitivity analysis to explore the sources of heterogeneity, such as different countries and asthmatic status. Subgroup analyses were conducted to determine the effects of acute PM_{2.5} exposure on children of different asthmatic status and in different countries.

Results: A total of 11 studies with 4314 participants from Brazil, China and Japan were included finally. A 10 µg/m³ increase of PM_{2.5} was associated with a 1.74L/min (95% CI: -2.68, -0.90) decrease in peak expiratory flow (PEF). Since the asthmatic status and country could partly explain the heterogeneity, we conducted the subgroup analysis. Children with severe asthma were more susceptible to PM_{2.5} exposure (-3.11 L/min per 10 µg/m³ increase, 95% CI -4.54, -1.67) than healthy children (-1.61 L/min per 10 µg/m³ increase, 95% CI -2.34, -0.91). In the children of China, PEF decreased by 1.54 L/min (95% CI -2.33, -0.75) with a 10 µg/m³ increase in PM_{2.5} exposure. In the children of Japan, PEF decreased by 2.65 L/min (95% CI -3.82, -1.48) with a 10 µg/m³ increase of PM_{2.5} exposure. In contrast, no statistic association was found between every 10 µg/m³ increase of PM_{2.5} and lung function in children of Brazil (-0.38 L/min, 95% CI -0.91, 0.15).

Conclusion: Our results demonstrated that the acute PM_{2.5} exposure exerted adverse impacts on children's lung function, and children with severe asthma were more susceptible to the increase of PM_{2.5} exposure. The impacts of acute PM_{2.5} exposure varied across different countries.

Keywords: particulate matter 2.5, PM_{2.5}, children, peak expiratory flow, PEF, acute exposure, meta-analysis

Introduction

Air pollution, a culprit of human respiratory problems, is challenging human health worldwide.¹ The fine particulate matters of different aerodynamic diameters, such as particulate matter 2.5 (PM_{2.5}), PM_{1.0}, PM₁₀, are the major contributors to air pollution. PM_{2.5} is defined as the most harmful type of air fine particulate matter with an aerodynamic equivalent diameter of less than 2.5µm.² As a major pollutant, PM_{2.5} is characterized by small size, complex composition, allergen absorptivity and sensitization-enhancing property.³ The sources of PM_{2.5} include automobile emissions, urban constructions, smokestacks, power plants, industrial and biomass burning.³ PM_{2.5} not only penetrates into the deep tissue of the human respiratory system due to its small size but also carries toxic and harmful substances, such as transition metals and polycyclic aromatic hydrocarbons (PAHs), into human bodies.⁴ PM_{2.5} brings with a myriad of different adverse effects, such as asthma,⁵ chronic obstructive pulmonary disease (COPD),³ cardiovascular disease,⁶ and cancer.⁷ Exposure to PM_{2.5} confers an increased risk of wheeze-associated disorders,⁸ asthma-related emergency and hospitalization in children.⁹

Lung function is an early indicator to evaluate and quantify the effect of air pollution on the respiratory system and a sub-clinical marker with clinical implications for lung health across the lifespan.¹⁰ Children are more susceptible to air pollution because of their faster breath rate and immature immunity.¹¹ The developmental trajectory of lungs is divided into three phases: the growth phase, the plateau phase, and the decrement phase.¹² The growth phase is critical for lung function.¹² Toxic exposure in the growth phase is associated with future adverse clinical outcomes, such as propensity to develop respiratory diseases and early multimorbidity.¹³ Hence, it is urgent to investigate the effects of PM_{2.5} exposure on childhood lung function.

Previous meta-analyses indicated that both acute and long-term exposure to outdoor PM_{2.5} was significantly associated with decreased lung function in healthy and asthmatic adults.^{14,15} One meta-analysis based on European birth cohort study revealed that long-term exposure to PM_{2.5} resulted in decreased lung function in schoolchildren.¹⁶ However, this study only focused on the relation between PM_{2.5} exposure and FEV₁ alteration during a long-term exposure. Acute and long-term PM_{2.5} exposure may have different impacts. Multiple meta-analyses revealed that the acute exposure of PM_{2.5} had an adverse impact on pediatric asthma hospital visits and exacerbation.^{17,18} Children undergo a growth phase of lungs, but there were few meta-analyses clarifying the association between acute exposure of PM_{2.5} and childhood lung function. The objective of this study was to quantify the effect of acute outdoor PM_{2.5} exposure on the lung function of children by performing a comprehensive systematic review and meta-analysis.

Methods

Patients and Ethics

No patients involved.

