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Original Article

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

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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 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 $\ge 25 \ \mu g/m^3 PM_{2.5}$. 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, PM2.5, respiratory tract disease, meta-analysis, cohort study

The author reported no conflict of interests.

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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^[1–2]. 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 in the atmosphere and inhalation capacity through the respiratory tract^[6]. PM is primarily categorized as coarse (PM₁₀), of median aerodynamic diameter ≤ 10 µm, and fine (PM_{2.5}), of median aerodynamic diameter

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 PM2.5 air pollution. Search strings, both free text and medical subject headings (MeSH), included (PM2 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. I^2 showed that heterogeneity accounts for a percentage of the overall variability in random error. $l^2 < 40\%$, 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 μ g/m³. There were seven articles on trafficrelated 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 PM2.5 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).

Table 1 Characteristics of cohort studies with PM _{2.5} exposure							
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
Tiitanen 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)	German (Europe)	13.4 °
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 °
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 °
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 ^[52]	1986-1997	-	lung cancer	1,940	55 to 69 (adult)	Netherlands (Europe)	28.2 °
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 ^[35]	1996-2006	the PIAMA birth cohort	wheezing	3,863	8 (children)	Netherlands (Europe)	16.9 °
Gurley 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 ^[51]	-	the ESCAPE study	lung cancer	2,095	43 to 73 (adult)	(Europe)	5 °
Evans et al. 2014 ^[38]	2002-2007	-	asthma	530	3 to10 (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
MacIntyre et al. 2014 ^{d[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)	$\frac{PM_{2.5}}{(\mu g/m^3)}$
Mölter et al. 2014 ^{d [40]}	-	6 birth cohort	asthma	10,377	8 / 10 (children)	(Europe)	5
Puett et al. 2014 ^[50]	1994-2010	-	lung cancer	2,155	67±8.3 (women)	United States (North America)	10
Wendt et al. 2014 ^[41]	2005-2007	-	asthma	18,289	1to17 (children)	United States (North America)	14.97
Young et al. 2014 ^[42]	2003-2009	-	wheezing, cough, asthma	50,884	55±9 (adult)	United States (North America)	3.6 ^b
Jacquemin et al. 2015 ^{d [43]}	-	the ESCAPE study	asthma	23,704	adult (adult)	(Europe)	5
Rice et al. 2015 ^[44]	1998-2011	-	wheezing, bronchitis, cough, asthma	4,444	50.4 (12.4) (adult)	United States (North America)	10.8 ^a
Teresa et al. 2015 ^[45]	1998-2006	the CNBSS study	asthma	29,549	40 to 59 (adult)	Canada (North America)	12.57
Gehring et al. 2016 ^[47]	1996-2010	4 European birth cohorts	asthma	6,864	14 to 16 (children)	(Europe)	10
Guo et al. 2016 ^[49]	1990-2009	-	lung cancer	368,762	> 30 (adult)	China (Asia)	10
Tétreault et al. 2016 ^[48]	1996-2011	QICDSS	asthma	162,752	13 (children)	Canada (North America)	6.5 ^b

LRI: Lower respiratory illness; PM_{2.5}: 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, GASPII, GINI and LISA, MAAS, PIAMA and four INMA cohorts; 4 European birth cohorts: BAMSE, PIAMA, GINI and LISA birth cohort



