Title	Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis
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Citation	International Journal of Chronic Obstructive Pulmonary Disease, 2016, v. 11, p. 3079-3091
Issued Date	2016
URL	http://hdl.handle.net/10722/239492
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International Journal of COPD

Dovepress
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ORIGINAL RESEARCH

Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis

This article was published in the following Dove Press journal:
International Journal of COPD
12 December 2016
Number of times this article has been viewed

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Background: Short-term exposure to major air pollutants (O_3, CO, NO_2, SO_2, PM_{10}, and $PM_{2.5}$) has been associated with respiratory risk. However, evidence on the risk of chronic obstructive pulmonary disease (COPD) exacerbations is still limited. The present study aimed at evaluating the associations between short-term exposure to major air pollutants and the risk of COPD exacerbations.

Methods: After a systematic search up until March 30, 2016, in both English and Chinese electronic databases such as PubMed, EMBASE, and CNKI, the pooled relative risks and 95% confidence intervals were estimated by using the random-effects model. In addition, the population-attributable fractions (PAFs) were also calculated, and a subgroup analysis was conducted. Heterogeneity was assessed by I^2.

Results: In total, 59 studies were included. In the single-pollutant model, the risks of COPD were calculated by each 10 μg/m^3 increase in pollutant concentrations, with the exception of CO (100 μg/m^3). There was a significant association between short-term exposure and COPD exacerbation risk for all the gaseous and particulate pollutants. The associations were strongest at lag0 and lag3 for gaseous and particulate air pollutants, respectively. The subgroup analysis not only further confirmed the overall adverse effects but also reduced the heterogeneities obviously. When 100% exposure was assumed, PAFs ranged from 0.60% to 4.31%, depending on the pollutants. The adverse health effects of SO_2 and NO_2 exposure were more significant in low-/middle-income countries than in high-income countries: SO_2, relative risk: 1.012 (95% confidence interval: 1.001, 1.023); and NO_2, relative risk: 1.019 (95% confidence interval: 1.014, 1.024).

Conclusion: Short-term exposure to air pollutants increases the burden of risk of COPD acute exacerbations significantly. Controlling ambient air pollution would provide benefits to COPD patients.

Keywords: COPD exacerbations, air pollution, meta-analysis, acute exposure

Introduction

Air pollution has been a serious environmental problem and a major concern for public health worldwide. It continues to be a major environmental health risk, particularly in developing countries where the motor vehicle traffic and industrialization increase quickly.[1] The respiratory system (tract and lung) is vulnerable to air pollutants, including ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matters ($PM_{2.5}$, PM_{10}). In the course of pulmonary ventilation and gas exchange, these pollutants could induce oxidative stress and inflammation, resulting in airway injury and dysfunction.[2]

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http://dx.doi.org/10.2147/COPD.S122282

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide. It is estimated that the number of COPD patients has reached a record of 7.3 billion in 2015.[3] Factors that cause exacerbation of COPD include clinical and medical care status, natural and social environmental changes, and lifestyles.[4] The exacerbation symptoms mainly include the increase in dyspnea, sputum production, or purulence and then the emergency hospitalization or even mortality.[5] In some parts of the world, acute exacerbation of COPD accounts for 1 of 10 leading causes of hospital admission, which bring formidable challenges to the world health and socioeconomic systems.[6]

The acute effects of air pollution exposure on COPD exacerbations have been investigated by several studies, but the results still remain inconsistent. Some reported that air pollutions significantly increased the risk of exacerbation or mortality,[7,8] whereas others found no associations[9,10] or relationships only for selected pollutants.[11,12] Moreover, several recent investigations were conducted in certain regions and were just focused on particulate air pollutions.

To the authors' knowledge no comprehensive and systematic meta-analysis has yet been published to investigate the association of acute COPD exacerbations with short-term air pollutants exposure. Therefore, the aim of the present study was to systematically review the evidence evaluating the acute risk for COPD patients when exposed to short-term air pollution.

