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ORIGINAL RESEARCH

The Relationship between Particulate Matter (PM_{10}) and Hospitalizations and Mortality Of Chronic Obstructive Pulmonary Disease: A Meta-Analysis

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Abstract

Background: **Numerous studies have reported variable associations between ambient particulate matter (PM) and chronic obstructive pulmonary disease (COPD) hospitalizations and mortality.** ***Objective:*** **To conduct a systematic study assessing the associations between hospitalizations and mortality from COPD and ambient PM_{10} (particulate matter with aerodynamic diameters ≤ 10 μm, PM_{10}).** ***Methods:*** **Systematic searches were conducted in 6 common electronic databases. A meta-analysis was performed to estimate the odds ratio (OR) to evaluate the relationship between PM_{10} and COPD hospitalizations and mortality. Publication bias and heterogeneity of samples were tested by Begg funnel plot and Egger test, respectively. Study findings were analyzed using random-effect model and fixed-effect model.** ***Results:*** **The search yielded 31 studies suitable for the meta-analysis during the period from Jan 1, 2000 to Oct 31, 2011. A 10μg/m³ increase in PM_{10} was associated with a 2.7% (95%CI = 1.9%-3.6%) increase in COPD hospitalizations with an OR of 1.027 (95%CI: 1.019–1.036), and a 1.1% (95%CI: 0.8%–1.4%) increase in COPD mortality with an OR of 1.011 (95%CI: 1.008-1.014).** ***Conclusions:*** **Ambient PM_{10} is associated with increased COPD hospitalizations and mortality. Further research is needed to elucidate whether this association is causal and to clarify its mechanisms.**

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible and chronic inflammation of the lungs (1). It is a major and increasingly prevalent global health problem in both developed and developing countries. Epidemiologic studies suggest that COPD affects 5% to 19% of the adult population above 40 years of age (2,3). By far, cigarette smoking (active or passive) is considered to be the major reason for the development of most COPD cases. In addition, there are other risk factors, including inflammation, occupational dust exposures, outdoor and indoor air pollution from fuel burning, and lower socioeconomic status, etc. (4,5). Of all the other risk factors, exposure to ambient particulate matter (PM), especially the inhalable particulate matter (PM_{10}), has become an important risk factor for the development of respiratory diseases including COPD.

In the last few decades, many epidemiological studies have examined the short-term effects of air pollution exposure on patients with COPD. Most of them have reported significant associations between PM and increased COPD hospitalizations and mortality (6,7). Among the air pollutants, PM_{10}

Keywords: Particulate matter, COPD, hospitalizations, mortality, meta-analysis

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(particulate matter with aerodynamic diameters ≤ 10 μm, PM_{10}) is now recognized as one of the potential environmental agents that is responsible for the respiratory diseases. It shows a stronger association with COPD than many other factors, even after adjusting for other major risk factors such as cigarette smoking (8). However, inconsistent results have been found on the association between PM_{10} and COPD hospitalizations and mortality in different countries and regions; sometimes even in the same regions.

Zanobetti et al. (9) demonstrated a significant and positive association between PM_{10} and the risk of hospitalizations for COPD in Chicago with a significant increase of 2.5% (95%CI: 1.8%–3.3%) in COPD hospitalization per 10μg/m^3 increase of PM_{10}. However, Anderson et al. (10) found a decrease of 1.8% (95%CI: -6.9%–3.5%) in COPD hospitalization per 24.4μg/m^3 increase in PM_{10} in Birmingham. Results on the association between PM_{10} and COPD mortality are also inconsistent. Moolgavkar (11) demonstrated a significant and positive association between PM_{10} and the risk of mortality for COPD with a significant increase of 2.66% (95%CI: 0.12%–5.20%) in COPD mortality per 25μg/m^3increase in PM_{10} in Cook. On the contrary, also in Cook city, Bateson and Schwartz (12) found a lack of association between PM_{10} and the risk of mortality for COPD with an estimate percent change of 0.58% (95%CI: -0.82%–2.00%) per 10μg/m^3increase in PM_{10}.