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

Adult Bennett 2007 Asthma Bennett 2007 Wheezing Bennett 2007 Cough Johnston 2006 Asthma Mar 2004 Cough Mar 2004 Cough Mar 2004 Wheezing Rice 2015 Sasthma Rice 2015 Wheezing Rice 2015 Wheezing Teresa 2015 Asthma Young 2014 Asthma Young 2014 Cough Young 2014 Cough Young 2014 Cough Young 2014 Wheezing Guo 2016 lung cancer Puett 2014 lung cancer Beelen 2008 lung cance	$\begin{array}{c} 0.91 \ (0.55, 1.49) \\ 1.08 \ (0.79, 1.48) \\ 0.74 \ (0.47, 1.15) \\ 1.00 \ (0.98, 1.03) \\ 0.99 \ (0.85, 1.04) \\ 0.89 \ (0.66, 1.20) \\ 0.99 \ (0.84, 1.17) \\ 0.97 \ (0.85, 1.10) \\ 0.98 \ (0.86, 1.11) \\ 1.08 \ (0.84, 1.38) \\ 0.98 \ (0.86, 1.11) \\ 1.03 \ (0.84, 1.25) \\ 1.20 \ (0.99, 1.46) \\ 0.95 \ (0.88, 1.03) \\ 1.14 \ (1.04, 1.26) \\ 1.07 \ (1.06, 1.09) \\ 1.06 \ (0.91, 1.25) \\ 0.81 \ (0.63, 1.04) \\ 1.18 \ (0.96, 1.46) \\ 1.11 \ (0.91, 1.34) \\ 1.04 \ (0.88, 1.23) \\ 1.02 \ (0.99, 1.06) \\ 1.02 \ (1.00, 1.03) \\ 1.27 \ (0.90, 1.79) \end{array}$	0.23 0.53 0.28 3.36 3.12 0.57 1.36 1.79 1.80 0.77 1.80 1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
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Li 2013 Astima Mar 2004 Cough Mar 2004 Wheezing Rice 2015 Bronchitis Rice 2015 Bronchitis Rice 2015 Wheezing Teresa 2015 Astima Young 2014 Astima Young 2014 Astima Young 2014 Wheezing Guo 2016 lung cancer Puett 2014 lung cancer Beelen 2008 lung cancer Bielen 2008 lung cancer Beelen 2008 lung cancer Jacquemin 2015 Astima Subtotal (I-squared = 64.6%, p = 0.000)	$\begin{array}{c} 0.99 \ (0.59, 1.04)\\ 0.89 \ (0.66, 1.20)\\ 0.99 \ (0.84, 1.17)\\ 0.97 \ (0.85, 1.10)\\ 0.98 \ (0.86, 1.11)\\ 1.08 \ (0.84, 1.23)\\ 1.20 \ (0.99, 1.46)\\ 0.95 \ (0.84, 1.25)\\ 1.20 \ (0.99, 1.46)\\ 1.11 \ (1.04, 1.26)\\ 1.07 \ (1.06, 1.09)\\ 1.06 \ (0.91, 1.25)\\ 0.81 \ (0.63, 1.04)\\ 1.18 \ (0.96, 1.46)\\ 1.11 \ (0.96, 1.42)\\ 1.04 \ (0.88, 1.23)\\ 1.02 \ (0.99, 1.06)\\ 1.02 \ (1.00, 1.03)\\ 1.27 \ (0.90, 1.79)\\ \end{array}$	3.12 0.57 1.36 1.79 1.80 0.77 1.80 1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Mar 2004 Cougn Mar 2004 Wheezing Rice 2015 Asthma Rice 2015 Deronchitis Rice 2015 Cough Rice 2015 Wheezing Teresa 2015 Asthma Young 2014 Asthma Young 2014 Asthma Young 2014 Asthma Young 2014 Wheezing Guo 2016 lung cancer Puett 2014 lung eancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Jacquemin 2015 Asthma Subtotal (I-squared = 64.6%, p = 0.000)	$\begin{array}{c} 0.89 \ (0.86, 1.20) \\ 0.99 \ (0.84, 1.17) \\ 0.97 \ (0.85, 1.10) \\ 0.98 \ (0.86, 1.11) \\ 1.08 \ (0.84, 1.38) \\ 0.98 \ (0.86, 1.11) \\ 1.03 \ (0.84, 1.25) \\ 1.20 \ (0.99, 1.46) \\ 0.95 \ (0.88, 1.03) \\ 1.14 \ (1.04, 1.26) \\ 1.07 \ (1.06, 1.09) \\ 1.06 \ (0.91, 1.25) \\ 0.81 \ (0.63, 1.04) \\ 1.18 \ (0.96, 1.46) \\ 1.11 \ (0.91, 1.34) \\ 1.04 \ (0.88, 1.23) \\ 1.02 \ (0.99, 