Design

This study followed the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁹

Literature Search and Selection

A comprehensive literature search was conducted to identify articles published on the acute effect of PM_{2.5} on children's lung function. We systematically searched Embase, PubMed, the Cochrane library, Web of Science, China biomedical literature database (CNKI), and Chinese Biomedical Literature (CBM) databases for literature published before February 2022 and identified the studies describing the relationship between acute PM_{2.5} exposure and lung function in children aged 18 years or younger with no geographical or linguistic restrictions. The PubMed search string used was as follows:

(PM_{2.5} OR Ultrafine Fibers OR Ultrafine Fiber OR Fiber, Ultrafine OR Airborne Particulate Matter OR Particulate Matter, Airborne OR Air Pollutants, Particulate OR Particulate Air Pollutants OR Ambient Particulate Matter OR Particulate Matter, Ambient OR Particulate Matter*) AND (children OR Child*) AND (Function Test, Respiratory OR Function Tests, Respiratory OR Test, Respiratory Function OR Tests, Respiratory Function OR Pulmonary Function Tests OR Function Test, Pulmonary OR Function Tests, Pulmonary OR Test, Pulmonary Function OR Tests, Pulmonary Function OR Lung Function Tests OR Function Test, Lung OR Function Tests, Lung OR Lung Function Test OR Test, Lung Function OR Tests, Lung Function OR Pulmonary Function Test OR Respiratory Function Tests*).

Detailed search strategies are presented in [Additional Table 1](#). In order to avoid bias, two reviewers independently assessed the eligible studies by examining the full text of articles based on the pre-defined eligibility criteria.

Inclusion and Exclusion Criteria

Studies examining the relationship between acute (daily) exposure to outdoor air PM_{2.5} and lung function in children were eligible for this review. The review process is shown in [Figure 1](#). Studies were included when meeting all the following criteria: (i) quantitatively analyzing the changes in lung function indexes with every 10 µg/m³ PM_{2.5} increase; (ii) involving children aged 18 years or younger as study subjects; (iii) published in full-text; (iv) analyzing acute

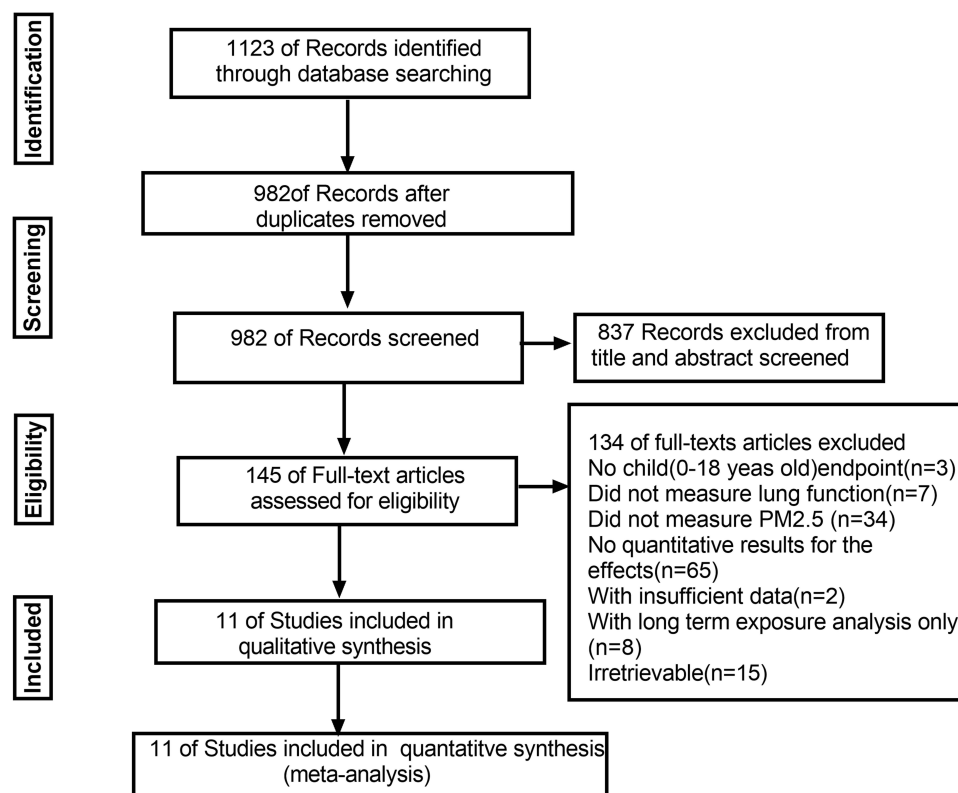


Figure 1 Flow diagram of the selection procedure of studies.

Notes: A PRISMA flow diagram that details the inclusion and exclusion of studies considered for this systematic review. PRISMA figure adapted from Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009, 339:b2535. Creative Commons.¹⁹

exposure to PM_{2.5}. Studies were excluded if meeting any of the following criteria: (i) published in reviews, conference abstracts, editorial letters, or comments; (ii) not related to ambient PM_{2.5} (eg, only related to indoor, passive smoking or other pollutions); (iii) without measurement of lung function in children; (iv) without quantitative results for the effects; (v) only analyzing long-term exposure to PM_{2.5}; (vi) with insufficient data.