Meanwhile, age, socioeconomic status, and education level were able to modify the effects of PM_{10}. In addition, the PM_{10} concentration metrics used in previous studies are different, which makes it difficult to compare the results over studies. To quantitatively clarify the relationship between COPD and PM_{10}, we conducted a systematic literature review and a meta-analysis of studies in order to give an over estimation on the associations between PM_{10} and COPD hospitalization and mortality. The results will be helpful for us to draw a quantitative and credible conclusion on the relationship between PM_{10} exposure and acute hospitalizations and mortality from COPD, which may also be helpful for the government to make related environmental decisions.

Methods

Search strategy

We identified related publications between Jan 1, 2000 to Dec 31, 2011 by systematic searches in English literature databases: PubMed/Medline, EMBASE, Google scholar, Ovid, and Web of science. We conducted a literature search for particulate matter/PM_{10}; COPD hospital admissions/ emergency department visits, and mortality; using "RR/OR/Percent" and "AND" as combining terms for exposure and outcome.

Inclusion criteria

Two reviewers (Zhu and Liu) collected articles eligible for further review by performing an initial screen of identified abstracts or titles. Broad inclusion criteria for articles were: (1) original studies (not review articles) and reporting the association of inhalable particulate matter (PM_{10}) with COPD hospital admissions and mortality; (2) results were reported in a quantitative exposure-response relationship expression (RR/OR /Percent and 95% confidence intervals (CIs)) and evaluated with time-series and case-crossover designs; (3) daily PM_{10} data were obtained from multiple air monitoring stations with no missing days or only a few missing days; (4) studies had defined COPD according to the American Thoracic Society (ATS) (13) and Global Initiative for Obstructive Lung Disease (GOLD) (14) criteria.

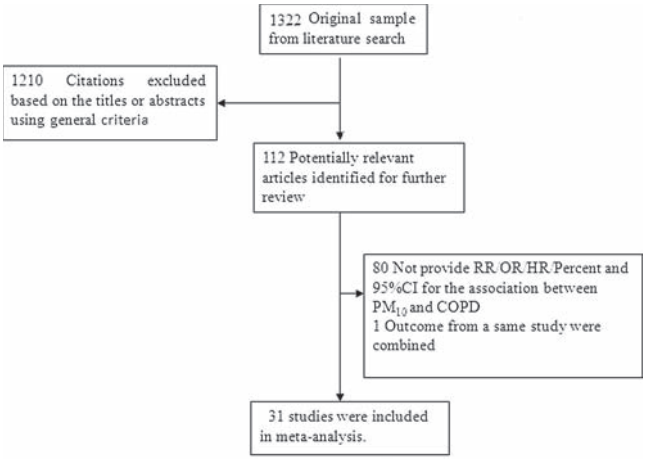

Figure 1. Study selection flow chart. The initial search found 1322 titles, of which 1210 citations were excluded after identification based on abstracts and titles, and there were 31 original studies that met the inclusion criteria for this meta-analysis.

Exclusion criteria

The exclusion criteria for articles were (1) inadequate information; (2) different designs, such as panel study; (3) not original; not full-length articles or did not provide calculable or reported RR/OR/ Percent and 95%CIs; (4) the diagnosis of COPD was uncertain. The articles which met all the above criteria were reviewed (Figure 1). Those articles that formally meet the inclusion and exclusion criteria were analyzed using a data form.

Statistical methods

The OR was used as the common measure of association. The RR was transformed to OR according to the existing literature (15). Briefly, the formula OR = RR $[(1-P_0)+(P_0\times OR)]$ was used, in which P_0 is the incidence of the outcome of interest in the non-exposed group. In the present analysis, the problem of RR and OR is of no importance given that the increased risk for COPD is generally very low and the two measures are almost equivalent. As for effects on COPD hospitalizations and mortality, we chose a 10 ug/m^3 increase in PM_{10} as the concentration metric for daily PM_{10} and used the formula $OR=[e^{\beta}-1]\times 100\%$. If the concentration metric was not 10 ug/m^3, we used an alternative formula

$OR=[e^{(\beta \times IQR)}-1]\times 100\%$ to transform the estimate, where β and IQR stand for the effect estimate and an interquartile range, respectively (16). Eventually we calculated the effects size (OR) on COPD hospitalizations and mortality corresponding to an increase of 10 ug/m^3 in PM_{10}.