1.06) \\ \end{array}$	0.37 1.36 1.79 1.80 0.77 1.80 1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Mar 2004 Wite2ning Rice 2015 Sashma Rice 2015 Bronchitis Rice 2015 Wheezing Teresa 2015 Ashma Young 2014 Ashtma Young 2014 Cough Young 2014 Wheezing Guo 2016 lung cancer Puett 2014 lung cancer Beelen 2008 lung c	$\begin{array}{c} 0.99 \ (0.84, 1.17) \\ 0.97 \ (0.85, 1.10) \\ 0.98 \ (0.86, 1.11) \\ 1.08 \ (0.84, 1.38) \\ 0.98 \ (0.84, 1.25) \\ 1.20 \ (0.99, 1.46) \\ 0.95 \ (0.88, 1.03) \\ 1.14 \ (1.04, 1.26) \\ 1.07 \ (1.06, 1.09) \\ 1.06 \ (0.91, 1.25) \\ 0.81 \ (0.63, 1.04) \\ 1.18 \ (0.96, 1.46) \\ 1.11 \ (0.91, 1.34) \\ 1.04 \ (0.88, 1.23) \\ 1.02 \ (0.99, 1.06) \\ \end{array}$	1.30 1.79 1.80 0.77 1.80 1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Rice 2015 Stronchitis Rice 2015 Cough Rice 2015 Cough Rice 2015 Asthma Young 2014 Asthma Young 2014 Asthma Young 2014 Wheezing Guo 2016 lung cancer Puett 2014 lung cancer Beelen 2008 lung	$\begin{array}{c} 0.97 \ (0.53, 1.10)\\ 0.98 \ (0.86, 1.11)\\ 1.08 \ (0.84, 1.23)\\ 0.98 \ (0.86, 1.11)\\ 1.03 \ (0.84, 1.25)\\ 1.20 \ (0.99, 1.46)\\ 0.95 \ (0.88, 1.03)\\ 1.14 \ (1.04, 1.26)\\ 1.07 \ (1.06, 1.09)\\ 1.06 \ (0.91, 1.25)\\ 0.81 \ (0.63, 1.04)\\ 1.18 \ (0.96, 1.46)\\ 1.11 \ (0.96, 1.43)\\ 1.04 \ (0.88, 1.23)\\ 1.02 \ (0.99, 1.06)\\ \end{array}$	1.79 1.80 0.77 1.80 1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Rice 2015 Douclinits Rice 2015 Wheezing Teresa 2015 Asthma Young 2014 Asthma Young 2014 Cough Young 2014 Cough Young 2014 Wheezing Guo 2016 lung cancer Beelen 2008 lung cancer Subtotal (I-squared = 64.6%, p = 0.000) Children	$\begin{array}{c} 0.96 \ (0.84, 1.38) \\ 0.98 \ (0.84, 1.38) \\ 0.98 \ (0.84, 1.25) \\ 1.20 \ (0.99, 1.46) \\ 0.95 \ (0.88, 1.03) \\ 1.14 \ (1.04, 1.26) \\ 1.07 \ (1.06, 1.09) \\ 1.06 \ (0.91, 1.25) \\ 0.81 \ (0.63, 1.04) \\ 1.18 \ (0.96, 1.46) \\ 1.11 \ (0.91, 1.34) \\ 1.04 \ (0.88, 1.23) \\ 1.02 \ (0.99, 1.06) \\ \end{array}$	0.77 1.80 1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Rice 2015 Wheezing Teresa 2015 Asthma Young 2014 Asthma Young 2014 Cough Young 2014 Wheezing Guo 2016 lung cancer Puett 2014 lung cancer Beelen 2008 lung cancer Be	$\begin{array}{c} 0.98 & (0.86, 1.11)\\ 1.03 & (0.84, 1.25)\\ 1.20 & (0.99, 1.46)\\ 0.95 & (0.88, 1.03)\\ 1.14 & (1.04, 1.26)\\ 1.07 & (1.06, 1.09)\\ 1.06 & (0.91, 1.25)\\ 0.81 & (0.63, 1.04)\\ 1.18 & (0.96, 1.46)\\ 1.11 & (0.94, 1.34)\\ 1.04 & (0.88, 1.23)\\ 1.02 & (0.99, 1.06)\\ \end{array}$	1.80 1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Rice 2013 Writering Teresa 2015 Asthma Young 2014 Asthma Young 2014 Cough Young 2014 Wheezing Guo 2016 lung cancer Puett 2014 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Subtotal (I-squared = 64.6%, p = 0.000) Children	$\begin{array}{c} 0.96 \left(0.84, 1.25\right)\\ 1.02 \left(0.99, 