Data Extraction

Two reviewers extracted the data from the eligible literature, including study time, study types, country, sample size, average age of population, daily mean concentration of PM_{2.5}, controlled variables, lag days of exposure, and statistical analysis model. All effect measurements were transformed to per 10 µg/m³ increase in PM_{2.5}, assuming a linear relationship between the concentration of particulate matter and lung function. Some studies assessed the effect of acute exposure to air pollution by different time periods (lag of 0, 1, or 2 days, etc.). We defined the acute exposure effect as 1 day (lag 1) to 7 days (lag 7) after exposure to PM_{2.5}. In order to reduce the heterogeneity among the original studies, we recorded the effect noted at 1 day after exposure whenever possible. The reviewers then used a standardized data extraction format in Microsoft Office Excel 2019 to extract all the data needed. A third person resolved the disagreement between the two reviewers. Extraction of these data is presented in Table 1, according to the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA) guidelines.¹⁹

Study Quality Assessment

Two investigators independently performed quality assessment of the cohort studies using the Newcastle-Ottawa Scale (NOS).²⁰ NOS contains 8 items with 9 as the highest score, and a maximum of 2 scores could be obtained for comparability. The scales and grading are presented in Additional Figure 1. Adjustment for confounding was based on three factors: (a) asthma status, asthmatic medicinal usage, passive smoking; (b) environmental parameters, such as

Table 1 Study Characteristics

Authors/Year	Region/Country	Study Type	Population (Number)	Average Age (Years Old)	Daily Mean Concentration of PM _{2.5} (μg/m ³)	Lag (Days)	Outcome: Observed Change (Change per 10 μg/m ³ PM _{2.5} Increase in Pollutant When Applicable)	Statistical Model
Lu Ma/2008 ²²	Yotsukaido, Japan	Cohort study	Children with severe asthma (19)	Mean age 12.9	22.6	Lag0–1	PEF:-3.40L/min (95% CI:-6.47, -0.33)	Generalized Estimating Equation model
BingYu /2010 ²³	Taiwan,China	Cohort study	Healthy, asthmatic, and allergic rhinitis school children (100)	Mean age 10.6	28.2	Lag0–1	FVC:-0.16L (95% CI:-0.23, -0.08) FEV1:-0.12L (95% CI:-0.20, -0.05)	Mixed-effects models
Yamazak /2011 ²⁴	Yotsukaido, Japan	Cohort study	Children with severe asthma (17)	8–15	24	Lag0–1	PEF:-2.96L/min (95% CI:-4.55, -1.37)	Generalized Estimating Equations
Ludmilla/2012 ²⁵	Amazon,Brazilian	Cohort study	Healthy and asthmatic children (280)	Mean age 10.4	24.34	Lag0–1	PEF:-0.29L/min (95% CI:-0.52, -0.07)	Mixed-effects models
Ludmilla/2014 ²⁶	Tangara,Brazil	Cohort study	Healthy and asthmatic children (220)	Mean age 10.3	19.6	Lag0–4	PEF:-0.54L/min (95% CI:-0.946, -0.137)	Mixed-effects models
Masanari/2016 ²⁷	Matsue,Japan	Cohort study	Healthy,asthmatic, allergic rhinitis children (339)	10–12	23	Lag0–1	PEF:-1.72 L/min (95% CI:-3.82, 0.36)	Linear mixed model
Dandan Xu/2018 ²⁸	Nanjing, China	Cohort study	Healthy School children (86)	Mean age 9	84.3	Lag0–1	PEF:-1.76L/min (95% CI: -3.549, 0.024) FVC: -0.023L (95% CI: -0.033, -0.013) FEV1:-0.019 L (95% CI: -0.029, -0.009)	Mixed-effects regression mode
Liu Weiyan/2019 ¹⁰	Hangzhou,China	Cohort study	Healthy school children (1685)	Mean age 9.8	50	Lag0–1	PEF:-2.34L/min (95% CI:-4.02, -0.72)	Linear mixed model
Dandan Xu/2020 ²⁹	Zhejiang, China.	Cohort study	Healthy and asthmatic school children (848)	Mean age 9.7	67.58	Lag 1	PEF:-4.02L/min (95% CI: -5.36, -2.73) FVC:-0.034L (95% CI: -0.045, -0.023) FEV1:-0.033L (95% CI: -0.044, -0.021)	Mixed-effects regression mode
Yang Xiaoyan/2020 ¹¹	Beijing, China	Cohort study	Healthy school children (51)	9–12	57.75	Lag4	PEF:-0.49L/min (95% CI:-2.84, 1.87) FVC:-0.033L (95% CI:-0.050, -0.015) FEV1:0.003L (95% CI:-0.015, 0.020)	Linear mixed effects model
WU Xingbin/2020 ³⁰	Jinan, China	Cohort study	Healthy school children (484)	Not reported	90	Lag0–1	PEF:-1.54L/min (95% CI:-2.33, -0.76) FVC: -0.008L (95% CI:-0.014, -0.003) FEV1:-0.008L (95% CI:-0.012,-0.003)	Multiple linear regression model

Abbreviations: PEF, peak expiratory flow; FVC, forced vital capacity; FEV1, the forced expiratory volume in one second; CI, confidence interval.

temperature and humidity; (c) individual factors, such as age, gender, BMI, height, weight and other co-morbidities (eg, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy and medication use). The quality was considered good if all 3 factors, fair if 2 factors and poor if 1 or less factors were adjusted.