Meta-analysis was performed using STATA version 11.0 (STATA, College Station, Texas, USA). The natural logarithm of the RR/OR and its 95%CI of the lnOR were used to estimate the pooled effect size over different studies. The OR and 95%CI data were entered as two separate data sets for COPD in Stata11.0. To assess the heterogeneity of RR across studies, the Chi-squared (χ^2 significant level at $p \le 0.10$) and the I^2 were calculated before analysis. The criteria for random-effect model was determined by significant heterogeneity with an I^2 statistic value > 50% or $p \le 0.10$ and fixed-effect model was determined by significant heterogeneity with an I^2 statistic value ≤ 50% or $p > 0.10$. Heterogeneity between different studies was systematically examined by multivariable meta-regression. Begg funnel plot (17,18) and the Egger test (17) were used to assess publication bias.

Results

The initial search found 1322 titles, of which 1210 citations were excluded after identification based on abstracts and titles, and there were 31 original studies that met the inclusion criteria for this meta-analysis. Of all the included papers, nine were case-crossover studies and 22 were time-series studies. Data from the 31 studies were sampled across 13 different countries and 23 areas starting from Jan 1, 2000 to Oct 31, 2011. The short-term effects (lag days 0–7) of PM_{10} on COPD were evaluated. Of all the 31 studies, there were 18 studies dealing with PM_{10} and COPD hospitalizations and 13 studies dealing with PM_{10} and COPD mortality (Table 1).

Effects estimate

COPD hospitalizations and PM10

Random-effect models were used to calculate the pooled effect size for OR (chi-squared $\chi^2 = 117.82$, [degree of freedom, $df = 19$], $I^2 = 83.9\%$, $p < 0.001$; and $Z = 6.61$, $p < 0.001$). The random pooled effect size (OR) for COPD hospitalizations due to PM_{10} was 1.03 (95%CI = 1.02–1.04) (Figure 2). A 10 ug/m^3increase in daily PM_{10} was associated with a 2.7% (95%CI=1.9%–3.6%) increase in COPD hospitalizations.

COPD mortality and PM10

Fixed effect models were used to calculate the pooled effect size for OR ($\chi^2 = 23.03$, $df = 15$, $I^2 = 34.9\%$, $p > 0.05$; and $Z = 7.40$, $p < 0.001$). The pooled effect size (OR) for COPD mortality and PM_{10} was 1.011 (95%CI = 1.008–1.014) (Figure 3). A 10 ug/m^3increase in daily PM_{10} was associated with a 1.1% (95%CI = 0.8%–1.4%) increase in COPD mortality.

Publication bias

Publication bias was tested using funnel plots for both COPD hospitalization and mortality. A funnel plot of the two types of studies did not show significant Begg test results. The combined data obtained from Egger's test for COPD hospitalization (bias = 1.97, $P > |t| = 0.250$) and COPD mortality (bias = 0.16, $P > |t| = 0.882$) showed that there was no evidence of publication bias on the associations between PM_{10} and COPD hospitalizations and mortality (Figure 4 and Figure 5).

Heterogeneity by meta-analysis

We performed a stratified analysis according to a set of key study characteristics including ages range and socioeconomic status for the eligible articles (Table 2). We found that these study characteristics did not contribute to the heterogeneity among studies in this meta-analysis. But they all showed significant associations with COPD hospitalizations and mortality ($p < 0.05$).

Discussion

COPD, the fourth-leading cause of death in the world, represents an important public health challenge that is both preventable and treatable. Globally, the COPD burden is projected to increase in coming decades because of continuing exposure to COPD risk factors and aging of population (45). Air pollution exposure has been recognized as a risk factor for cardiorespiratory illnesses, including COPD for a long time. The number of studies focusing on the association between outdoor air pollution and cardiorespiratory diseases has been increasing rapidly in developed countries such as the United States and western European countries. A better understanding of the importance of PM on the development and progression of COPD is important for the development of preventive measures including health education programs.

