Effect of exposure to ambient PM$_{2.5}$ pollution on the risk of respiratory tract diseases: a meta-analysis of cohort studies

Qian Liu$^{1,2,\Delta}$, Cheng Xu$^{1,2,5,\Delta}$, Guixiang Ji$^{3,\Delta}$, Hui Liu$^{1,2}$, Wentao Shao$^{1,2}$, Chunlan Zhang$^{1,2}$, Aihua Gu$^{1,2}$, Peng Zhao$^{4,✉}$

1 State Key Laboratory of Reproductive Medicine, Institute of Toxicology, Nanjing Medical University, Nanjing, Jiangsu 211166, China;
2 Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China;
3 Nanjing Institute of Environmental Sciences/Key Laboratory of Pesticide Environmental Assessment and Pollution Control, Ministry of Environmental Protection, Nanjing, Jiangsu 210042, China;
4 Department of Neurosurgery, The First Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu 210029, China;
5 Department of Cardiothoracic Surgery, Children's Hospital of Nanjing Medical University, Nanjing, Jiangsu 211166, China.

**Abstract**

The International Agency for Research on Cancer and the World Health Organization have designated airborne particulates, including particulates of median aerodynamic diameter $\leq 2.5$ $\mu$m (PM$_{2.5}$), as Group 1 carcinogens. It has not been determined, however, whether exposure to ambient PM$_{2.5}$ is associated with an increase in respiratory related diseases. This meta-analysis assessed the association between exposure to ambient fine particulate matter (PM$_{2.5}$) and the risk of respiratory tract diseases, using relevant articles extracted from PubMed, Web of Science, and Embase. In results, of the 1,126 articles originally identified, 35 (3.1%) were included in this meta-analysis. PM$_{2.5}$ was found to be associated with respiratory tract diseases. After subdivision by age group, respiratory tract disease, and continent, PM$_{2.5}$ was strongly associated with respiratory tract diseases in children, in persons with cough, lower respiratory illness, and wheezing, and in individuals from North America, Europe, and Asia. The risk of respiratory tract diseases was greater for exposure to traffic-related than non-traffic-related air pollution. In children, the pooled relative risk (RR) represented significant increases in wheezing (8.2%), cough (7.5%), and lower respiratory illness (15.3%). The pooled RRs in children were 1.091 (95%CI: 1.049, 1.135) for exposure to $< 25$ $\mu$g/m$^3$ PM$_{2.5}$, and 1.126 (95%CI: 1.067, 1.190) for exposure to $\geq 25$ $\mu$g/m$^3$ PM$_{2.5}$. In conclusion, exposure to ambient PM$_{2.5}$ was significantly associated with the development of respiratory tract diseases, especially in children exposed to high concentrations of PM$_{2.5}$.

**Keywords:** particulate matter, PM$_{2.5}$, respiratory tract disease, meta-analysis, cohort study
PM$_{2.5}$ pollution and respiratory tract diseases

Introduction

Air pollution is a complicated process involving the spread of distinct pollutants throughout the atmosphere. Air pollution has been found to induce diseases in humans and disorders in other living organisms, as well as destruction of the natural environment$^{[11-2]}$. One type of pollutant, particulate matter (PM)$^{[3]}$, has been associated with serious public health problems$^{[4]}$, as has combinations of PM and other air pollutants$^{[5]}$. PM is classified according to its aerodynamic diameter, and the gold standard used to evaluate its transport capacity through the respiratory tract$^{[6]}$. PM is primarily categorized as coarse (PM$_{10}$), of median aerodynamic diameter $\leq$10 μm, and fine (PM$_{2.5}$), of median aerodynamic diameter $\leq$2.5 μm$^{[6]}$.

PM originates from a wide range of sources, including road dust, agricultural dust, industrial emissions, construction sites, mining operations, river beds, crustal materials, and combustion, or as secondary aerosols from distant sources$^{[7-9]}$. Due to the diversity of sources, human exposure is high. Entry of PM into the respiratory tract depends on the physical characteristics, breathing mode and rate, and size of an individual$^{[10]}$. Moreover, PM size has been significantly related to the etiology of pertinent diseases. Frequently, smaller PM such as PM$_{2.5}$ penetrates the respiratory tract more deeply at a higher rate, and is deposited in the respiratory bronchioles and alveoli or enters the bloodstream, influencing lung function and eventually causing other disorders$^{[11]}$. Exposure to PM has been shown to be harmful to public health, increasing the incidence of respiratory symptoms, reducing lung function, and aggravating respiratory and cardiovascular diseases$^{[12]}$.

PM$_{2.5}$ can also act as a carrier of other harmful constituents, such as heavy metal ions, which add to the deleterious effects of "inert" material$^{[13]}$. Studies analyzing the induction of respiratory diseases by exposure to PM$_{2.5}$ have yielded different outcomes. To quantitatively and accurately assess the effects of exposure to PM$_{2.5}$ on respiratory tract diseases, we performed a meta-analysis that included all relevant cohort studies published to date. This meta-analysis showed that exposure to PM$_{2.5}$ increased the risk of respiratory tract disease.