Methods

Search strategy

Systematic searches were performed to identify the studies on the associations between major air pollutants and COPD exacerbation. The comprehensive online electronic databases included both English and Chinese databases through March 30, 2016: Web of Science (1956–2016), Ovid MEDLINE and Ovid MEDLINE in the process (1946–2016), EMBASE (1974–2005), Environmental Sciences and Pollution Management Index, CINAHL, Google Scholar and Cochrane database (2005–2016), and CNKI. Moreover, references were checked for additional publication details. Supplementary material S1 contains the search strategy. Duration of up to 7 days (lag6) was selected. If the included papers had insufficient data, the corresponding authors were contacted by email, and the papers were excluded only if there was no response from the corresponding authors.

Selection of studies

The inclusion criteria (Supplementary material S2) were as follows: 1) a case-crossover or time-series study; and 2) evaluation of the short-term effects of air pollutants on the acute risk of COPD with recorded end points. Figure 1 summarizes the selection procedures in a flow chart.

One reviewer (JH Li) performed all the initial evaluations of titles and abstracts. The other investigator (QY Huang) randomly assessed 500 samples, and no controversy was found. Full text of these potential studies was then screened to determine the eligibility by these two authors independently. During full-text selection, conflicts were settled by consensus or adjusted by a third reviewer (SZ Sun).

Quality score assessment

This meta-analysis was conducted according to the items of PRISMA and MOOSE.[13,14] Although Mustafic et al suggested to evaluate the quality of time-series or case-crossover studies,[15] there were still no validated scales recommended.[16] Therefore, a 4-component scoring system (0–1 point for each item) was designed as follows: 1) the quality of air pollution assessment (<25% of the values for one specific day were missing);[15] 2) the validation of COPD exacerbation (the disease was coded according to the International Classification of Diseases, Revision 10, American Thoracic Society or other laboratory/clinical prognosis golden criteria, such as FEV_1/FVC <0.7 for lung function); 3) the adjustment for confounders (temperature, seasonality, long-term trend, etc were adjusted); and 4) the generalizability of the outcomes (providing clear defined hospitals or health maintenance organizations).[17]

Data extraction and statistical synthesis

The two investigators (JH Li and QY Huang) conducted the data extraction independently, and discordance was resolved by discussing with another researcher (LW Tian). By assuming a linear relationship between air pollution and COPD, the relative risks (RRs) with 95% confidence interval (CI) for a standardized increment of pollutants' concentrations were pooled as follows: 10 μg/m^3 for $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 and 100 μg/m^3 for CO. These values were frequently used in the previous air-pollution-related studies.[18] If percentage change with 95% CI were reported, then it could be transformed to RR with 95% CI. Besides, if odds ratios were found, they could be considered equivalent to RRs in time-series or case-crossover studies.[19] Then, the standardized risk was unified according to the method by Yang et al.[17]

The present study was designed to have short-term exposure because the risk factors varied constantly in this period and could not be promptly confounded by fluctuating and meteorological parameters.[20] There had been no standard criteria for reporting lag patterns so far, and most studies