This systematic review yielded 31 studies that clearly and adequately evaluated COPD hospitalizations and mortality as outcomes in association with PM_{10}. Our analysis suggests an overall PM_{10} effect on COPD hospitalizations and mortality, which is similar to the results reported in the European APHEA study (46) and a recent meta-analysis (47). We found that an increase of 10 ug/m^3in PM_{10} was associated with a 2.7% increase in COPD hospitalizations and a 1.1% increase in COPD mortality, respectively. However, there are significant variations between the studies included in this meta-analysis in terms of study design, exposure assessment and potential confounders. All these factors added substantial statistic heterogeneity between different studies, which might have influenced the risk estimation.

Significant publication bias was not found in studies focusing on the relationship between PM_{10} and COPD hospitalizations and mortality. After stratification by different subgroups to test the heterogeneity, we found that ages range and different socioeconomic status also

Table 1. Studies included in the meta-analysis investigating the short term effects between PM_{10} on COPD

Source	Study Location	Lag days	Study design	OR	95%CI	No. of COPD	Study period	Ages ranges	Confounding factors
PM_{10} and COPD hospitalizations									
Chen et al. 2000 (19)	Reno-Sparks Nevada	0	Time–series	1.018	1.004–1.033	3,115	1990–1994	All ages	temperature wind speed, dummies for study, April November
Zanobetti et al. 2000 (20)	10 cities USA	5	Time–series	1.025	1.018–1.033	NA[b]	1986.10–1994.12	≥65	temperature relative-humidity, pressure
Zanobetti et al. 2000 (9)	Chicago USA	0	Time–series	1.019	1.008–1.030	NA	1986–1994	All ages	sex, race, age group
Anderson et al. 2001 (10)	Birmingham USA	0–1	Time–series	0.993	0.972–1.014	NA	1994.10–1996.12	All ages	temperature humidity
Chen et al. 2004 (21)	Vancouver Canada	0–3	Time–series	1.162	1.068–1.263	4,409	1995.1.1–1999.3.3	≥65	temperature relative-humidity
Yang et al. 2005 (22)	British Canada	7	Time–series	1.157	1.060–1.253	6,027	1994–1998	≥65	temperature relative-humidity
Peel et al. 2005 (23)	Atlanta USA	1	Time–series	1.018	0.994–1.043	NA	1993.1.1–2000.8.1	All ages	temperature dew point
Medina-Ramon et al. 2006 (24)	36 cities USA	1	Time–series	1.015	1.093–1.021	578,006	1986–1999	≥65	days of week, temperature
Ko et al. 2007 (25)	Hong Kong China	0–5	Time–series	1.024	1.021–1.028	119,225	2000–2005	All ages	temperature relative-humidity
Lee et al. 2007 (26)	Kaohsiung Taiwan(≥25 °C)	0	Case–crossover	1.044	1.025–1.065	25,108	1996–2003	All ages	temperature humidity
	(<25 °C)			1.081	1.060–1.103				
Yang and Chen 2007 (27)	Taipei Taiwan (≥ 20 °C)	0	Case–crossover	1.050	1.037–1.064	46,491	1996–2003	All ages	temperature humidity
	(< 20 °C)			1.013	0.998–1.029				
Johnston et al. 2007 (28)	Darwin Australia	0	Time–series	1.21	1.00–1.47	NA	4.1–11.30 2000,2004,2005	All ages	temperature relative-humidity precipitation
Arbex et al. 2009 (29)	Sao-Paulo Brazil	6	Time–series	1.091	1.021–1.174	1,796	2001–2003	>64	Temperature relative humidity
Sauerzapf et al. 2009 (30)	Norwich USA	0–7	Case–crossover	1.079	0.980–1.188	1,050	2006.1.3–2007.2.3	All ages	maximum temperature pollen influenza-infection
David et al. 2009 (31)	7 cities Canada	0	Time–series	0.997	0.984–1.011	NA	1990s–2000s	All ages	weather temporal cycles, day of week and holiday
Belleudi et al. 2010 (32)	Rome Italy	0	Case-crossover	1.003	0.990–1.016	15,087	2001.4.10–2005.12.31	≥35	temperature pressure
Morgan et al. 2010 (33)	Sydney Australia	2	Time-series	1.038	1.014–1.063	36,772	1994.1.1–2002.6.30	≥65	temperature relative-humidity
Tam et al. 2011 (34)	Hong Kong China	2	Case-crossover	1.05	1.01–1.09	111,419	1998–2002	All ages	temperature relative-humidity
PM_{10} and COPD mortality									
Tellez-Rojo et al. 2000 (35)	Mexico city Mexico	3	Time-series	1.041	1.013–1.069	2,294	1994	≥65	Temperature
Moolgavkar 2000 (11)	Cook USA	2	Time-series	1.011	1.00-1.021	NA	1987–1995	All ages	temperature relative humidity