Materials and methods

Systematic ascertainment of correlative studies

The online databases, including PubMed (National Library of Medicine, Bethesda, MD, USA), Web of Science (Thompson Scientific, Philadelphia, PA, USA), and Embase (Excerpta Medica Database, the Netherlands) were searched for cohort studies published and indexed through May 4, 2016 on the epidemiology of respiratory tract diseases associated with PM$_{2.5}$ air pollution. Search strings, both free text and medical subject headings (MeSH), included (PM$_{2.5}$ OR "particulate matter") AND (wheezing OR bronchitis OR cough OR asthma OR pneumonia OR COPD OR "lung cancer" OR "respiratory infections" OR "respiratory tract diseases"). Based on article titles, abstracts, and full texts, these cohort studies were screened for those fulfilling our inclusion criteria. Cohort-specific results reported in previous meta-analyses alone were also considered in the current analysis.

Inclusion criteria

All epidemiological studies involving the impact on human health of exposure to PM$_{2.5}$ were screened. Health outcomes of interest were morbidities of respiratory tract diseases, according to ICD9 or ICD10, including pneumonia, asthma, bronchitis, upper respiratory tract infections, lower respiratory infections (LRI), wheezing, cough, chronic obstructive pulmonary disease, and lung cancer (Supplementary Table 1). Studies were included if they had cohort designs for respiratory diseases and if they reported relative risk (RR) or odds ratio (OR) with 95% confidence intervals (CIs).

If multiple studies reported an association between respiratory tract disease and PM$_{2.5}$ in the same study cohort at different times, the latest one was chosen. However, if these studies reported different outcomes in the same cohort, each was included. Only studies published in English and exclusively involving human subjects were included. Cohort-specific results reported in previous meta-analyses were considered. If that cohort was included in a meta-analysis that included several other cohorts, the latest publication by this cohort was included.

Exclusion criteria

Case-control studies, case series, and case reports were excluded, as were studies lacking appropriate data (e.g. useful RRs or ORs and 95% CIs in related cohort studies). These criteria were used to maximize sensitivity and ensure non-omission of any relevant study.

Data extraction

All selected publications were screened independently by two investigators (Q.L. and C.X.), and
data extracted using a standardized form. Conflicts were resolved by discussions between the two investigators.

Meta-analysis

Effect estimates for all data collected from the selected studies were summarized using STATA software (version 11; Stata Corp, College Station, TX, USA). The unadjusted RRs and ORs with their 95% CIs were integrated to analyze the strength of the risk of respiratory tract diseases in participants exposed to PM$_{2.5}$. Heterogeneity among studies was examined using a chi-square-based Q-statistic test and the standard $I^2$ test. The Q-statistic test can only determine the presence or absence of heterogeneity, not the degree of heterogeneity. As the $I^2$ test may quantify the extent of heterogeneity in a meta-analysis$^{[14]}$, two methods were chosen to simultaneously assess heterogeneity. Between-study heterogeneity reflected variations in study outcomes among different studies due to inherent differences in study design/populations/exposures, not to chance alone. All pooled RRs were calculated using a random effects model. $P$ showed that heterogeneity accounts for a percentage of the overall variability in random error. $I^2 < 40\%$, 30%-60%, 50%-90%, and 75%-100% represented unimportant, medium, substantial, and high degree of heterogeneity, respectively$^{[15]}$.

Subjects were stratified into subgroups based on heterogeneity, age, region, PM$_{2.5}$ exposure level and source, and differences between groups and risk factors were calculated$^{[16]}$. Moreover, sensitivity analyses were performed to estimate the stability of the outcomes. That is, one study at a time was iteratively removed and the results of the remaining studies were determined$^{[17]}$. Begg funnel plots and the Egger test of asymmetry were performed to statistically evaluate publication bias; a $P$ value $< 0.05$ was considered indicative of publication bias.

Results

Characteristics of the eligible studies assessed by meta-analysis

A review of the PubMed, Web of Science and Embase identified 1,126 eligible studies published in English. Based on the inclusion/exclusion criteria for the effects of exposure to PM$_{2.5}$ pollution on respiratory tract diseases, 35 related studies were retrieved$^{[18-52]}$. A flow diagram of the literature search and selection procedure is shown in Fig. 1. Table 1 shows the details of each of the 35 studies; in these articles, there were 12 outcomes related to wheezing, 5 to bronchitis, 12 to cough, 14 to asthma, 1 to pneumonia, 4 to lower respiratory tract illness (LRI), 0 to upper respiratory tract illness (URI), 4 to lung cancer, 0 to COPD, and 2 to respiratory infections. These 35 articles included a total of 1,135,203 subjects with different respiratory tract diseases. Primary outcomes in our meta-analysis included the incidence of newly developed or exacerbated respiratory tract diseases. These participants resided in a variety of countries or regions and included subjects in different age groups. The mean, median and 50% interquartile range (IQR) for PM$_{2.5}$ ranged from 3.60 to 100 $\mu$g/m$^3$. There were seven articles on traffic-related air pollution and two meta-analyses that included unpublished data of some birth cohort studies (Table 1).