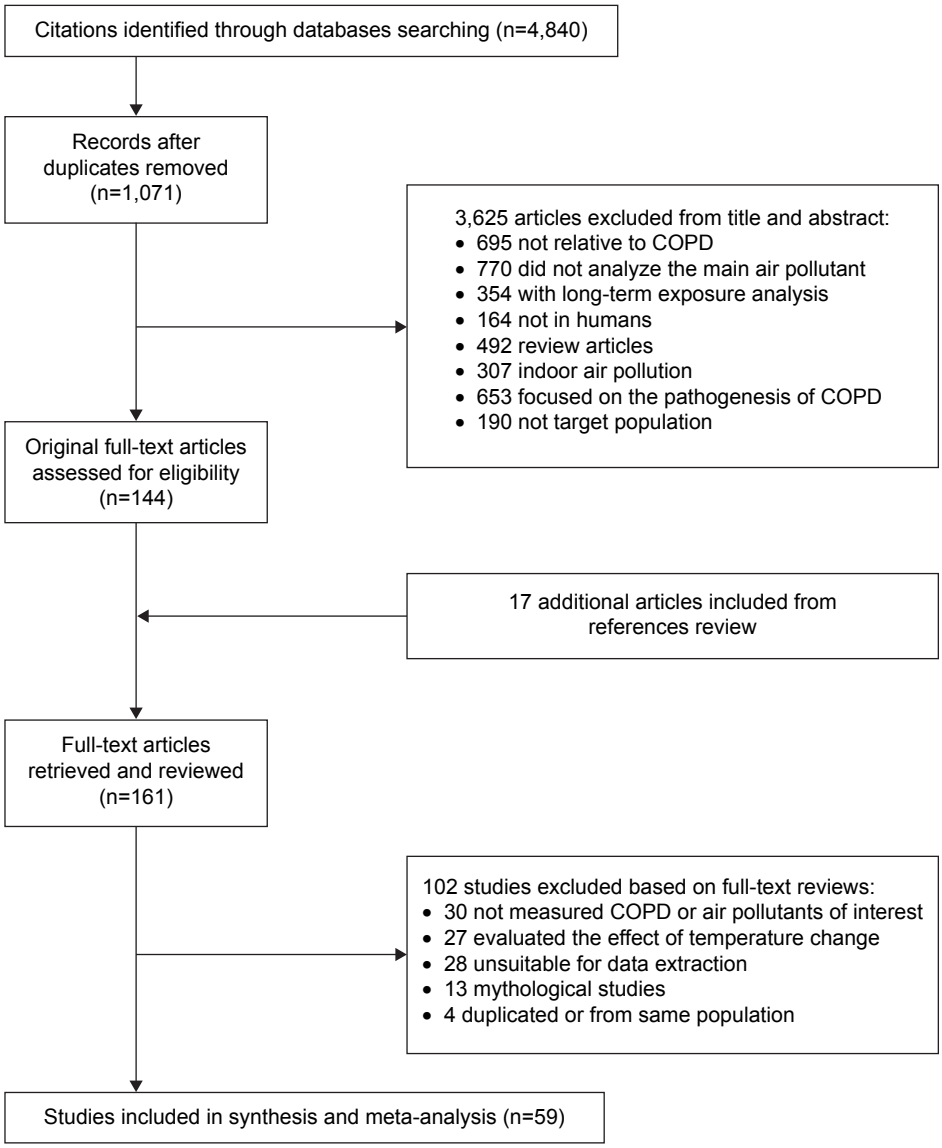

Figure 1 PRISMA flow chart of identified, included, and excluded studies.
Abbreviation: COPD, chronic obstructive pulmonary disease.

employed single-day lag; therefore, lag selection procedure was based on "priori lag" theory of Atkinson et al.[11] Briefly, when only one lag estimate was presented, it would be adopted first; if numerous lags were reported, our selection was based on the following algorithms: 1) the most frequently used lag in all the selected studies was under consideration; and 2) compared to the cumulative/distributed lags, single lags were chosen as priorities.

The heterogeneity was assessed by I^2. When heterogeneity was significant (I^2>25%), the random-effects model was applied; otherwise, the fixed-effects model was used.[21] In order to explore the sources of heterogeneity, subgroup and meta-regression analyses were performed based on study design, population location, age, and outcome category. In order to determine whether the findings could be affected by removing one or two studies, sensitivity analysis was conducted to explore robustness.[22] If the omission of any study would not affect the overall results, then the outcome of the review can be regarded with a higher degree of certainty.[23]

The population-attributable fractions (PAFs) are reduced proportions of disease hospitalization or mortality in the population when the exposure risk factor was reduced to an expected scenario. First, they were assumed to be 100% in some industrialized areas according to the recognized method by Dr Mustafic.[15] Besides, in some light-polluted regions, the prevalence percentages were suggested to be assumed lower, in which case the estimated prevalence values were 80% and 20% in the present study.[19] The equation is as follows: $\{PAF = k*(RR-1)/[k*(RR-1)+1]\}$ (where k indicates the air pollution exposure percentages).[15]

Publication bias was evaluated by using Begg's funnel plot method and confirmed by Egger's method.[24] Asymmetry was then corrected through trim and fill method, and an adjusted summary was achieved by using all the original studies together with "filled" data.[19] Moreover, the pooled effect estimates based on income status of country defined by the gross national income per capita of World Bank were also explored.[25]

The statistical analyses were conducted by using STATA Version 12.1 (STATA/SE, College Station, TX, USA) and R Software (Version 3.1.2). Significance for pooled estimates was defined as two-sided $P<0.05$.