Statistical Analysis

To determine the effect of acute PM_{2.5} exposure on lung function in children, we conducted the meta-analysis separately for different indices such as PEF, FEV₁ and FVC. Effect estimates per 10 µg/m³ were combined to calculate summary effect estimates using generic inverse variance method assuming a random effects model or a fixed effects model. A forest plot was used to assess visually the change of indicators of children's lung function and corresponding 95% confidence. If a confidence interval was presented, the corresponding standard error was calculated as $(\text{upper CI} - \text{lower CI})/(\text{xn} - \text{x0} \times 3.92)$, where CI referred to confidence interval, xn denoted exposure at the level of group n, and x0 denoted exposure at the reference group. The standard error was calculated following the method recommended by published articles.²¹ Heterogeneity among studies was statistically investigated with the Q-test and the I² statistics. When I²>50%, the random effects model was used; when I²<50%, the fixed effects model was used. Publication bias was assessed using funnel plot and Egger's linear regression method. We also performed meta-regression analysis of the source of heterogeneity. Considering that the heterogeneity between groups of FEV₁ and FVC was 0%, meta-regression and subgroup analysis were conducted to clarify the impact of asthmatic status on PEF of children. Meta-regression included the following potential covariates: country, severe asthma status, sample size, statistic methods, and publication year. We also performed a subgroup analysis by dividing the children into three country groups and severe asthma status. We performed sensitivity analysis by omitting one study in each turn to assess the stability of the results of change of PEF. All analyses were performed using the R computing framework (www.r-project.org).

Results

Literature Search

We systematically searched PubMed, Embase, Web of Science, the Cochrane library, China biomedical literature database (CBM) and Chinese National Knowledge Infrastructure (CNKI) and identified 1123 studies in the initial search (Figure 1). Among the 145 studies published in full-text reviews, 134 were excluded, and ultimately 11 studies were included in this meta-analysis.^{10,11,22–30} The primary reason for exclusion was the lack of quantitative results about the effects. Other reasons included the lack of outdoor PM_{2.5} measurement or lung function.

Characteristics of Included Studies

The characteristics of the 11 studies examining the association between acute exposure to outdoor PM_{2.5} and lung function in children are described in Table 1. Of these studies, ten studies examined the association between PEF and acute exposure to PM_{2.5}.^{10,11,22,24–30} Data from 4129 individuals from three different countries were examined in these reports. Among these studies, six were conducted in China, three in Japan, and two in Brazil. Two studies included children with severe asthma, three studies included both healthy and asthmatic children, two studies included healthy, asthmatic, allergic rhinitis school-age children, and four studies only included healthy children. All the studies focused on the acute exposure of PM_{2.5} and lung function in children.

Risk of Bias Among Included Studies

The quality of included studies was assessed by the two authors. By applying the NOS, study quality was appraised as follows: eight studies were rated as good,^{10,22–27,29} and three as fair.^{11,28,30} Five studies that included both asthmatic and healthy children failed to provide the exact information about the quantitative lung function change of two groups of children,^{23,25–27,29} so they were not considered as healthy or asthmatic group in subgroup analysis. The results for each item from each study are shown in Additional Table 2.

Meta-Analyses

The association between acute exposure to ambient PM_{2.5} and lung function indicators in children is graphically displayed in Figure 2. A significant association was found between PM_{2.5} exposure and PEF (L/min) in children ($P < 0.01$). A 10 $\mu\text{g}/\text{m}^3$ increase of PM_{2.5} was associated with a change in PEF of $-1.74\text{L}/\text{min}$ (95% CI: $-2.68, -0.90$). In contrast, no statistically significant associations of a 10 $\mu\text{g}/\text{m}^3$ increase of PM_{2.5} with FVC and FEV1 were observed (-0.03L [95% CI: $-0.08, -0.01$] and -0.02L [95% CI: $-0.05, 0.00$], respectively). There was substantial heterogeneity among studies included in the PEF analysis ($I^2 = 70.89\%$), but low heterogeneity among