Evidence synthesis

Pooled analysis of the 35 included articles showed that exposure to PM$_{2.5}$ pollution significantly increased the RR for respiratory tract diseases for (RR = 1.076, 95% CI: 1.050, 1.103; $P_{\text{heterogeneity}} < 0.001$, $I^2 = 93.6\%$). To assess differences among subgroups, studies were divided by the age of the participants (children or adults), geographic areas (North America, Europe, Oceania, or Asia), types of diseases, and sources of PM$_{2.5}$ (traffic-related or non-traffic related air pollution) (Figs. 2-5). Studies in children were stratified by types of disease, and extent of exposure concentrations (Table 2, Fig. 6). The pooled RRs in the random-effects model were 1.104 (Table 2 and Fig. 2) for children, 1.099 for Europe, 1.090 for North America, 1.064 (Fig. 3) for Asia, 1.073 for wheezing, 1.153 for LRI, and 1.048 (Fig. 4) for cough. In addition, the pooled RRs exposed to traffic-related and non-traffic related air pollution were 1.085 and 1.076 (Fig. 5), respectively. The pooled RRs in children showed that the rates of wheezing (8.2%), cough (7.5%), and LRI (15.3%) were significantly increased. In adults, however, no positive association was found (Table 2). The pooled RRs in children exposed to PM$_{2.5}$ concentrations $< 25$ $\mu$g/m$^3$ and $\geq 25$ $\mu$g/m$^3$ were 1.091 and 1.126 (Fig. 6), respectively. However, other subgroups showed no association between RR and exposure to PM$_{2.5}$.

Sensitivity analysis

Sensitivity analysis was performed by re-analyzing RR after removing one study at a time. The correlation between exposure to PM$_{2.5}$ pollution and the RR of respiratory tract disease was not driven by any individual study, with no alterations in the significance of the pooled RRs, suggesting that the combined RR remained stable and reliable. Sensitivity analysis indicated that the omission of any one study resulted in RRs between 1.057 (95% CI: 1.038, 1.075) and 1.080 (95% CI: 1.049, 1.112).
| Author (published year) | Study year | Cohort / Study | Outcomes of included studies | Sample number | Age (year) (group) | Country (Continent) | PM$_{2.5}$ (μg/m$^3$) |
|-------------------------|------------|----------------|-----------------------------|---------------|-------------------|---------------------|----------------------|
| Neas et al. 1994 [18]   | 1983-1988  | -              | wheezing, cough, bronchitis, asthma, LRI | 1,237         | 7 to 11 (children) | United States (North America) | 31.1                |
| Romieu et al. 1996 [19] | 1991-1992  | -              | wheezing, cough, LRI | 71           | 5 to 13 (children) | Mexico (North America) | 85.7                |
| Titaen et al. 1999 [20] | 1995       | the PEACE study | cough | 76           | 8-13 (children) | Finland (Europe) | 15 a                |
| Schwartz et al. 2000 [21] | 1990-1991 | the Harvard Six City Study | cough, LRI | 1,844 | school-aged (children) | United States (North America) | 15                |
| Gehring et al. 2002 [22] | 1997-1999  | the PIAMA birth cohort | respiratory infections | 1,606 | Infants (children) | Germany (Europe) | 13.4 c               |
| Gent et al. 2003 [23]   | 2001       | -              | wheezing, cough | 271 | <12 (children) | New England (Europe) | 13.1                |
| Mar et al. 2004 [24]    | 1997–1999  | -              | wheezing, cough | 25 | children and adults | United States (North America) | 10                |
| Millstein et al. 2004 [25] | 1994-1995 | -              | wheezing | 2,034 | 9.6 (0.4) (children) | United States (North America) | 5.24               |
| Pino et al. 2004 [26]   | 1995-1996  | -              | bronchitis | 504 | infants (children) | Chile (South America) | 52                 |
| Johnston et al. 2006 [27] | 2004      | -              | asthma | 235 | children and adults | Australian (Oceania) | 11.1               |
| Bennett et al. 2007 [28] | 1998-2005  | -              | wheezing, cough, asthma | 1,446 | 37.2 (7.2) (adult) | Australian (Oceania) | 6.8                 |
| Brauer et al. 2007 [29] | 1999-2003  | the PIAMA birth cohort | bronchitis, cough | 4,146 | 4 (children) | Netherlands (Europe) | 16.9 c               |
| Morgenstern et al. 2007 [30] | 1999-2000 | GINI and LISA birth cohort | wheezing, bronchitis, cough, respiratory infections | 2,908 | children (children) | Germany (Europe) | 12.8 c               |
| Picciotto et al. 2007 [31] | 1994-2003 | -              | bronchitis | 1,492 | 3 to 4.5 (children) | United States (North America) | >25                |
| Rodriguez et al. 2007 [32] | 1996-2003 | -              | wheezing, cough | 263 | 5 (children) | Australian (Oceania) | 8.534               |
| Beelen et al. 2008 [32] | 1986-1997  | -              | lung cancer | 1,940 | 55 to 69 (adult) | Netherlands (Europe) | 28.2 c               |
| Nuñez et al. 2008 [33]  | 2003-2005  | the EVA cohort | wheezing, cough | 197 | 6 to 14 (children) | Mexico (North America) | 27.8 c               |
| Clark et al. 2010 [34]  | 1999-2000  | -              | asthma | 3,484 | 3 to 4 (children) | United States (North America) | 4.67                |
| Gehring et al. 2010 [33] | 1996-2006 | the PIAMA birth cohort | wheezing | 3,863 | 8 (children) | Netherlands (Europe) | 16.9 c               |
| Gurlay et al. 2013 [36] | 2008-2011  | -              | LRI | 257 | 2 (children) | Bangladesh (Asia) | 100                 |
| Li et al. 2013 [37]     | 2006-2009  | -              | asthma | 412,832 | >18 (adult) | United States (North America) | 11.6                |
| Nielsen et al. 2013 [31] | -         | the ESCAPE study | lung cancer | 2,095 | 43 to 73 (adult) | (Europe) | 5 c                 |
| Evans et al. 2014 [38]  | 2002-2007  | -              | asthma | 530 | 3 to 10 (children) | United States (North America) | 8.6                 |
| Loftus et al. 2014 [39] | 2010-2012  | -              | wheezing | 58 | school-aged (children) | United States (North America) | 6.9 b               |
| Machtens et al. 2014 [46] | -         | 10 European birth cohorts | pneumonia | 14,009 | 36 month (children) | (Europe) | 5                  |
| Author (published year) | Study year | Cohort / Study | Outcomes of included studies | Sample number | Age (year) (group) | Country (Continent) | PM2.5 (μg/m³) |
|-------------------------|------------|----------------|-----------------------------|---------------|--------------------|---------------------|----------------|
| Möller et al. 2014      | -          | 6 birth cohort  | asthma                      | 10,377        | 8 / 10 (children)  | Europe              | 5              |
| Puett et al. 2014       | 1994-2010  | -              | lung cancer                 | 2,155         | 67±8.3 (women)     | United States       | 10             |
| Wendt et al. 2014       | 2005-2007  | -              | asthma                      | 18,289        | 1 to 17 (children) | United States       | 14.97          |
| Young et al. 2014       | 2003-2009  | -              | wheezing, cough, asthma     | 50,884        | 55±9 (adult)       | United States       | 3.6 b          |
| Jacquemin et al. 2015   | -          | the ESCAPE     | asthma                      | 23,704        | adult (adult)      | Europe              | 5              |
| Rice et al. 2015        | 1998-2011  | -              | wheezing, bronchitis, cough, asthma | 4,444         | 50.4 (12.4) (adult) | United States       | 10.8 a         |
| Teresa et al. 2015      | 1998-2006  | the CNBSS study | asthma                      | 29,549        | 40 to 59 (adult)   | Canada              | 12.57          |
| Gehring et al. 2016     | 1996-2010  | 4 European birth cohorts | asthma          | 6,864        | 14 to 16 (children) | Europe              | 10             |
| Guo et al. 2016         | 1990-2009  | -              | lung cancer                 | 368,762       | > 30 (adult)       | China (Asia)        | 10             |
| Tétreault et al. 2016   | 1996-2011  | QICDSS         | asthma                      | 162,752       | 13 (children)      | Canada (North America) | 6.5 b         |