Continued

Table 2. Continued

Source	Study Location	Lag days	Study design	OR	95%CI	No. of COPD	Study period	Ages ranges	Confounding factors
Braga et al. 2001 (36)	10 cities USA	7	Time-series	1.017	1.001–1.033	NA	1986–1993	All ages	temperature relative humidity pressure
Sunyer and Basagana 2001 (37)	Barcelona Spain	0	Case-crossover	1.042	1.00–1.089	2,305	1990–1995	All ages	temperature humidity hot days and influenza days
Wong et al. 2002 (38)	Hong Kong China	0-3	Time-series	1.017	1.002–1.033	NA	1995–1998	All ages	temperature relative humidity
Kan and Chen 2003 (39)	Shanghai China	0	Time-series	1.005	0.999–1.011	NA	2000.6.1–2001.12.1	All ages	temperature relative-humidity dew point
Fischer et al. 2003 (40)	Dutch Netherland	0-6	Time-series	1.038	0.897–1.317	NA	1986–1994	<45	temperature relative humidity
				1.035	0.958–1.135			45–64	
				1.042	0.998–1.093			65–74	
				1.017	0.991–1.045			≥75	
Kim et al. 2003 (7)	Seoul Korea	0	Time-series	1.010	0.997–1.023	NA	1995–1999	All ages	temperature humidity pressure
Bateson and Schwartz 2004 (12)	Cook USA	0	Case-crossover	1.006	0.992–1.02	16,403	1988–1991	All ages	temperature humidity pressure
Zeka et al. 2005 (41)	20 cities USA	1	Case-crossover	1.004	0.986–1.010	NA	1989–2000	All ages	temperature dew point
Neuberger et al. 2007 (42)	Vienna Austria	0–1	Time-series	1.035	1.004–1.067	2,872	2000–2004	All ages	seasonal temperature relative humidity, pressure day of week influenza
Forastiere et al. 2008 (43)	9 cities Italy	2	Case-crossover	1.008	1.002-1.015	34,627	1997-2004	≥65	temperature pressure
Fischer et al. 2011 (44)	Dutch Netherland	0-6	Time-series	1.018	1.011-1.024	NA	1992-2006	All ages	temperature relative humidity pressure

COPD, chronic obstructive pulmonary disease; OR, odds ratio; NA[b], not available.

did not contribute to the heterogeneity. However, there were significant associations between these factors and COPD hospitalizations and mortality. In previous studies, these factors are individual effect modifiers of the PM_{10} effects. For example, higher PM_{10} effect estimates were found in elderly people. Chen et al. (21) demonstrated a RR of 1.128 (95%CI: 1.054–1.028) for COPD hospitalizations associated with an IQR increase of 7.9 ug/m^3 in the preceding 24-hour average PM_{10} concentration after adjusting for temperature and relative humidity in Vancouver. The authors also confirmed that the risk for COPD hospitalizations was increasing with age; the RR in people with 85+ years of age was almost the twice of that in people with 65–74 years of age. Schwartz et al. (48) estimated that an increase of 50 ug/m^3in PM_{10} was associated with a 10% to 25% increase in COPD hospitalizations according to previous studies, which is consistent with our results. We also found that PM_{10} effect on COPD mortality were stronger in developing countries. Because few studies about COPD hospitalizations associated with PM_{10} were conducted in developing countries, we were not able to estimate the overall association between PM_{10} and COPD hospitalizations in developing counties. Liu et al. (49) performed a meta-analysis in both high and low-income countries and documented that exposure to indoor air pollutants