Results

Literature search and study characteristics

Figure 1 shows the selection process of the identified 4,840 studies. A total of 59 studies fulfilled all the criteria and were included in the analysis, consisting of 13 case-crossover studies and 46 time-series studies.

Table 1 summarizes the basic characteristics of the included publications. The number of populations ranged from 4,989 to 58 million. All the research studies were published between 1992 and 2015 and were performed in Asia (People's Republic of China, Japan, Korea, and India),

Table 1 Contextual details of the studies included in the meta analysis

Study (year)	Location	Design	Period	Outcome	Population	Events	Age	Confounders
Kloog et al[46] (2014)	USA	CC	2000–2006	HA	58.0 million	0.42 million	≥65 yrs	A
Meng et al[47] (2013)	China	TS	1996–2008	Mortality	34.0 million	32.2/day	All	A.B
Tellez-Rojo et al[48] (2000)	Mexico	TS	1994–1995	Both	0.9 million	2,294	≥65 yrs	A.B.C.D.E.F
Wordley et al[49] (1997)	UK	TS	1992–1994	Both	1 million	HA 3.2/day, M 2/day	All	A.B
Neuberger et al[7] (2007)	Austria	TS	1972–1983	Mortality	1.6 million	2,878	≥65 yrs	A.B.E.G.H
Yorifuji et al[50] (2014)	Japan	CC	2006–2010	HA	6,925	761	≥65 yrs	A.B.H
Schikowski et al[51] (2014)	Taiwan	CC	2006–2010	HA	1.5 million	7.7/day	All	A.B.C.E.I
Tao et al[52] (2013)	China	TS	2001–2005	HA	NA	2.0/day	All	A.B.C.G.F
Moolgavkar et al[53] (1997)	Europe	TS	1986–1991	HA	NA	2.6/day	All	A.C.F.I
Hinwood et al[54] (2006)	Australia	CC	1992–1998	HA	1.2 million	3.3/day	All	A.B.C.D
Milutinovic et al[55] (2009)	Serbia	TS	2002–2003	HA	0.17 million	12.5/day	All	A.B.G.J.K.L.M
Arbex et al[56] (2009)	Brazil	TS	2001–2003	HA	11.2 million	1.7/day	≥40 yrs	A.B.C.E.F
Forastiere et al[57] (2008)	Italy	CC	1997–2004	Mortality	0.32 million	19.6/day	≥35 yrs	A.B.C.E.I.H.G.
Ko et al[58] (2007)	Hong Kong	TS	2000–2004	HA	7 million	65.3/day	All	A.B.C.D.E
Zanobetti et al[59] (2000)	USA	TS	1986–1994	HA	1.8 million	22/day	≥65 yrs	A.B
Morgan et al[60] (1998)	Australia	TS	1990–1994	HA	NA	9.7/day	≥65 yrs	A.B.C.D.E
Anderson et al[61] (1997)	Europe	TS	1977–1992	HA	18.2 million	49.2/day	≥65 yrs	A.B.H.E
Peel et al[8] (2005)	USA	TS	1993–2000	HA	4.0 million	7.4/day	All	A.B.C.G.F.D.N
Chen et al[62] (2003)	Canada	TS	2002–2003	HA	NA	4,409	≥65 yrs	A.B.E.F
Wong et al[63] (2002)	Hong Kong	TS	1995–1998	Mortality	8.5 million	6.0/day	All	A.B.C.F
Tenias et al[64] (2002)	Spain	TS	1994–1995	HA	0.8 million	1.8/day	≥14 yrs	A.B.C.D.F.H
Yang et al[10] (2004)	Canada	TS	1994–1998	HA	2.0 million	3.3/day	≥65 yrs	A.B.G.E.O
Qiu et al[65] (2012)	Hong Kong	TS	2000–2005	HA	0.7 million	81.1/day	All	A.B.C.D.E.F.H
Stieb et al[66] (2009)	Canada	TS	1990–2000	HA	4.0 million	40.5/day	All	A.B.C.D.G.O
Wong et al[67] (1999)	Hong Kong	TS	1994–1995	HA	7.0 million	NA	All	A.B.C.D.E.F
Schouten et al[68] (1996)	the Netherlands	TS	1977–1989	HA	0.76 million	1.7/day	All	A.B.C.D.F
Fusco et al[34] (2001)	Rome	TS	1995–1997	HA	3.0 million	13.0/day	All	A.B.C.D.H
Sauerzapf et al[69] (2009)	UK	CC	2006–2007	HA	0.8 million	1,050	≥18 yrs	A.B.H.P
Ramon et al[70] (2005)	USA	CC	1986–1999	HA	NA	578,006	≥65 yrs	A.B.C
Janssen et al[71] (2013)	Europe	TS	2008–2009	Mortality	16.5 million	17.2/day	All	A.B.C.D.F.G.H
Lin et al[72] (2012)	Taiwan	TS	2000–2009	HA	6.0 million	15.0/day	All	A.B.C.D.H.M
Bateson et al[73] (2004)	USA	CC	1988–1991	Mortality	0.06 million	16,403	≥65 yrs	A.B.G
Sunyer et al[74] (2001)	Spain	CC	1985–1995	Mortality	NA	2,305	≥35 yrs	A.B.C.H
Kan et al[75] (2003)	China	CC	2000–2001	Mortality	NA	11.0/day	All	A.B
Braga et al[76] (2001)	USA	TS	1986–1993	Mortality	12.5 million	13.2/day	All	A.B.E.G
Schwartz et al[77] (1992)	USA	TS	1973–1980	Mortality	1.7 million	0.9/day	All	A.B.C.E.O
Fischer et al[78] (2003)	the Netherlands	TS	1986–1994	Mortality	14.8 million	15.0/day	≥65 yrs	A.B.D
Wong et al[79] (2009)	Hong Kong	TS	1996–2000	Both	8.0 million	M 5.9/day, HA 91.5/day	All	B.H