LRI: Lower respiratory illness; PM2.5: mean, a median or b 50% IQR (Interquartile Range); Traffic-related air pollution: c; meta: d 6 birth cohorts: MAAS, BAMSE, PIAMA, GINI and LISA birth cohort; 10 European birth cohorts: BAMSE, GASPSI, GINI and LISA, MAAS, PIAMA and four INMA cohorts; 4 European birth cohorts: BAMSE, PIAMA, GINI and LISA birth cohort

**Table 1 Characteristics of cohort studies with PM2.5 exposure (continued)**

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**Fig. 1** Literature search and article selection protocol used in the present meta-analysis.
Publication bias

Table 2 shows no funnel plot asymmetry, while \( P \) values of the Begg and Egger tests were greater than 0.05 in both the global and stratified analyses, respectively. These findings indicated a lack of publication bias.

Discussion

Previous epidemiological and experimental studies have been unable to definitively determine the specific mechanisms by which exposure to PM has adverse effects on human health. However, accumulated evidence suggests that the most deleterious effects of PM are dependent on particle size, with PM2.5 being especially harmful\(^{53-54}\). Exposure to PM2.5 has been found to increase health risks, particularly with regard to respiratory tract diseases\(^{55}\). Mortality has been regarded as the one important indicator of the effects of PM2.5 pollution on health outcomes\(^{56}\). Several case-control studies have also assessed daily hospital