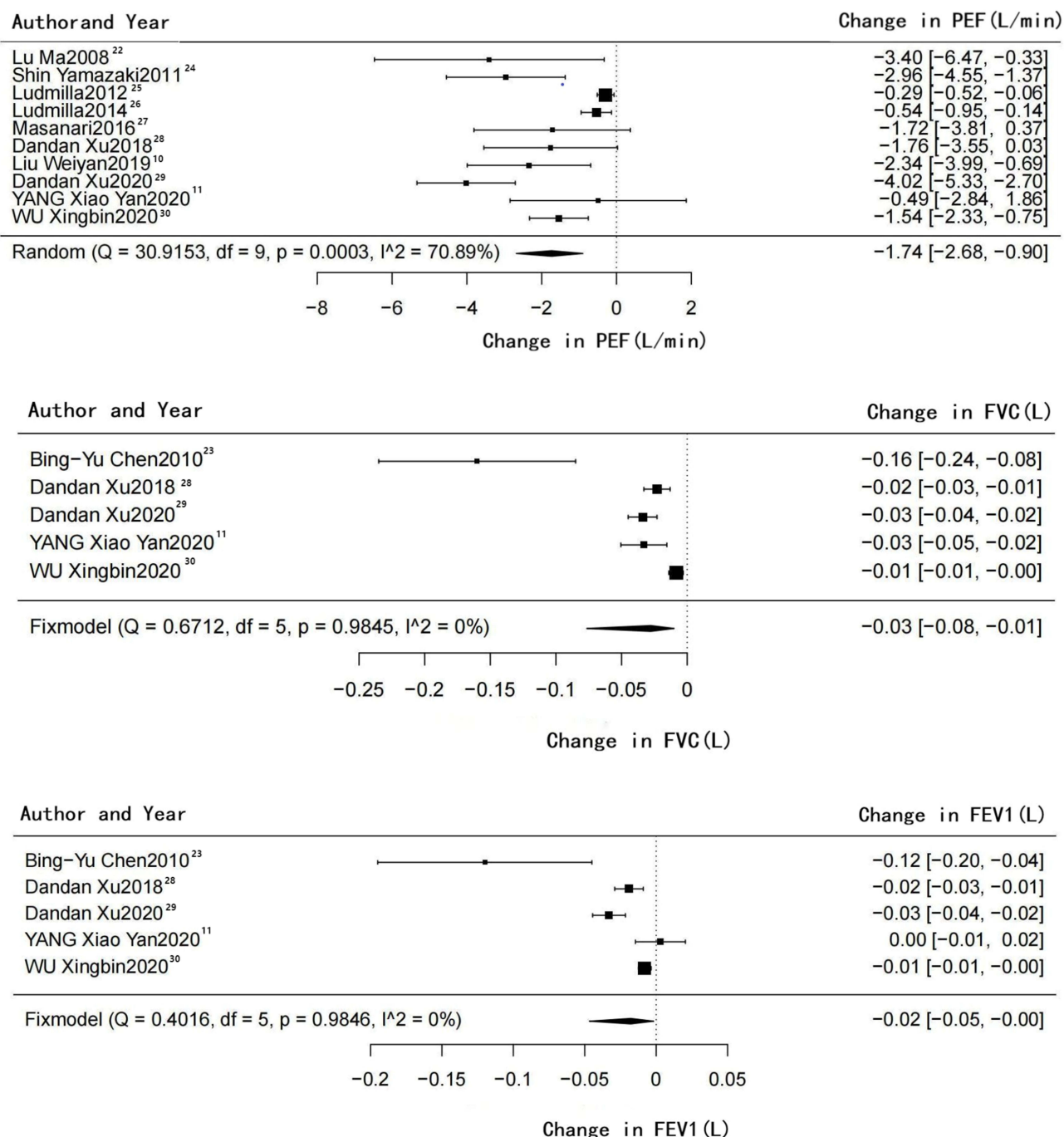


Figure 2 Forest plots of changes in PEF, FVC, FEV1 per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} level.

Notes: The summary estimate for PEF was calculated using a random-effects meta-analysis. The summary estimates for FVC, FEV1 were calculated using a fixed-effects meta-analysis.

Table 2 Subgroup Analysis by Asthma and Country Examining the Relationship Between PM2.5 and PEF in Children

Subgroups	Estimate (n)	Included Studies	Change in PEF per 10 μ g/ m ³ of PM2.5 (95% CI)	P value	I ²	P value for Heterogeneity
Asthma						
Severe Asthma group	2	Lu Ma/2008, ²² Yamazaki /2011 ²⁴	-3.11 L/min (-4.54, -1.67)	<0.001	0%	0.775
Health group	4	Dandan Xu/2018, ²⁸ Liu Weiyan/ 2019, ¹⁰ Yang Xiaoyan/2020, ¹¹ WU Xingbin/2020 ³⁰	-1.61 L/min (-2.34, -0.91)	<0.001	0%	0.634
Country						
China	5	Dandan Xu/2020, ²⁹ Dandan Xu/2018, ²⁸ Liu Weiyan/ 2019, ¹⁰ Yang Xiaoyan/2020, ¹¹ WU Xingbin/2020 ³⁰	-1.54 L/min (-2.33, -0.75)	<0.001	53.6%	0.071
Japan	3	Masanari/2016, ²⁷ Yamazaki /2011, ²⁴ Lu Ma/ 2008 ²²	-2.65 L/min (-3.82, -1.48)	<0.001	0%	0.525
Brazil	2	Ludmilla/2012, ²⁵ Ludmilla/2014 ²⁶	-0.38 L/min (-0.91, 0.15)	0.162	0%	0.659