(*Continued*)

Table 1 (*Continued*)

Study (year)	Location	Design	Period	Outcome	Population	Events	Age	Confounders
Xu et al[9] (2000)	China	TS	1992–1993	Mortality	3.1 million	6.2/day	All	A.B.D
Janssen et al[80] (2002)	USA	TS	1985–1994	HA	NA	NA	≥65 yrs	A.B.C.D.G
Dominici et al[81] (2006)	USA	TS	1999–2002	HA	11.5 million	26.0/day	≥65 yrs	A
Yang et al[82] (2000)	USA	TS	1990–1994	HA	NA	3,115	All	A.B.C.D.E.F.G
Schwartz et al[83] (1994)	USA	TS	1986–1989	HA	0.9 million	2.0/day	≥65 yrs	A.B.G.E.F
Schwartz(s) et al[44] (1994)	USA	TS	1986–1989	HA	2.5 million	3.0/day	≥65 yrs	A.B.G.F
Schwartz(t) et al[84] (1994)	USA	TS	1986–1989	HA	4.4 million	5.8/day	All	A.B.E.G
Sunyer et al[85] (1993)	Spain	TS	1985–1989	HA	NA	15.8/day	≥45 yrs	A.B.C.O
Lippmann et al[86] (2000)	USA	TS	1982–1994	Both	NA	8.0/day	All	A.B.E.H
Dab et al[87] (1996)	France	TS	1987–1992	Both	6.14 million	12.0/day	All	A.B.C.D.E.H.Q
Leitte et al[88] (2009)	Romania	TS	2001–2002	Both	0.1 million	1.4/day	All	A.B.D.E.H.G.R
Pande et al[89] (2002)	India	TS	1997–1998	HA	NA	22.0/day	All	A.B.E.F
Cirera et al[90] (2011)	UK	TS	1995–1998	HA	0.2 million	2.0/day	All	A.B.C.E.H.G
Yang et al[91] (2007)	Taiwan	CC	1996–2003	HA	2.6 million	15.9/day	All	A.B
Lee et al[92] (2007)	Taiwan	CC	1996–2003	HA	1.5 million	8.6/day	All	A.B
Peacok et al[93] (2010)	UK	TS	1995–1997	HA	NA	94	≥65 yrs	A.B.E
Zhang et al[94] (2013)	China	TS	2008–2011	HA	8.7 million	2,000	All	A.B.F.G
Cho et al[95] (2013)	Korea	CC	2005–2009	HA	4,989	548	≥44 yrs	A.B.S.D
Tian et al[96] (2014)	Hong Kong	TS	2001–2007	HA	8.0 million	57.0/day	All	A.B.C.D
To et al[97] (2015)	Canada	TS	2003–2010	HA	13.0 million	615,540	All	A.C.E.O.T
Cai et al[98] (2015)	China	TS	2006–2008	HA	7.0 million	121,463	All	A.B.E.F