| Study                  | RR (95% CI) | Weight% |
|------------------------|-------------|---------|
| Adult                  |             |         |
| Bennett 2007 Asthma    | 0.51 (0.55, 0.80) | 0.23   |
| Bennett 2007 Wheezing  | 1.00 (0.79, 1.29) | 0.53   |
| Bennett 2007 Cough     | 0.54 (0.47, 1.15) | 0.28   |
| Johnston 2006 Asthma   | 1.00 (0.98, 1.02) | 3.36   |
| Lii 2013 Asthma        | 0.99 (0.92, 1.06) | 3.12   |
| Mar 2004 Cough         | 0.99 (0.96, 1.02) | 0.57   |
| Mar 2005 Wheezing      | 0.99 (0.94, 1.04) | 1.36   |
| Rice 2015 Asthma       | 0.97 (0.85, 1.10) | 1.79   |
| Rice 2015 Bronchitis   | 0.98 (0.96, 1.00) | 1.20   |
| Rice 2015 Cough        | 1.00 (0.99, 1.00) | 0.77   |
| Rice 2015 Wheezing     | 0.99 (0.86, 1.11) | 1.00   |
| Terrie 2015 Asthma     | 1.00 (0.84, 1.25) | 1.07   |
| Young 2014 Asthma      | 1.06 (0.99, 1.06) | 1.16   |
| Young 2014 Cough       | 0.95 (0.88, 1.02) | 2.57   |
| Young 2014 Wheezing    | 1.04 (1.02, 1.06) | 2.28   |
| Gao 2016 lung cancer   | 1.06 (0.91, 1.24) | 1.00   |
| Pani 2014 lung cancer  | 0.81 (0.63, 1.04) | 0.76   |
| Beeden 2008 lung cancer| 1.18 (0.96, 1.45) | 0.95   |
| Bleeker 2008 lung cancer| 1.11 (0.91, 1.35) | 1.11   |
| Beeden 2008 lung cancer| 1.04 (0.88, 1.23) | 1.34   |
| Subtotal (\( I^2 \)-squared = 44.6%, \( p = 0.000 \)) | 1.02 (0.99, 1.05) | 31.70   |

| Children               |             |         |
|------------------------|-------------|---------|
| Clark 2010 Asthma      | 1.02 (1.00, 1.04) | 3.43   |
| Evans 2014 Asthma      | 1.27 (0.96, 1.69) | 0.45   |
| Goering 2014 Asthma    | 1.26 (1.06, 1.50) | 0.53   |
| Gent 2003 Cough        | 1.00 (0.91, 1.09) | 2.37   |
| Gent 2005 Wheezing     | 1.03 (0.92, 1.15) | 1.73   |
| Garley 2013 LRI        | 1.04 (0.99, 1.08) | 3.14   |
| Johnson 2006 Asthma    | 1.01 (0.96, 1.07) | 3.22   |
| Loffe 2004 Wheezing    | 1.31 (1.18, 1.47) | 2.17   |
| Mar 2004 Cough         | 1.18 (0.99, 1.38) | 1.20   |
| Mar 2004 Wheezing      | 0.55 (0.49, 0.61) | 0.05   |
| Milestone 2004 Wheezing| 1.03 (0.87, 1.21) | 1.36   |
| Naus 1994 Asthma       | 0.84 (0.68, 1.04) | 0.47   |
| Naus 1994 Bronchitis   | 1.18 (0.99, 1.42) | 1.22   |
| Naus 1994 Cough        | 1.05 (0.85, 1.28) | 1.00   |
| Naus 1994 LRI          | 1.13 (0.99, 1.28) | 1.69   |
| Naus 1994 Wheezing     | 1.05 (0.87, 1.26) | 1.18   |
| Piccirillo 2007 Bronchitis | 1.00 (1.04, 1.08) | 1.86   |
| Pine 2004 Bronchitis   | 1.05 (1.00, 1.09) | 3.14   |
| Roche 2007 Cough       | 1.00 (1.00, 1.01) | 3.47   |
| Roche 2007 Wheezing    | 1.00 (0.99, 1.01) | 3.47   |
| Romieu 1996 Cough      | 1.19 (1.06, 1.36) | 2.01   |
| Romieu 1996 LRI        | 1.21 (1.08, 1.42) | 2.03   |
| Romieu 1996 Wheezing   | 1.09 (0.95, 1.27) | 1.58   |
| Schwartz 1999 Cough    | 1.07 (0.96, 1.21) | 1.53   |
| Schwartz 1999 LRI      | 1.31 (1.10, 1.57) | 1.25   |
| Tannen 1999 Cough      | 1.48 (1.20, 1.81) | 0.40   |
| Wrench 2014 Asthma     | 1.12 (1.03, 1.23) | 2.47   |
| Wrench 2014 LRI        | 1.02 (0.91, 1.21) | 0.06   |
| Wrench 2014 Bronchitis | 1.31 (1.28, 1.34) | 3.46   |
| Wrench 2014 Cough      | 1.23 (0.78, 1.95) | 0.21   |
| Wrench 2014 Wheezing   | 0.88 (0.66, 1.16) | 0.06   |
| Wrench 2014 Asthma     | 1.11 (0.94, 1.31) | 1.35   |
| Wrench 2014 LRI        | 0.90 (0.80, 1.00) | 0.04   |
| Wrench 2014 Wheezing   | 1.04 (0.82, 1.31) | 1.02   |
| Wrench 2014 Thrust     | 1.03 (0.93, 1.15) | 1.73   |
| Wrench 2014 Cough      | 0.95 (0.88, 1.02) | 1.26   |
| Wrench 2014 LRI        | 1.09 (0.94, 1.27) | 1.52   |
| Wrench 2014 Wheezing   | 1.10 (0.96, 1.25) | 1.75   |
| Wrench 2014 Asthma     | 1.09 (1.03, 1.15) | 2.86   |
| Wrench 2014 LRI        | 1.16 (1.03, 1.31) | 2.82   |
| Wrench 2014 Bronchitis | 1.19 (1.07, 1.34) | 68.30  |
| Overall (\( I^2 \)-squared = 93.6%, \( p = 0.000 \)) | 1.08 (0.95, 1.10) | 190.69  |