Abbreviations: PEF, peak expiratory flow; CI, confidence interval.

studies included in the FVC ($I^2 = 0.0\%$) and FEV1 ($I^2 = 0.0\%$) analyses, respectively. There was no statistical evidence of publication bias for any of the analyses (Egger's regression test: $p = 0.15$ for PEF, $p = 0.40$ for FVC, and $p = 0.52$ for FEV1). Forest plots of change in PEF, FVC, FEV1 with per 10 $\mu\text{g}/\text{m}^3$ increase in PM2.5 level are shown in [Figure 2](#). Funnel plots for the publication bias are provided in [Additional Figures 2–4](#).

Meta-Regression and Subgroup Analysis

We conducted the univariate meta-regression analysis and subgroup analysis for the studies included in the PEF analysis. Meta-regression results demonstrated that the studies in Brazil showed significant heterogeneity compared with those in other countries ($P = 0.0261$, $R^2 = 30.99\%$). The following factors could partly explain the heterogeneity but did not contribute to statistical significance: severe asthma status ($P = 0.0906$, $R^2 = 16.71\%$), study country ($P = 0.0713$, 36.79%), sample size ($P = 0.0684$, 21.71%). Since severe asthma status could partly explain the heterogeneity, we conducted subgroup analyses of the studies that included children with severe asthma and healthy children. There were two studies including the children with severe asthma and four studies including healthy children, so we performed subgroup analysis on these six studies. Four studies including both asthmatic and healthy children were not included in subgroup analysis due to insufficient data of the original research. When the concentration of ambient PM2.5 showed a 10 $\mu\text{g}/\text{m}^3$ increase, there was a significant decrease in PEF (-1.61 L/min, -2.34, -0.91) in healthy subgroup, but a more significant decrease was found in severe asthmatic group (-3.11 L/min, -4.54, -1.67). We also conducted subgroup analyses of the studies in different countries. There were 10 studies involving three countries. Studies in Brazil showed a PEF changed by -0.38 L/min (-0.91, 0.15), which was not statistically significant. The results in China and Japan showed PEF changed by -1.54 L/min (-2.33, -0.75) and -2.65 L/min (-3.82, 0.36), respectively. The results of subgroup analysis and meta-regression are described in [Table 2](#) and [Additional Table 3](#), respectively.

Sensitivity Analysis

Sensitivity analysis was performed by excluding one study at a time to assess the stability of the results of PEF. The decreases in PEF remained significant after excluding the articles one by one. When we removed the article of Ludmilla²⁵ or Dandan Xu,²⁵ the heterogeneity was reduced to 60.22% and 55.60%, respectively, indicating that the two studies were the source of heterogeneity. Ludmilla's research was conducted in Brazil and Dandan Xu's research had a large sample size (848), which might contribute to the heterogeneity.

Discussion

This study is, to our knowledge, the first meta-analysis assessing the effects of acute exposure to outdoor PM2.5 on lung function in children. We found that an increase in PM2.5 level was significantly associated with a decrease in PEF

($-1.74\text{L/min per } 10\mu\text{g/m}^3$ increase in $\text{PM}_{2.5}$). Elevated $\text{PM}_{2.5}$ exposure was also associated slight alteration of FVC and FEV1 but without significant difference.

The effect of acute $\text{PM}_{2.5}$ exposure on PEF was more significant in children with severe asthma, suggesting that asthmatic children are more vulnerable to $\text{PM}_{2.5}$ exposure than healthy ones. Zhang et al³¹ showed that $\text{PM}_{2.5}$ exposure induced higher variation in Nitric Oxide Synthase 2 (NOS2) in children with asthma, which contributed to a greater alteration of lung function. In addition, patients with severe asthma produced more cytokines than healthy ones when exposed to $\text{PM}_{2.5}$.³² In contrast, Ludmilla's research²⁵ indicated that $\text{PM}_{2.5}$ exposure had little effect on asthmatic children. However, it is also revealed that there was a significant reduction in PEF with a $10\mu\text{g/m}^3$ increase of $\text{PM}_{2.5}$ in non-asthmatic children. This discovery may result from the fact that the asthmatic subjects tend to take medication when they perceive the deteriorating air quality. Previous studies showed that anti-inflammatory medication in asthmatic children could significantly alleviate the effect of $\text{PM}_{2.5}$ exposure on PEF.³³ The impact of acute $\text{PM}_{2.5}$ exposure was more obvious in studies involving children with severe asthma, suggesting that asthma status may amplify the effect of acute $\text{PM}_{2.5}$ exposure on lung function.