Note: Both= the outcome includes HA and Mortality.
Abbreviations: A, temperature; B, humidity; C, day of week; CC, case-crossover study; D, holiday; E, seasonality; F, long-term trend; G, barometric pressure; H, influenza; HA, hospital admission; I, chronic time trend; J, rainfall; K, precipitation; L, overcast; M, wind velocity; N, hospital entry/exit; NA, not available; O, animal trend; P, pollen; Q, linear effects; R, nonlinear effects, S, sunlight hours; T, socioeconomic status; TS, time-series study; yrs, years old.

North America (the USA and Canada), South America (Mexico and Brazil), Australia, and Europe; 12 citations focused on the association between short-term air pollution exposure and COPD mortality, whereas 41 focused on the COPD emergency hospitalization. The final 6 citations paid attention to both. The most frequently reported age-group was all age-group, followed by the group >65 years old. Table 1 shows the potentially adjusted confounders. Furthermore, Table S1 lists the components of air pollution and average concentrations. Most publications provided multiple estimates for single lags (eg, lag0, lag1, and lag2), whereas some provided cumulative or distributed lags that were adopted only in the overall analysis. The 4-score system showed that the majority was judged to be of good or intermediate quality.

Overall analysis

There was a significant association between short-term exposure and the risk of COPD exacerbations for all the gaseous and particulate pollutants (Figure 2; Table 2). Figure S1 shows the details explicitly. Table 2 presents PAFs with all the prevalence of exposure. The associations, for gaseous air pollutants, were found to be strongest at lag0 and decreased as the time increased. Conversely, the most significant associations appeared at lag3 for particulate air pollutants.

Through sensitivity analysis, after excluding studies that increased risk of bias, no difference was found in the overall effect estimates (Table S2). Publication bias was observed in pollutants of SO_2, O_3, and PM_{10} by using Egger's test for asymmetry $P<0.05$ (Table 2; Figure S2). After adjusting the symmetry with the trim and fill method, it was found that the effect directions of all air pollutants did not change, but it yielded the effects adjusted for funnel plot asymmetry as expected.

Subgroup analyzes

Lag exposure

Based on the lag exposure subgroup analysis, it was found that the following outcome of lag subgroup analysis for each air pollutant were consistent with the results of overall analysis (RR [95% CI], I^2, Egger's test [P]): lag0 for SO_2 (1.007 [1.003, 1.011]; 91.5%; P=0.31), NO_2 (1.030 [1.026, 1.033]; 94.9%; P=0.78), and $PM_{2.5}$ (1.002 [1.001, 1.005]; 76.8%; P=0.36); lag1 for CO (1.000 [0.985, 1.005]; 61.4%; P=0.41); lag3 for O_3 (1.013 [1.010, 1.016]; 5.90%; P=0.35) and PM_{10} (1.009 [1.006, 1.011]; 55.8%; P=0.12). Figure 2 and Table S3 present more detailed results.