FIG. 2 Combined RRs with 95% CIs for the association between PM\(_{2.5}\) exposure and respiratory tract diseases in all subjects and in subpopulations of children and adults.
admissions or emergency department visits. However, these variables are limited by the lack of persistent observation, restriction of end points, and recall bias. Therefore, this meta-analysis was performed to clarify the relationship between exposure to PM$_{2.5}$ and the incidence or aggravation rate of respiratory tract diseases in cohort studies. In addition, studies were stratified by age, geographic location, and the source and concentration of PM$_{2.5}$.

This systematic review found that exposure to PM$_{2.5}$ was positively correlated with risk of respiratory tract disease, especially in children; in subjects with wheezing, cough, and LRI; and in populations in Europe, North America, and Asia. The pooled RRs were greater

| Study | RR(95% CI) | Weight% |
|-------|------------|----------|
| Oceania | | |
| Bennett 2007 Asthma | 0.91 (0.55, 1.49) | 92.3 |
| Bennett 2007 Wheezing | 0.89 (0.79, 1.00) | 93.3 |
| Bennett 2007 Cough | 0.74 (0.47, 1.15) | 92.8 |
| Jefferon 2006 Asthma | 1.01 (0.98, 1.03) | 3.3 |
| Jefferon 2006 Asthma | 1.00 (0.98, 1.03) | 3.3 |
| Rodriguez 2007 Cough | 1.00 (0.99, 1.01) | 3.47 |
| Rodriguez 2007 Wheezing | 1.00 (0.99, 1.01) | 3.47 |
| Sultani (F-squared = 0.00%, p = 0.043) | 1.00 (0.99, 1.01) | 14.65 |
| North America | | |
| Braver 2007 Bronchiolitis | 0.88 (0.66, 1.18) | 9.60 |
| Braver 2007 Cough | 1.11 (0.94, 1.33) | 1.35 |
| Clark 2010 Asthma | 1.02 (0.90, 1.13) | 3.45 |
| Evans 2014 Asthma | 1.27 (0.90, 1.80) | 9.65 |
| Li 2013 Asthma | 0.99 (0.95, 1.04) | 1.12 |
| Lathi 2014 Wheezing | 1.11 (1.18, 1.53) | 2.17 |
| Mar 2004 Cough | 1.18 (0.99, 1.42) | 1.22 |
| Mar 2004 Cough | 0.99 (0.66, 1.46) | 0.57 |
| Mar 2004 Wheezing | 0.95 (0.19, 0.64) | 0.95 |
| Mar 2004 Wheezing | 0.99 (0.64, 1.57) | 1.25 |
| Milllican 2004 Wheezing | 1.03 (0.87, 1.23) | 1.26 |
| Naus 1994 Asthma | 0.84 (0.60, 1.17) | 9.47 |
| Naus 1994 Bronchiolitis | 1.18 (0.99, 1.42) | 1.22 |
| Naus 1994 Cough | 1.05 (0.85, 1.29) | 1.60 |
| Naus 1994 LRI | 1.13 (0.99, 1.26) | 1.69 |
| Naus 1994 Wheezing | 1.05 (0.87, 1.26) | 1.18 |
| Nunez 2009 Cough | 1.09 (0.90, 1.25) | 2.46 |
| Nunez 2009 Cough | 1.10 (1.03, 1.17) | 2.82 |
| Pizziello 2007 Bronchiolitis | 1.00 (0.99, 1.01) | 1.50 |
| Pizziello 2007 Bronchiolitis | 1.05 (0.99, 1.01) | 1.50 |
| Rau 2015 Asthma | 0.97 (0.85, 1.10) | 1.79 |
| Rau 2015 Bronchiolitis | 0.98 (0.86, 1.11) | 1.80 |
| Rau 2015 Cough | 1.04 (0.88, 1.28) | 9.77 |
| Rau 2015 Wheezing | 0.99 (0.66, 1.46) | 1.50 |
| Rau 1996 Cough | 1.19 (1.06, 1.33) | 2.01 |
| Rau 1996 LRI | 1.21 (1.08, 1.35) | 2.01 |
| Rau 1996 Wheezing | 1.09 (0.95, 1.27) | 1.58 |
| Schrader 1999 Cough | 1.07 (0.90, 1.26) | 1.23 |
| Schrader 1999 LRI | 1.35 (1.11, 1.65) | 1.25 |
| Teresa 2013 Asthma | 1.03 (0.84, 1.23) | 1.07 |
| Wang 2014 Asthma | 1.12 (0.85, 1.48) | 2.47 |
| Young 2014 Asthma | 1.28 (0.99, 1.64) | 1.10 |
| Young 2014 Cough | 0.99 (0.88, 1.10) | 2.57 |
| Young 2014 Wheezing | 1.14 (0.94, 1.38) | 2.29 |
| Peet 2011 lung cancer | 1.06 (0.91, 1.25) | 1.45 |
| Sultani (F-squared = 73.6%, p = 0.000) | 1.09 (1.05, 1.13) | 37.26 |
| Europe | | |
| Gehringer 2002 Respiratory infections | 0.98 (0.80, 1.20) | 1.04 |
| Gehringer 2010 Asthma | 1.04 (0.87, 1.17) | 1.03 |
| Gehringer 2010 Wheezing | 1.29 (1.00, 1.66) | 9.75 |
| Gehringer 2012 Asthma | 1.00 (0.91, 1.09) | 2.17 |
| Gehringer 2012 Wheezing | 0.99 (0.92, 1.06) | 0.95 |
| Gehringer 2012 Wheezing | 1.00 (0.92, 1.06) | 0.95 |
| Jacquetins 2013 Asthma | 0.94 (0.78, 1.11) | 9.27 |
| Maufer 2014 Asthma | 1.22 (0.88, 2.73) | 1.34 |
| Maufer 2014 Asthma | 1.12 (0.87, 1.47) | 1.34 |
| Mergersman 2007 Bronchiolitis | 1.05 (0.92, 1.20) | 1.75 |
| Mergersman 2007 Cough | 1.05 (0.83, 1.33) | 1.26 |
| Mergersman 2007 Cough | 1.05 (0.83, 1.33) | 1.26 |
| Mergersman 2007 Respiratory infections | 1.09 (0.84, 1.37) | 1.52 |
| Mergersman 2007 Wheezing | 1.10 (0.86, 1.42) | 1.75 |
| Tittarelli 1999 Cough | 1.06 (0.82, 1.37) | 1.06 |
| Murchie 2014 pneumonia | 0.88 (0.61, 1.27) | 0.96 |
| Nollet 2012 lung cancer | 1.16 (0.86, 1.58) | 0.89 |
| Berken 2008 lung cancer | 0.81 (0.63, 1.04) | 0.76 |
| Berken 2008 lung cancer | 1.11 (0.89, 1.40) | 1.11 |
| T’Rachki 2016 Asthma | 1.31 (1.28, 1.34) | 1.40 |
| Sultani (F-squared = 83.7%, p = 0.000) | 1.19 (1.09, 1.29) | 21.51 |
| Asia | | |
| Guledsky 2013 LRI | 1.04 (0.99, 1.08) | 3.14 |
| Guo 2016 lung cancer | 1.07 (0.96, 1.19) | 3.44 |
| Sultani (F-squared = 47.3%, p = 0.166) | 1.00 (0.93, 1.08) | 6.58 |
| Overall (F-squared = 95.6%, p = 0.000) | 1.08 (1.05, 1.10) | 100.00 |