1.46\right)\\ 0.95 \left(0.88, 1.03\right)\\ 1.14 \left(1.04, 1.26\right)\\ 1.07 \left(1.06, 1.09\right)\\ 1.06 \left(0.91, 1.25\right)\\ 0.81 \left(0.63, 1.04\right)\\ 1.18 \left(0.96, 1.46\right)\\ 1.11 \left(0.91, 1.34\right)\\ 1.04 \left(0.88, 1.23\right)\\ 1.02 \left(0.99, 1.06\right)\\ \end{array}$	1.07 1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Voung 2014 Asthina Young 2014 Cough Young 2014 Cough Young 2014 Wheezing Guo 2016 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Subtotal (I-squared = 64.6%, p = 0.000) Children	$\begin{array}{c} 1.50 & (0.59, 1.46) \\ 0.95 & (0.88, 1.03) \\ 1.14 & (1.04, 1.26) \\ 1.07 & (1.06, 1.09) \\ 1.06 & (0.91, 1.25) \\ 0.81 & (0.63, 1.04) \\ 1.18 & (0.96, 1.46) \\ 1.11 & (0.91, 1.34) \\ 1.04 & (0.88, 1.23) \\ 1.02 & (0.99, 1.06) \end{array}$	1.10 2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Young 2014 Asumia Young 2014 Kumia Young 2014 Wheezing Guo 2016 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2015 Asthma Subtotal (1-squared = 64.6%, p = 0.000)	$\begin{array}{c} 1.20 \ (0.79, 1.40)\\ 0.95 \ (0.88, 1.03)\\ 1.14 \ (1.04, 1.26)\\ 1.07 \ (1.06, 1.09)\\ 1.06 \ (0.91, 1.25)\\ 0.81 \ (0.63, 1.04)\\ 1.18 \ (0.96, 1.46)\\ 1.11 \ (0.91, 1.34)\\ 1.04 \ (0.88, 1.23)\\ 1.02 \ (0.99, 1.06)\\ \end{array}$	2.57 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Voing 2014 Wheezing Guo 2016 lung cancer Puet 2014 Ung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Subtotal (I-squared = 64.6%, p = 0.000) Children	$\begin{array}{c} 0.36 \ (0.58, 1.03) \\ 1.14 \ (1.04, 1.26) \\ 1.07 \ (1.06, 1.09) \\ 1.06 \ (0.91, 1.25) \\ 0.81 \ (0.63, 1.04) \\ 1.18 \ (0.96, 1.46) \\ 1.11 \ (0.91, 1.34) \\ 1.04 \ (0.88, 1.23) \\ 1.02 \ (0.99, 1.06) \end{array}$	2.37 2.28 3.44 1.43 0.76 0.99 1.11 1.34 31.70
Guo 2016 Iung cancer Puett 2014 Iung cancer Beelen 2008 Iung cancer Beelen 2008 Iung cancer Beelen 2008 Iung cancer Subtotal (I-squared = 64.6%, p = 0.000)	$\begin{array}{c} 1.07 (1.06, 1.09) \\ 1.07 (1.06, 1.09) \\ 1.06 (0.91, 1.25) \\ 0.81 (0.63, 1.04) \\ 1.18 (0.96, 1.46) \\ 1.11 (0.91, 1.34) \\ 1.04 (0.88, 1.23) \\ 1.02 (0.99, 1.06) \\ \end{array}$	3.44 1.43 0.76 0.99 1.11 1.34 31.70
Decle 2016 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2008 lung cancer Beelen 2015 Asthma Subtotal (1-squared = 64.6%, p = 0.000)	1.07 (1.03, 1.09) 1.06 (0.91, 1.25) 0.81 (0.63, 1.04) 1.18 (0.96, 1.46) 1.11 (0.91, 1.34) 1.04 (0.88, 1.23) 1.02 (0.99, 1.06) 1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	1.43 0.76 0.99 1.11 1.34 31.70
Reclen 2008 lung cancer Nielsen 2013 lung cancer Beelen 2008 lung cancer Jacquemin 2015 Asthma Subtotal (1-squared = 64.6%, p = 0.000)	1.06 (0.63, 1.04) 0.81 (0.63, 1.04) 1.18 (0.96, 1.46) 1.11 (0.91, 1.34) 1.04 (0.88, 1.23) 1.02 (0.99, 1.06) 1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	0.76 0.99 1.11 1.34 31.70