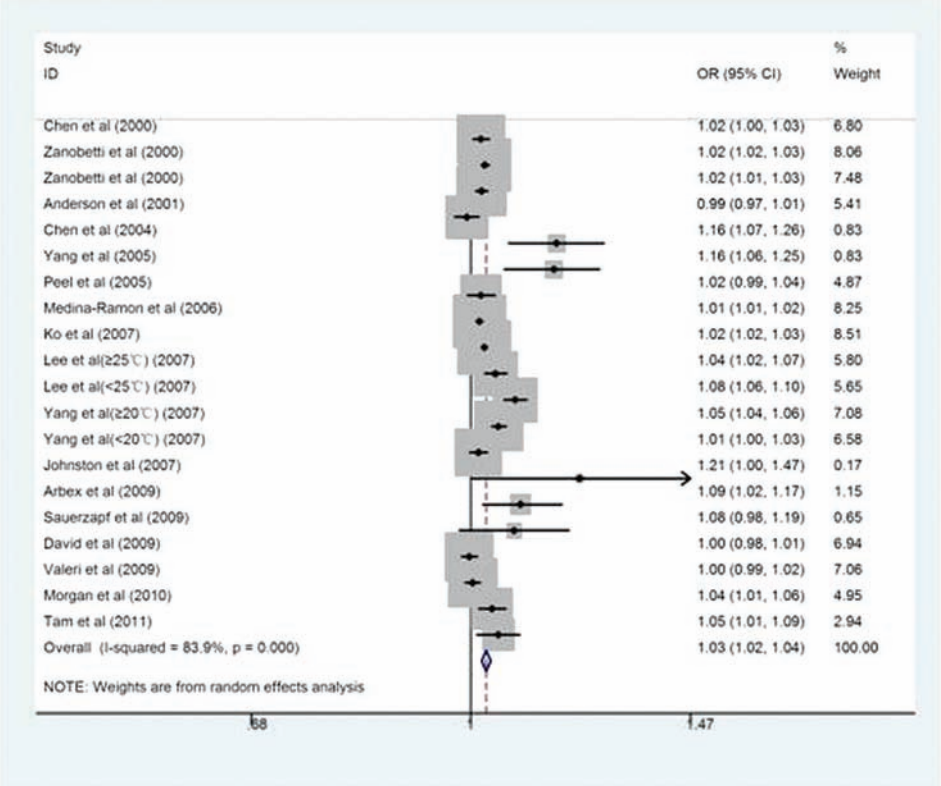

Figure 2. Forest plot of COPD hospitalizations and PM_{10} in the meta-analysis Random-effect models were used to calculate the pooled effect size for OR (chi-squared $\chi^2 = 117.82$, [degree of freedom, $df = 19$], $I^2 = 83.9\%$, $p < 0.001$; and $Z = 6.61$, $p < 0.001$). The random pooled effect size (OR) for COPD hospitalizations due to PM_{10} was 1.03 (95%CI = 1.02–1.04).