$\text{PM}_{2.5}$ exposure appeared to exert a profounder effect on children's lung function than that of adults, indicating that children are more vulnerable to $\text{PM}_{2.5}$ exposure than adults. One meta-analysis found a $10\mu\text{g/m}^3$ increase of $\text{PM}_{2.5}$ was associated with a 1.02L/min decrease of PEF in non-smoking asthmatic adults, while no decrease of PEF was found in smokers.⁴ Ge Mu showed a $10\mu\text{g/m}^3$ increase of $\text{PM}_{2.5}$ was associated with a 0.972L/min decrease of PEF among 4697 urban adults.³⁴ The change of PEF in our finding was more obvious than these previous studies. In addition, Jingchun Fan's meta-analysis showed that the risk of asthma emergency department visits due to per $10\mu\text{g/m}^3$ increase in $\text{PM}_{2.5}$ was much higher in children than in adults.³⁵ Sandra also revealed that younger children were more susceptible to air pollution.²⁶ Compared with adults, children have undeveloped lungs, higher baseline respiratory rates, more time spending outdoors, more frequent mouth-breathing, and larger lung surface area per unit of body weight, all making them more vulnerable to $\text{PM}_{2.5}$ exposure.³⁶

The reduction of lung function can be attributed to the inflammatory response, oxidative stress, and bronchial epithelium cell apoptosis caused by $\text{PM}_{2.5}$. Pro-inflammatory response induced by airborne PM can weaken pulmonary function in schoolchildren.²⁷ An *in vivo* study suggested that a variety type of cells might cause inflammation response through different pathways when exposed to $\text{PM}_{2.5}$: Macrophages released proinflammatory mediators via the LPS/MyD88 pathway, while type II alveolar cells mainly caused oxidative stress-dependent inflammation.³⁷ Decreased lung function was related to not only proinflammatory mediators but also microRNAs. After $\text{PM}_{2.5}$ -inhalation, Balb/c mice showed decreased MiR-146a and miR-146b, and dramatically increased IL-6, INF- γ and TNF- α ; miR-146a level was found negatively related to PEF.³⁸ Persistent endoplasmic reticulum stress caused by oxidative stress contributes to the lung damage induced by $\text{PM}_{2.5}$ exposure.³⁹ An *in vitro* study demonstrated that $\text{PM}_{2.5}$ could not only cause inflammatory responses and oxidative injury but also trigger the autophagy-mediated apoptosis of mice bronchial epithelium cells via PI3K/AKT/mTOR pathway.⁴⁰

In the analysis stratified by geographical location, $\text{PM}_{2.5}$ showed varied effects on PEF of children in different countries. The results indicated that $\text{PM}_{2.5}$ exposure in different countries might have different physiologic consequences. Firstly, this phenomenon may result from different concentrations, compositions, and inflammatory chemotaxis of $\text{PM}_{2.5}$ in these countries.^{9,41,42} The effect of air pollution may be less obvious in areas with low $\text{PM}_{2.5}$ concentrations, so larger sample sizes are needed to illustrate the associations between $\text{PM}_{2.5}$ exposure and lung function in different areas.^{9,41} The effects of $\text{PM}_{2.5}$ exposure on lung function in children may depend more on the pro-inflammatory response to the PM composition than on the PM mass concentration.^{9,41} The different contents of allergens, polycyclic aromatic hydrocarbons, especially heavy metals in $\text{PM}_{2.5}$ exposure can lead to various inflammatory responses.^{9,41,43} Secondly, population susceptibility, gene polymorphisms and dietary habits may also contribute to different effects of $\text{PM}_{2.5}$ exposure among countries. A cohort study in China found that gene-environment interaction of Sirtuin 1 (SIRT1) was associated with mortality caused by $\text{PM}_{2.5}$ exposure among the elder people.⁴⁴ DNA repair gene XPC might play a role in the pathogenesis of respiratory diseases, and children with the CC alleles of XPC polymorphisms were found to be more susceptible to the adverse effects of ambient air pollution.⁴⁵ People often eating antioxidant food such as fruits

and vegetables may be less vulnerable to the adverse effects of PM.⁴⁶ Lastly, the distinct climate, temperatures and humidity may also contribute to the varied effects of PM_{2.5} exposure in different countries.⁴⁷

In the subgroup analysis, we found the alteration of PEF in children's pulmonary function was not statistically significant in Brazil. However, the change of PEF of Chinese children was significant. This may be explained by the lower PM_{2.5} concentration in Brazil than in China. In our study, the PM_{2.5} concentration in China fluctuated between 50 and 90 $\mu\text{g}/\text{m}^3$, but between 19.6 and 24.34 $\mu\text{g}/\text{m}^3$ in Brazil. The relatively higher PM_{2.5} concentration in China is responsible for the bigger change of PEF in children. In addition, in the non-severe asthmatic children of Brazil, inhaling drugs such as corticosteroids during air pollution deterioration made the effect on PEF slighter, according to the study. The results of meta-regression showed significant heterogeneity among the studies of Brazil. The non-statistically significant change of PEF in Brazilian children may contribute to the heterogeneity. This could also be partially explained by the small number of studies in Brazil. In contrast, the average PM_{2.5} concentration in Japan was lower than that in China, but the change of PEF in Japanese children was larger. This may be caused by the fact that two studies only focused on severe asthmatic children in Japan.