Recent 2003 lung cancer Beelen 2008 lung cancer Jacquemin 2015 Asthma Subtotal (I-squared = 64.6%, p = 0.000)	1.18 (0.96, 1.46) 1.11 (0.91, 1.34) 1.04 (0.88, 1.23) 1.02 (0.99, 1.06) 1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	0.70 0.99 1.11 1.34 31.70
Subtotal (1–squared = 64.6%, p = 0.000)	1.18 (0.91, 1.34) 1.11 (0.91, 1.34) 1.04 (0.88, 1.23) 1.02 (0.99, 1.06) 1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	0.99 1.11 1.34 31.70
Subtotal (1-squared = 64.6%, p = 0.000)	1.02 (1.09, 1.03) 1.02 (0.99, 1.06) 1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	1.11 1.34 31.70
Subiotal (I-squared = 64.6%, p = 0.000)	1.02 (1.00, 1.03) 1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	31.70
Children	1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	31.70
Children	1.02 (1.00, 1.03) 1.27 (0.90, 1.79)	2.42
Clark 2010 Asthma	1.27 (0.90, 1.79)	3.43
Evans 2014 Asthma		0.45
Cebring 2014 Astima	1 29 (1 00 1 66)	0.75
Gent 2010 Cough	1.00 (0.91, 1.00)	2.37
Gent 2003 Wheering	1.05 (0.92, 1.20)	1.72
Gurlay 2013 I PI	1.04 (0.99, 1.08)	3.14
Guiley 2015 LKt	1.01 (0.99, 1.08)	3.14
Johnston 2000 Astimuta	1.31 (1.18, 1.45)	2.17
Long 2014 wheeling	1.18 (0.99, 1.42)	1.22
Mar 2004 Wheering	0.55 (0.19, 1.64)	0.05
Mail 2004 Wheesing	1.03 (0.97, 1.21)	1.36
Ministen 2004 witezang	0.84 (0.60, 1.17)	0.47
Neas 1004 Bronchiis	1 18 (0.99, 1.47)	1.22
Neas 1994 Courb	1.05 (0.85, 1.20)	1.00
Near 1004 1.D1	1.13 (0.00, 1.20)	1.60
Neas 1974 LKI	1.05 (0.97, 1.30)	1.09
Neas 1994 Whetezing	1.60 (1.41, 1.82)	1.10
Pice 2007 Biolemas	1.05 (1.00, 1.09)	3.14
Padeimer 2007 Couch	1.00 (1.00, 1.01)	3.47
Rodringuez 2007 Cough	1.00 (1.00, 1.01)	3.47
Roming Up6 Course	1.10 (1.06, 1.33)	2.01
Rominu 1990 Cougn	1.19 (1.06, 1.35)	2.01
Romicu 1990 LKI	1.21 (1.08, 1.33)	2.03
Romed 1990 Wheeling	1.07 (0.93, 1.27)	1.30
Schwarz 1999 Cough	1.07 (0.90, 1.20)	1.55
Schwarz 1999 LKI	1.33 (1.11, 1.38)	0.40
Intranen 1999 Cougn	1.48 (1.02, 2.13)	0.40
Wendetz014 Astima	2.58 (0.01, 7.27)	2.47
Macintyre 2014 pheumoma	2.38 (0.91, 7.27)	0.06
I inteaut 2010 Astima	1.31 (1.28, 1.33)	5.40
Moner 2019 Asuma	1.25 (0.78, 1.95)	0.27
Drauer 2007 Dionemits	0.88 (0.66, 1.18)	0.00
Brauer 2007 Cougn	1.11 (0.94, 1.31)	1.55
Gening 2002 Respiratory infections	0.98 (0.80, 1.20)	1.04
Gening 2010 wheezing	1.04 (0.85, 1.28)	1.03
Morgenstern 2007 Bronenius	1.05 (0.92, 1.20)	1.75
Morgenstern 2007 Cough	1.05 (0.88, 1.25)	1.26
Morgenstern 2007 Respiratory infections	1.09 (0.94, 1.27)	1.52
Morgenstern 2007 Wheezing	1.10 (0.96, 1.25)	1.75
Nunez 2008 Cough	1.09 (1.03, 1.15)	2.96
Nunez 2008 Wheezing Subtotal (1-squared = 95.4% , p = 0.000)	1.10(1.03, 1.17) 1.10(1.07, 1.14)	2.82 68.30
Overall (1-smured = 93.6%, n = 0.000)	1.08 (1.05, 1.10)	100.00
NOTE: Weights we from random effects analysis	1.00 (1.05, 1.10)	100.00
	1	