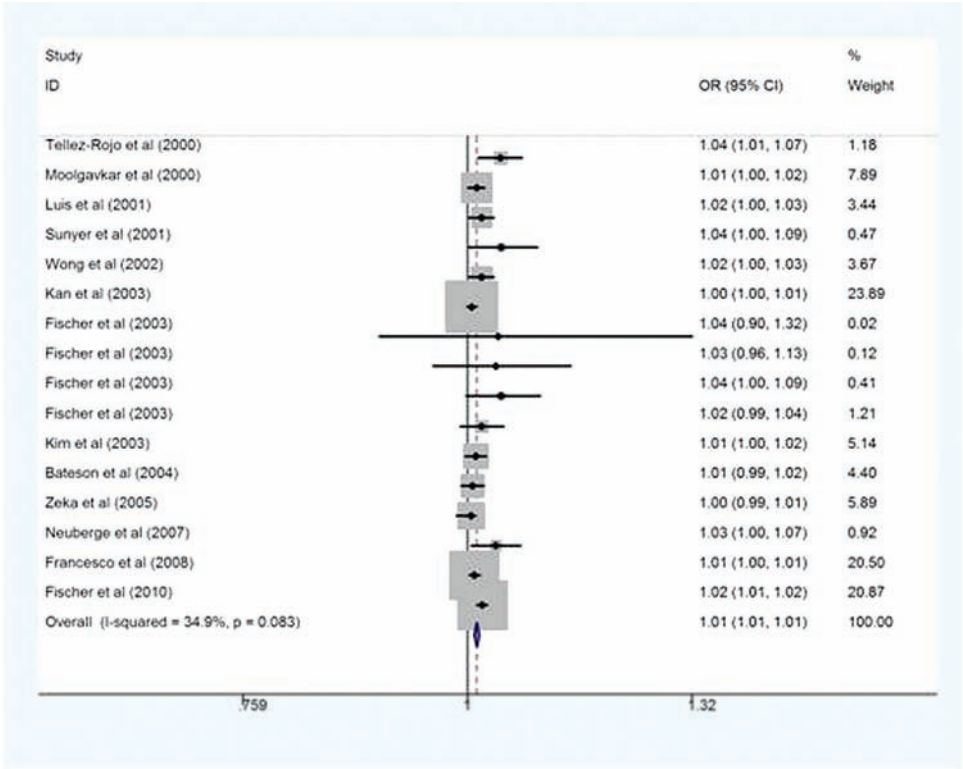

Figure 3. Forest plot of COPD mortality and PM_{10} in the meta-analysis Fixed effect models were used to calculate the pooled effect size for OR ($\chi^2 = 23.03$, $df = 15$, $I^2 = 34.9\%$, $p > 0.05$; and $Z = 7.40$, $p < 0.001$). The pooled effect size (OR) for COPD mortality and PM_{10} was 1.011 (95%CI = 1.008 –1.014).

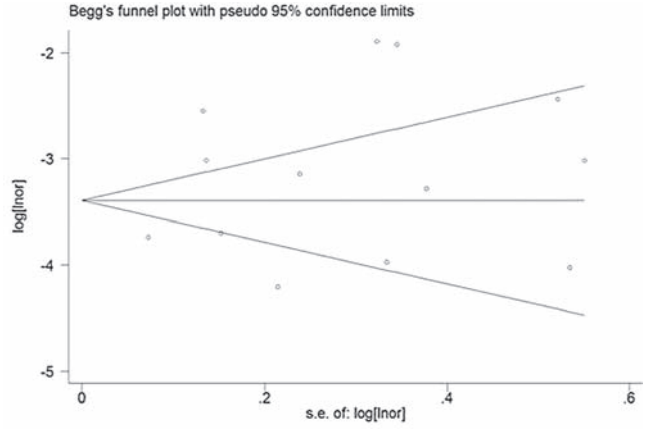

Figure 4. Funnel plot for PM_{10} and COPD hospitalizations in the meta-analysis. Publication bias was tested by using funnel plots for COPD hospitalization. The combined data obtained from Egger's test for COPD hospitalization (bias = 1.97, *P*>|t| = 0.250) showed that there was no evidence of publication bias on the association between PM10 and COPD hospitalizations with PM_{10}. The pseudo 95% CI is computed as part of the analysis that produces the funnel plot, and corresponds to the expected 95%CI for a given standard error (SE). OR indicates odds ratio.