The results of sensitivity analysis revealed that Dandan Xu's study,²⁵ which had a large sample size (848), was one source of heterogeneity, but it did not change the statistical significance of the pooled result. The result of sensitivity analysis and meta-regression indicated that the different sample size of the studies spanning over 25 years could partly explain the heterogeneity. Another possible explanation for the heterogeneity was that the proportions of asthmatic children were different across studies excluding individuals with severe asthma and the children who could not be divided into asthmatic or healthy group due to incomplete information.

The alteration of FVC and FEV1 at PM_{2.5} exposure were slight in our study, showing no statistical significance. In contrast, Ge Mu found that each 10 $\mu\text{g}/\text{m}^3$ increase in the previous-day personal PM_{2.5} exposure was associated with significant decreases in FVC and FEV1.³⁴ Ralph J. Delfino⁴⁸ also revealed that FEV1 decrements were significantly associated with the increasing personal PM_{2.5} exposure, but not the ambient PM_{2.5}. We speculate that the personal PM_{2.5} exposure might exert more significant impacts than ambient PM_{2.5} exposure on FVC and FEV1. Our result may also be influenced by the smaller sample size in studies including FVC and FEV1 in children exposed to ambient PM_{2.5}. Furthermore, the study of ESCAPE Project suggested¹⁶ that long-term exposure to PM_{2.5} might result in reduced FEV1 in schoolchildren, indicating that the different effects of long-term and short-term PM_{2.5} exposure on FEV1.

Our meta-analysis has some limitations. First, the number of studies in this meta-analysis was small. The results should therefore be interpreted with caution. Second, these studies were mainly on school-age children because the children of this age are more frequently exposed to PM_{2.5}. It was impractical to perform subgroup analysis stratified by age due to the similar age of children in different studies. Therefore, studies on children of other age groups are needed in the future. In addition, sex, passive smoking, purifier, and sex may also influence the results of the different studies. Third, we assumed that there was a linear relationship between PM_{2.5} exposure and lung function. We did not know whether this linear relationship did exist between PM_{2.5} and lung function because of the lack of data. But this method was also used in other meta-analyses about relationship between air pollution and lung function.^{5,14} Fourth, although we tried to choose the effect of one pollution model of lag 0–1 or lag 1 in order to reduce the heterogeneity of the original studies, we could not exclude the effect of other air pollutants and different lag days in the original studies. Lastly, we discussed the effect of ambient PM_{2.5} exposure on children's lung function, while the results may be different from those studies on personal PM_{2.5} exposure. The influence of co-morbidities, medications, and sex on the lung function of children cannot be ruled out, even though they were considered as concomitant variables in the original studies included in this meta-analysis. We could not conduct the subgroup analysis based on the above concomitant variables, because some of the studies did not analyze these variables. The results should be considered with caution. Hence, more researches are needed in future work.

Despite the limitations, our meta-analysis also has some strengths. First, as far as we know, it is the first meta-analysis about the association between acute PM_{2.5} exposure and lung function in children. Second, we attempted to reduce heterogeneity among studies by using a consistent lag time (one day) when possible and analyzing different subgroups by asthmatic status and countries. Third, we also demonstrated the different effects of PM_{2.5} exposure on lung function in children of three countries. Last, we strived to address the issue of confounding and performed subgroup analysis on

studies with severe asthmatic and healthy children, which demonstrated more obvious effects of acute PM_{2.5} exposure on children with severe asthma.

Conclusion

In summary, our results demonstrated that acute PM_{2.5} exposure was associated with reduced PEF in children. Acute PM_{2.5} exposure may induce more obvious effects on children with severe asthma. The impacts of PM_{2.5} vary across different countries. Measures such as wearing masks should be taken to protect children from ambient PM_{2.5} exposure, especially for asthmatic ones. The government should propose effective plans to reduce the environmental pollution. Further researches are required to better quantify and compare the adverse effects caused by different concentration of PM_{2.5}.

Abbreviations

CI, 95% confidence interval; PM_{2.5}, particulate matter 2.5; PEF, peak expiratory flow; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; PAHs, polycyclic aromatic hydrocarbons; COPD, chronic obstructive pulmonary disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses; NOS, Newcastle-Ottawa Scale; NOS2, Nitric Oxide Synthase 2; SIRT1, Sirtuin 1.

Data Sharing Statement

All data used in this meta-analysis are freely and publicly available from the cited papers used in the analysis; the full citations are in the reference list.

Ethics Approval and Consent to Participate

Not applicable here, as this is a systematic review and meta-analysis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no competing interests.

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