Fig. 3 Combined RRs with 95% CIs for the association between PM$_{2.5}$ exposure and respiratory tract diseases by geographic region (North America, Asia, Europe, and Oceania).
for traffic-related than non-traffic-related air pollution. Ultimately, we found that PM$_{2.5}$ in children was significantly associated with cough, wheezing, and LRI. Furthermore, in children, pooled RRs were greater for high ($\geq 25$ $\mu$g/m$^3$) than low ($< 25$ $\mu$g/m$^3$) PM$_{2.5}$ concentrations. These findings suggested that traffic-related PM$_{2.5}$ did greater harm to the human body, and that exposure to PM$_{2.5}$ pollution may pose an increased

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Fig. 4 Combined RRs with 95% CIs for the association between PM$_{2.5}$ exposure and respiratory tract diseases by type of disease (asthma, bronchitis, cough, LRI and wheezing).
risk for respiratory tract disease, especially in children exposed to high concentrations of PM$_{2.5}$. These results are consistent with those of previous reports$^{[58-59]}$, as well as being more accurate than the results of a previous meta-analysis of case-control studies$^{[60]}$.

Above all, this meta-analysis included many more articles with a larger population, especially birth cohorts, than previous meta-analyses. Second, longitudinal cohort studies with complete and reliable information are considered less likely to be influenced by confounding and better able to address the temporal sequence of events. Finally, this study not only revealed a strong association between PM$_{2.5}$ and respiratory tract diseases in general, but also strong correlations between PM$_{2.5}$ and specific types of respiratory tract diseases (wheezing, cough and LRI). Therefore, the results of this meta-analysis could amplify and complete those of earlier meta-analyses.