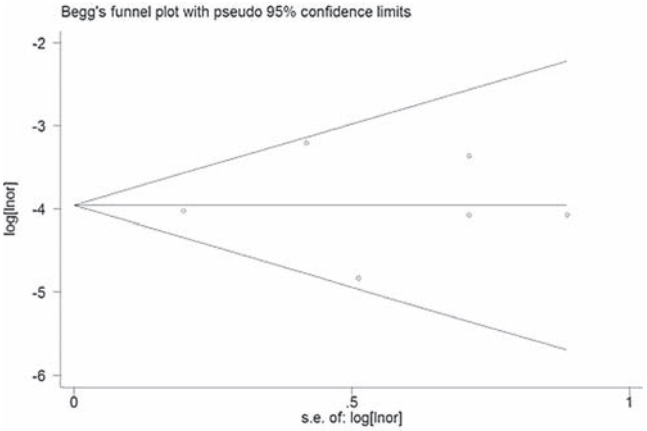

Figure 5. Funnel plot for PM_{10} and COPD mortality in the meta-analysis. Publication bias was tested by using funnel plots for COPD mortality. The combined data obtained from Egger's test for COPD mortality (bias = 0.16, *P*>|t| = 0.882) showed that there was no evidence of publication bias on the association between PM10 and COPD mortality with PM_{10}. The pseudo 95% CI is computed as part of the analysis that produces the funnel plot, and corresponds to the expected 95%CI for a given standard error (SE). OR indicates odds ratio.

from the combustion of solid fuels, which contributed significantly to the COPD burden in low-income counties, and non-smoking women were particularly at risk. Forastiere et al. (50) also found that the effect of particulate matter on mortality among COPD patients may be more pronounced among individuals with lower income or national economic status.

We observed a similar phenomenon in the present meta-analysis. The effect of PM_{10} on COPD hospitalization was stronger in patients in Asian countries, while patients in European counties and the United States suffered more from COPD mortality. Asian populations commonly have lower educational level and socioeconomic status. A previous study has found effect modification by social class in area specific analysis in both low socioeconomic status and high socioeconomic status communities (51) but there was little evidence of effect modification in a large study in the United States (52), which involved nationwide data. Other factors including inflammation, combinations and poor nutrition are also thought to be partly responsible for high COPD hospitalizations and mortality. Previous studies have demonstrated that the association between particulate matter and health effects is stronger in persons with increased baseline systemic inflammation and oxidative stress, such as patients with diabetes, obese individuals, and people not using statins (53,54). Nuvolone et al. (55) reported higher risk of acute myocardial infarction death with COPD. Given the consistency between our results and previous findings, we may conclude that the relevant question should no longer be whether this association exists, but rather whether this established association is causal.

Limitations of this meta-analysis should be considered. Firstly, literatures included in the analysis were limited and may not fully reflect publication bias. Second, the measurement methods and category of PM_{10} in different studies were not available and the duration of

Table 2. Studies included in the meta-analysis in different groups between PM_{10} and COPD hospitalizations and mortality

Groups	References	Amount	OR (95%CI)	*P*	Heterogeneity χ^2	Heterogeneity I^2	P>|t|
Ages							
All ages-Hos[a]	(9,10,19,23,25–28, 30–31,34)	11	1.029 (1.017–1.042)	P<0.001	77.33	85.8%	0.616
≥65-Hos	(20-22,24,29,33)	6	1.038 (1.020–1.056)	P<0.001	27.97	82.1%	0.130
All ages-Mor[b]	(7,11–12,36–39,41–42, 44)	10	1.011 (1.008–1.015)	P<0.001	15.42	41.6%	0.572
≥65-Mor	(35,40,43)	3	1.011 (1.005–1.017)	P<0.001	7.23	58.5%	—
Countries with different socioeconomic status							
Developed-Hos	(9,10,19-34)	18	1.027 (1.019–1.036)	P<0.001	117.82	83.9%	0.250
Developing-Hos	—	0	—	—	—	—	—
Developed-Mor	(7,11–12,36–38, 40–44)	11	1.013 (1.009–1.016)	P<0.001	13.87	6.3%	0.900
Developing-Mor	(35,39)	2	1.020 (0.986–1.056)	0.250	6.27	84.0%	—

Hos[a], hospitalizations; Mor[b], mortality; OR, odds ratio.

exposure and documentation of outcome were variable over different study settings.

Conclusions

In this meta-analysis study, we found that PM_{10} was associated with increased COPD hospitalizations and mortality. We did not find significant publication bias and heterogeneity among studies. Different ages and economic levels were all significantly associated with COPD hospitalization and mortality and elderly patients and developing countries suffered more with COPD hospitalizations and mortality. Further study is needed to clarify whether this association is causal and its underlying mechanisms.

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Declaration of Interest Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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