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.

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 $PM_{2.5}$ being especially harmful^[53–54]. Exposure to $PM_{2.5}$ 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 $PM_{2.5}$ pollution on health outcomes^[56]. Several case-control studies have also assessed daily hospital

Study	RR(95% CI)	Weigl
Oceania		10007
Bennett 2007 Asthma	0.91 (0.55, 1.49)	0.23
Bennett 2007 Wheezing	1.08 (0.79, 1.48)	0.53
Bennett 2007 Cough	0.74 (0.47, 1.15)	0.28
Johnston 2006 Asthma	• 1.01 (0.98, 1.04)	3.32
Johnston 2006 Asthma	• 1.00 (0.98, 1.03)	3.36
Rodriguez 2007 Cough	♦ 1.00 (1.00, 1.01)	3.47
Rodriguez 2007 Wheezing	♦ 1.00 (1.00, 1.01)	3.47
Subtotal (I-squared = 0.0%, p = 0.843)	1.00 (0.998, 1.01)	14.65
North America		
Brauer 2007 Bronchitis	0.88 (0.66, 1.18)	0.60
Brauer 2007 Cough	1.11 (0.94, 1.31)	1.35
Clark 2010 Asthma	• 1.02 (1.00, 1.03)	3.43
Evans 2014 Asthma	1.27 (0.90, 1.79)	0.45
.i 2013 Asthma	• 0.99 (0.95, 1.04)	3.12
oftus 2014 Wheezing	→ 1.31 (1.18, 1.45)	2.17
Mar 2004 Cough	1.18 (0.99, 1.42)	1.22
Mar 2004 Cough	0.89 (0.66, 1.20)	0.57
Mar 2004 Wheezing	0.55 (0.19, 1.64)	0.05
Mar 2004 Wheezing	0.99 (0.84, 1.17)	1.36
Aillstein 2004 Wheezing	1.03 (0.87, 1.21)	1.36
Neas 1994 Asthma	0.84 (0.60, 1.17)	0.47
leas 1994 Bronchitis		1.22
Jeas 1994 Cough	1.05 (0.85, 1.29)	1.00
leas 1994 LRI	1 13 (0.00 1 30)	1.69
leas 1994 Wheezing	105 (0.97, 1.30)	1.18
Junez 2008 Cough	1.05 (0.87, 1.20)	2.96
Junar 2008 Whaazing		2.90
societte 2007 Branchitic		1.02
icciolo 2007 Bronchilis	1.00 (1.40, 1.82)	1.00
ino 2004 Bronchius	1.05 (1.00, 1.109)	3.14
ace 2015 Astrina	0.97 (0.85, 1.10)	1.79
tice 2015 Bronchitis	0.98 (0.86, 1.11)	1.80
tice 2015 Cough	1.08 (0.84, 1.38)	0.77
tice 2015 Wheezing	0.98 (0.86, 1.11)	1.80
Romieu 1996 Cough	1.19 (1.06, 1.33)	2.01
Romieu 1996 LRI	1.21 (1.08, 1.35)	2.03
Romieu 1996 Wheezing	1.09 (0.95, 1.27)	1.58
Schwartz 1999 Cough		1.33
Schwartz 1999 LRI	1.33 (1.11, 1.58)	1.25
Teresa 2015 Asthma	1.03 (0.84, 1.25)	1.07
Wendt 2014 Asthma	➡ 1.12 (1.03, 1.22)	2.47
Young 2014 Asthma	1.20 (0.99, 1.46)	1.10
Young 2014 Cough	• 0.95 (0.88, 1.03)	2.57
Young 2014 Wheezing	1.14 (1.04, 1.26)	2.28
Puett 2014 lung cancer	1.06 (0.91, 1.25)	1.43
Subtotal (I-squared = 73.8%, p = 0.000)	0 1.09 (1.05, 1.13)	57.26
Europe		
Gehring 2002 Respiratory infections	0.98 (0.80, 1.20)	1.04
Jehring 2010 Wheezing	1.04 (0.85, 1.28)	1.03
Sehring 2016 Asthma	1.29 (1.00, 1.66)	0.75
Gent 2003 Cough	+ 1.00 (0.91, 1.09)	2.37
ent 2003 Wheezing	1.05 (0.92, 1.20)	1.73
acquemin 2015 Asthma	1.04 (0.88, 1.23)	1.34
folter 2014 Asthma	1.23 (0.78, 1.95)	0.27
forgenstern 2007 Bronchitis	1.05 (0.92, 1.20)	1.73
forgenstern 2007 Cough	1.05 (0.88, 1.25)	1.26
forgenstern 2007 Respiratory infections	1.09 (0.94, 1.27)	1.52
forgenstern 2007 Wheezing	1.10 (0.96, 1.25)	1.75
iitanen1999 Cough	1.48 (1.02, 2.13)	0.40
facIntyre 2014 pneumonia	2.58 (0.91, 7.27)	0.06
lielsen 2013 lung cancer	1.18 (0.96, 1.46)	0.99
Beelen 2008 lung cancer	0.81 (0.63, 1.04)	0.76
Beelen 2008 lung cancer	111(0.01 1.34)	1.11
"Itreault 2016 Asthma	1 31 (1 28 1 33)	3.40
Subtotal (I-squared = 83.7%, p = 0.000)	 1.31 (1.26, 1.33) 1.10 (1.01, 1.20) 	21.51
Asia		
Jurley 2013 LRI	♦ 1.04 (0.99, 1.08)	3.14
Guo 2016 lung cancer	• 1.07 (1.06, 1.09)	3.44
subtotal (I-squared = 47.8%, p = 0.166)	0 1.06 (1.03, 1.09)	6.58
		100.00
Overall (I-squared = 93.6%, p = 0.000)	Y 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).