**Fig. 5** Combined RRs with 95% CIs for the association between exposure to PM$_{2.5}$ and respiratory tract diseases exposed to traffic-related and non-traffic-related air pollution.
However, the pathological mechanisms underlying the effects of PM$_{2.5}$ exposure on the respiratory tract are not fully understood. PM size may be affected by chemical, biologic, and physical properties, resulting in various pathological consequences$^6$. There are several plausible biomedical explanations for associations between exposure to PM$_{2.5}$ and respiratory tract diseases. Owing to its fine consistency, PM$_{2.5}$ can be deposited more deeply into the lungs. Moreover, these particles may contain toxic components or contaminants, such as nitrates, sulfates, acids, and metals, originating from combustion processes or similar activities$^{61}$. These particles can therefore lead to stress, inflammation, and allergy. Our results showed that PM$_{2.5}$ exposure resulted in a greater incidence of cough, wheezing, and LRI in children than in adults, which may be related to differences in the structure of the respiratory tract in adults and children. Specifically, the immature respiratory system in children may be more sensitive to PM$_{2.5}$. PM$_{2.5}$ of aerodynamic diameter 2.5-10 $\mu$m mainly derives from the soil and abrasive mechanical processes. These particles may transport biologic materials, such as bacteria, molds, and pollens, which may have harmful effects on the respiratory system$^{62-63}$. Therefore, some infectious bacterial respiratory diseases or hay fever are more likely to manifest after lengthy exposure to PM$_{2.5}$ rather than PM$_{2.5}$. Our results are consistent with these findings.

We also found that the correlation between PM$_{2.5}$ exposure and respiratory diseases was stronger in...
European and North American populations, probably due to more studies of PM2.5 were conducted in these populations. The risk of respiratory diseases was also higher following exposure to high than low quantities of PM2.5, suggesting that the concentration of PM2.5 is also a risk factor for respiratory diseases.

This meta-analysis had several limitations. First, some of the outcomes demonstrated heterogeneity. We utilized a random-effects model, with stratified analysis performed to make up for this shortcoming. Second, non-English publications and unpublished results were excluded. Some of these studies may have included negative outcomes, which could have influenced our results. Third, we could not exclude residual confounders, which may have influenced our results. Fourth, the limitations of data collection from all studies prevented a comparison of results from different climate zones, with different temperatures and humidity, which may have influenced the correlation between PM2.5 exposure and respiratory diseases.

In conclusion, we found that PM2.5 may play an important role in respiratory tract diseases, especially in children exposed to high concentrations of PM2.5. Additional studies are needed to assess the quantification and identification of other, as yet undetermined, harmful compounds in ambient air particles, and to determine the underlying mechanisms that cause these particles to affect human health.

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| Table 2 | Association of PM$_{2.5}$ exposure with episodes of respiratory tract diseases in children and adult group. |
|-------------------|-------------------------------------------------|-------------------------------------|---------------------------|
| Symptom            | N | RR (95%CI) Random-effects | P ($I^2$) | P for Egger / Begg bias test |
|-------------------|---|--------------------------|----------|-----------------------------|
| **Children Symptom** | | | | |
| Wheezing           | 10 | 1.082 (1.011, 1.158) | 0.000 ($77.2\%$) | 0.079 / 0.107 |
| Bronchitis         | 5  | 1.145 (0.957, 1.370) | 0.000 (90.2%) | 0.593 / 1.000 |
| Cough              | 10 | 1.075 (1.019, 1.134) | 0.002 (65.4%) | 0.007 / 0.721 |
| Asthma             | 3  | 1.119 (0.989, 1.266) | 0.000 (98.5%) | 0.910 / 0.536 |
| Lower respiratory illness | 4 | 1.153 (1.033, 1.287) | 0.006 (76.2%) | 0.064 / 0.308 |
| Respiratory infections | 2 | 1.050 (0.930, 1.184) | **0.409 (0.00%)** | N/A / 1.000 |
| Pneumonia          | 1  | 2.580 (0.910, 7.270) | - | - |
| **Total**          | 40 | **1.104 (1.069, 1.139)** | 0.000 (95.4%) | 0.025 / 0.408 |
| **Adult Symptom**  | | | | |
| Wheezing           | 4  | 1.053 (0.964, 1.150) | **0.229 (30.5%)** | 0.593 / 1.000 |
| Bronchitis         | 1  | 0.980 (0.860, 1.110) | - | - |
| Cough              | 4  | 0.951 (0.885, 1.021) | **0.493 (0.00%)** | 0.713 / 0.308 |
| Asthma             | 7  | 0.999 (0.978, 1.021) | **0.553 (0.00%)** | 0.581 / 1.000 |
| Lung cancer        | 4  | 1.064 (0.991, 1.142) | **0.216 (30.8%)** | 0.691 / 0.806 |
| **Total**          | 20 | 1.022 (0.986, 1.058) | 0.000 (64.6%) | **0.132 / 0.546** |

$P (I^2)$: P-value for test of heterogeneity, $I^2$ of Higgins and Thompson reflecting the proportion of total variation in the estimate that is due to heterogeneity between studies. LRI: lower respiratory illness. Bold: significant results.
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