Study quality

This subgroup included 56 citations (20 studies fulfilling the high-quality score of 4 points and 36 studies receiving the middle quality score of 3 points). Except for SO_2 and O_3, all the other air pollutants revealed valid associations with COPD risk (Table S3). Among them [N, RR (95% CI); Egger's test, P], NO_2 (27 studies; 1.017 [1.015, 1.019]; P=0.147),

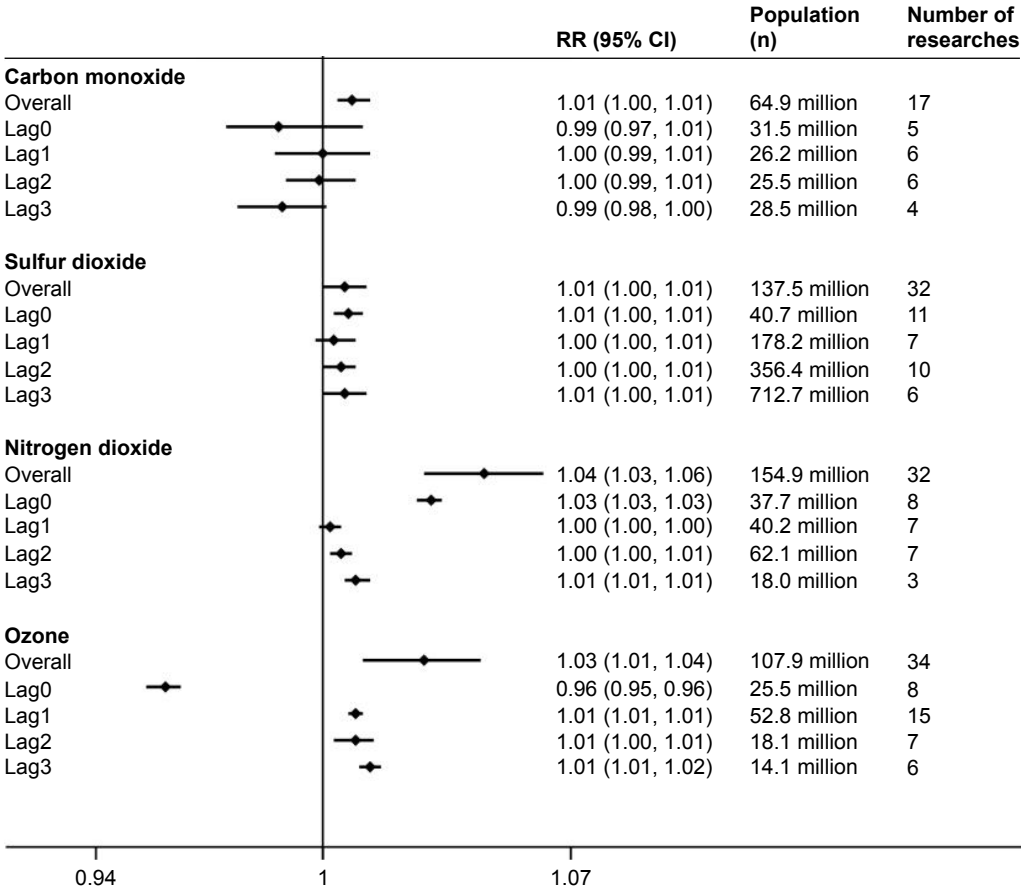

Figure 2 Associations between gaseous and particular air pollution and COPD risk stratified by time lag (days).
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

CO (13 studies; 1.006 [1.002, 1.011]; *P*=0.163), $PM_{2.5}$ (15 studies; 1.001 [1.000, 1.001]; *P*=0.187), and PM_{10} (34 studies; 1.001 [1.000, 1.001]; *P*=0.187) were proved to be unfavorable associations.

Property classification

As shown in Figure 3, this analysis was conducted based on COPD exacerbation outcomes (hospitalization or mortality), geographical location (Asia or non-Asia), population