admissions or emergency department visits^[57]. 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

	KK(95% C1)	wei
Asthma	0.91 (0.55, 1.40)	0.22
Jark 2017 Ashma	1.02 (1.00, 1.03)	3.43
Svans 2014 Asthma	1.27 (0.90, 1.79)	0.45
Gebring 2016 Asthma	1,29 (1.00, 1.66)	0.75
acquemin 2015 Asthma	1.04 (0.88, 1.23)	1.34
ohnston 2006 Asthma	1.01 (0.98, 1.04)	3.32
Johnston 2006 Asthma	1.00 (0.98, 1.03)	3.36
Li 2013 Asthma	0.99 (0.95, 1.04)	3.12
Molter 2014 Asthma	1.23 (0.78, 1.95)	0.27
Neas 1994 Asthma	0.84 (0.60, 1.17)	0.47
Rice 2015 Asthma	0.97 (0.85, 1.10)	1.79
Teresa 2015 Asthma	1.03 (0.84, 1.25)	1.07
Wendt 2014 Asthma	1.12 (1.03, 1.22)	2.47
Young 2014 Asthma	1.20 (0.99, 1.46)	1.10
F"treault 2016 Asthma	1.31 (1.28, 1.33)	3.40
Subtotal (1-squared = 97.4%, p = 0.000)	1.07 (0.99, 1.16)	26.57
Wheezing	1.08 (0.70, 1.48)	0.62
Sennet 2007 wheezing	1.08 (0.79, 1.48)	0.53
Senting 2010 wheezing	1.04 (0.85, 1.28)	1.03
Jent 2005 Wheezing	1.05 (0.92, 1.20)	1./5
Johns 2014 Wheezing	1.31 (1.18, 1.45)	2.17
Mar 2004 Wheezing	0.55 (0.19, 1.64)	0.05
All Levis Wheeling	1.03 (0.87, 1.31)	1.30
VIIIIStein 2007 Wincering	1.05 (0.87, 1.21)	1.50
Volgensen 2007 wheezing	1.10 (0.96, 1.25)	1.15
veas 1774 whitecang	1.05 (0.87, 1.26)	1.18
Nunez ZODO WIECZINg	1.10 (1.03, 1.17)	1.82
Activity 7007 Wheeting	0.98 (0.86, 1.11)	1.80
Wunguez 2007 Wincesting	1.00 (1.00, 1.01)	1.50
Vonine 1750 wheezing	1.14 (1.04, 1.26)	2.28
Subtotal (1-squared = 72.1%, p = 0.000)	1.07 (1.02, 1.13)	2.28 23.10
Cough		
Bennett 2007 Cough	0.74 (0.47, 1.15)	0.28
Brauer 2007 Cough	1.11 (0.94, 1.31)	1.35
Gent 2003 Cough	1.00 (0.91, 1.09)	2.37
Mar 2004 Cough	1.18 (0.99, 1.42)	1.22
Mar 2004 Cough	0.89 (0.66, 1.20)	0.57
Morgenstern 2007 Cough	1.05 (0.88, 1.25)	1.26
Neas 1994 Cough	1.05 (0.85, 1.29)	1.00
Sunez 2008, Couch	1.09 (1.03, 1.15)	2.96
Rice 2015 Cough	1.08 (0.84, 1.38)	0.77
Rodriguez 2007 Cough	1.00(1.00, 1.01)	3.47
Romieu 1996 Couch	1.19(1.06, 1.33)	2.01
chwartz 1999 Cough	1.07 (0.90, 1.26)	1 33
Citanen 1999 Cough	1.48(1.02, 2.13)	0.40
Acute 2014 Cough	0.95 (0.88, 1.03)	2.57
Subtotal (1-squared = 57.9% , p = 0.004)	1.05 (1.002, 1.10)	21.56
Bronchitis		
3rauer 2007 Bronchitis	0.88 (0.66, 1.18)	0.60
Morgenstern 2007 Bronchitis	1.05 (0.92, 1.20)	1.73
Neas 1994 Bronchitis	1.18 (0.99, 1.42)	1.22
Picciotto 2007 Bronchitis	1.60 (1.41, 1.82)	1.80
Pino 2004 Bronchitis	1.05 (1.00, 1.09)	3.14
Rice 2015 Bronchitis	0.98 (0.86, 1.11)	1.80
Subtotal (I-squared = 88.5%, p = 0.000)	1.12 (0.96, 1.29)	10.30
Respiratory infections	0.02 (0.20 1.20)	1.04
Johning 2002 Respiratory Infections	1.09 (0.04 1.27)	1.69
Subtotal (I-squared = 0.0%, p = 0.409)	1.05 (0.93, 1.18)	2.56
LRI		
Surley 2013 LRI	1.04 (0.99, 1.08)	3.14
Neas 1994 LRI	1.13 (0.99, 1.30)	1.69
Romieu 1996 LRI	1.21 (1.08, 1.35)	2.03
Schwartz 1999 LRI	1.33 (1.11, 1.58)	1.25
Subtotal (I-squared = 76.2%, p = 0.006)	1.15 (1.03, 1.29)	8.12
Pneumonia		0.05
MacIntyre 2014 pneumonia bubtotal (I-squared = .%, p = .)	2.58 (0.91, 7.27) 2.58 (0.91, 7.29)	0.06
Lung cancer		
Juo 2016 lung cancer	1.07 (1.06, 1.09)	3.44
Puett 2014 Jung cancer	1.06 (0.91, 1.25)	1.43
Nielsen 2013 lung cancer	1.18 (0.96, 1.46)	0.99
Seelen 2008 lung cancer	0.81 (0.63, 1.04)	0.76
Seelen 2008 Jung cancer	1.11 (0.91, 1.34)	1.11
Subtotal (1-squared = 30.8%, p = 0.216)	1.06 (0.99, 1.14)	7.73
	1.09 (1.05 1.10)	100.00
Overall (1-squared = 93.6%, p = 0.000)	1.08(1.05, 1.10)	100100

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).

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 ($\leq 25 \ \mu g/m^3$) 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

Study	RR(95% CI)	Weight%
Non-traffic-related	i	
Bennett 2007 Asthma	0.91 (0.55, 1.49)	0.23
Bennett 2007 Wheezing	1.08 (0.79, 1.48)	0.53
Bennett 2007 Cough	0.74 (0.47, 1.15)	0.28
Clark 2010 Asthma	• 1.02 (1.00, 1.03)	3.43
Evans 2014 Asthma	1.27 (0.90, 1.79)	0.45
Gehring 2016 Asthma	1.29 (1.00, 1.66)	0.75
Gent 2003 Cough	1.00 (0.91, 1.09)	2.37
Gent 2003 Wheezing	1.05 (0.92, 1.20)	1.73
Gurley 2013 LRI	1.04 (0.99, 1.08)	3.14
Jacquemin 2015 Asthma	1.04 (0.88, 1.23)	1.34
Johnston 2006 Asthma	1.01 (0.98, 1.04)	3.32
Johnston 2006 Asthma	1.00 (0.98, 1.03)	3.30
Lafue 2014 Wheering	1 21 (1.18, 1.45)	2.12
Mar 2004 Cough	1.31 (1.18, 1.43)	1.22
Mar 2004 Cough	0.89 (0.66, 1.20)	0.57
Mar 2004 Wheeving	0.55 (0.10, 1.20)	0.57
Mar 2004 Wheezing	0.55 (0.19, 1.64)	1.36
Millstein 2004 Wheering	1.03 (0.87, 1.21)	1.30
Nane 1004 Asthma	0.84 (0.60, 1.17)	0.47
Nose 1004 Bronchitie	1.18 (0.00, 1.17)	1.22
News 1004 Couch	1.18 (0.99, 1.42)	1.00
Nege 1004 I PI	1.03 (0.65, 1.29)	1.60
Noss 1004 Wheezing	1.15 (0.99, 1.30)	1.05
Pieciotto 2007 Bronchitis	1.05 (0.67, 1.20)	1.10
Picciolo 2007 Bronchitis	1.05 (1.00, 1.00)	2.14
Pine 2004 Biolicinus	0.07 (0.85, 1.10)	1.70
Rice 2015 Asuma Disa 2015 Pronshitis	0.97 (0.83, 1.10)	1.79
Pice 2015 Diolethus	1.08 (0.80, 1.11)	0.77
Rice 2015 Cough Bice 2015 Wheering	1.08 (0.84, 1.58)	1.80
Rice 2015 Wheezing Badriguar 2007, Cauch	1.00 (1.00, 1.01)	3.47
Rodriguez 2007 Cough Dedriguez 2007 Wheering		3.47
Pomiau 1006 Couch	1.10 (1.06, 1.33)	2.01
Pomiau 1990 Cougn	1.19 (1.00, 1.35)	2.01
Romieu 1990 LKI =	1.21 (1.06, 1.33)	1.58
Sahuarta 1000 Cauch	1.07 (0.90, 1.27)	1.30
Schwartz 1999 Cougn	1.07 (0.90, 1.26)	1.35
Taraca 2015 Acthma	1.35 (1.11, 1.36)	1.25
Titanan1000 Couch	1.05 (0.64, 1.25)	0.40
Wandt 2014 Asthma		2.47
Venue 2014 Asthma	1.12 (1.05, 1.22)	1.10
Young 2014 Couch	0.95 (0.98, 1.03)	2.57
Young 2014 Wheering	1.14 (1.04, 1.26)	2.37
Maclature 2014 macumonia	2.58 (0.91, 7.27)	0.06
Guo 2016 Jung cancer		3.44
Puett 2014 lung cancer	1.06 (0.91, 1.25)	1.43
Baelen 2008 lung cancer	0.81 (0.63, 1.04)	0.76
T"iteault 2016 Asthma	1 31 (1 28 1 33)	3.40
Molter 2014 Acthma	1.31 (1.26, 1.55)	0.27
Subtotal (I-covared = 94.8% n = 0.000)	1.076 (1.05, 1.11)	81.84
Subtolar (1 squared - 54.876, p - 0.000)	1.070 (1.05, 1.11)	01.04
Traffic-related	1	
Bruner 2007. Bronchitie	0.88 (0.66, 1.18)	0.60
Braner 2007 Cough	1 11 (0.04, 1.31)	1 35
Gebring 2002 Respiratory infections	0.08 (0.80, 1.20)	1.04
Gebring 2010 Wheezing	1.04 (0.85, 1.29)	1.03
Morgenstern 2007 Branchitis	1.05 (0.02, 1.28)	1.73
Morgenstern 2007 Cough	1.05 (0.92, 1.20)	1.26
Margenstern 2007 Respiratory infections	1.09 (0.94, 1.23)	1.52
Morgenstern 2007 Wheezing	1.10 (0.94, 1.27)	1.75
Nunez 2008 Cough	1.10 (0.20, 1.22)	2.96
Nunez 2008 Wheezing	+ 1.10 (1.03, 1.15)	2.82
Nielsen 2013 lung cancer	1 18 (0.96, 1.46)	0.99
Beelen 2008 lung cancer	111 (0.91, 1.34)	1.11
Subtotal (I-squared = 0.0% , p = 0.954)	0 1.085 (1.05, 1.12)	18.16
Overall (I-squared = 93.6%, p = 0.000)	• 1.08 (1.05, 1.10)	100.00
NOTE: Weights are from random effects analysis		
0.128	1 7 07	
0.150	1 7.27	

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.

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. 6 Combined RRs with 95% CIs for the association between exposure to low and high concentrations of PM_{2.5} and respiratory tract diseases in children.

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_c of aerodynamic diameter 2.5-10 µm 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_c 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

	Ν	RR (95%CI) Random-effects	$P(I^2)$	<i>P</i> for Egger / Begg bias test
Children Symptom				
Wheezing	10 [18,19,23-25,30,32,33,35,39]	1.082 (1.011, 1.158)	0.000 (77.2%)	0.079 / 0.107
Bronchitis	5 [18,26,29-31]	1.145 (0.957, 1.370)	0.000 (90.2%)	0.593 / 1.000
Cough	10 [18-21,23,24,29,30,32,33]	1.075 (1.019, 1.134)	0.002 (65.4%)	0.007 / 0.721
Asthma	8 [18,27,34,38,40,41,47,48]	1.119 (0.989, 1.266)	0.000 (98.5%)	0.910 / 0.536
Lower respiratory illness	4 [18,19,21,36]	1.153 (1.033, 1.287)	0.006 (76.2%)	0.064 / 0.308
Respiratory infections	2 [22,30]	1.050 (0.930,1.184)	0.409 (0.00%)	N/A / 1.000
Pneumonia	1 [46]	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 [24,28,42,44]	1.053 (0.964, 1.150)	0.229 (30.5%)	0.593 / 1.000
Bronchitis	1 [44]	0.980 (0.860, 1.110)	-	-
Cough	4 [24,28,42,44]	0.951 (0.885, 1.021)	0.493 (0.00%)	0.713 / 0.308
Asthma	7 ^[27,28,37,42-45]	0.999 (0.978, 1.021)	0.553 (0.00%)	0.581 / 1.000
Lung cancer	4 [49,50,51,52]	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

 $P(l^2)$: *P*-value for test of heterogeneity, l^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.

European and North American populations, probably due to more studies of $PM_{2.5}$ were conducted in these populations. The risk of respiratory diseases was also higher following exposure to high than low quantities of $PM_{2.5}$, suggesting that the concentration of $PM_{2.5}$ 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 $PM_{2.5}$ exposure and respiratory diseases.

In conclusion, we found that $PM_{2.5}$ may play an important role in respiratory tract diseases, especially in children exposed to high concentrations of $PM_{2.5}$. 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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