Table 2 Subgroup analysis by gaseous and particulate pollutants

	Gaseous pollutants				Particulate pollutants	
	Carbon monoxide	Nitrogen dioxide	Sulfur dioxide	Ozone	$PM_{2.5}$	PM_{10}
Increment	100 μg/m³	10 μg/m³	10 μg/m³	10 μg/m³	10 μg/m³	10 μg/m³
Mean pollutant	1.18	64.56	26.47	54.90	14.84	46.44
Standard deviation	0.38	20.32	10.75	22.87	8.05	29.50
Range (minimum–maximum)	0.40–3.04	10.23–126.40	9.08–59.68	13.19–119.47	5.20–94.59	11.98–135.17
Number of studies	15	29	28	29	14	35
Number of estimates	17	32	32	34	15	38
RR (95% CI)	1.008	1.045	1.006	1.028	1.024	1.017
	(1.004, 1.013)	(1.028, 1.062)	(1.001, 1.012)	(1.011, 1.044)	(1.005, 1.043)	(1.012, 1.022)
Heterogeneity, I^2	97.0	98.0	80.8	98.8	97.1	86.2
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PAF, % (95% CI)						
k=100%	0.79 (0.40, 1.28)	4.31 (2.72, 5.84)	0.60 (0.00, 1.19)	NA	2.34 (0.50, 4.12)	1.67 (1.19, 2.15)
k=80%	0.64 (0.32, 1.03)	3.47 (2.18, 4.67)	0.48 (0.08, 0.95)	NA	1.88 (0.40, 3.33)	1.34 (0.95, 1.73)
k=20%	0.16 (0.08, 0.26)	0.89 (0.56, 1.22)	0.12 (0.02, 0.24)	NA	0.48 (0.10, 0.85)	0.34 (0.24, 0.44)
Publication bias						
Egger regression test, *P*-value	0.160	0.147	0.007	<0.001	0.447	<0.001
Adjusted estimates (95% CI)	1.002	1.021	1.004	0.976	1.006	1.008
	(1.001, 1.003)	(1.004, 1.018)	(0.998, 1.011)	(0.962, 0.991)	(1.004, 1.008)	(1.004, 1.011)

Abbreviations: CI, confidence interval; NA, not available; RR, relative risk; PAF, population attributable fraction.

age (all age or age >65 years), and study design (time-series or case-crossover). When classified by geographical locations, the positive relationships were more significant in Asian countries than in the non-Asian countries for air pollutants. Similar associations were also observed in age subgroups: there was a tendency toward stronger relationships between these air pollutants and COPD. The property subgroups of case-crossover study and COPD deaths had borderline significance.

Furthermore, it was also identified that subgroup of age >65 years for SO_2 and O_3, COPD mortality subgroup for NO_2, CO, and $PM_{2.5}$, and subgroup of non-Asia population for PM_{10} reduced the heterogeneities of their pooled effects compared to overall analyzes. Table S4 shows further details.

Stratification by national income

Among all the included studies, 20% of the publications were from low-/middle-income countries in which ~60% of the population originated from the People's Republic of China. SO_2, NO_2, and PM_{10} were commonly measured in low-/middle-income countries, such as Mexico and Brazil. Compared with the developed countries, the SO_2 and NO_2 short-time exposure showed more pronounced associations with COPD acute risk in the developing countries. For them, the RRs (95% CI) in low-/middle-income and high-income countries were as follows: SO_2, 1.012 (1.001, 1.023) and 1.005 (0.996, 1.014); and NO_2, 1.019 (1.014, 1.024) and 1.017 (1.015, 1.019) (Figure 4). The mean concentrations of SO_2 and NO_2 in low-/middle-income countries were relatively higher than those of high-income countries, which was particularly concerning for the reason that these countries have disproportionate burdens of global acute exacerbation of COPD.

Heterogeneity by meta-regression

Considering the substantial heterogeneity exhibited in the overall analysis, meta-regression analysis identified that study design of NO_2 (coefficient =–0.166; *P*=0.014) and O_3 (coefficient =–0.072; *P*=0.017) contributed to heterogeneities significantly (Table S4). However, heterogeneity exploration similar to subgroups of location, age, and COPD subtype showed no significant contributors.

Discussion

Principal findings

To the authors' concurrent knowledge, this was the first study to report the comprehensive association between main gaseous and particulate pollutants' short-term exposure and COPD acute risk, indicating that improving air quality could reduce the risk of sudden onset of COPD and the burden of COPD worldwide. The present study found a significant association between short-term exposure to major air pollutants and COPD emergency risk, especially for O_3 and NO_2. Subgroup analysis showed lower heterogeneities and yielded similar associations in the overall analysis. The pooled estimates stratified by financial levels demonstrated stronger

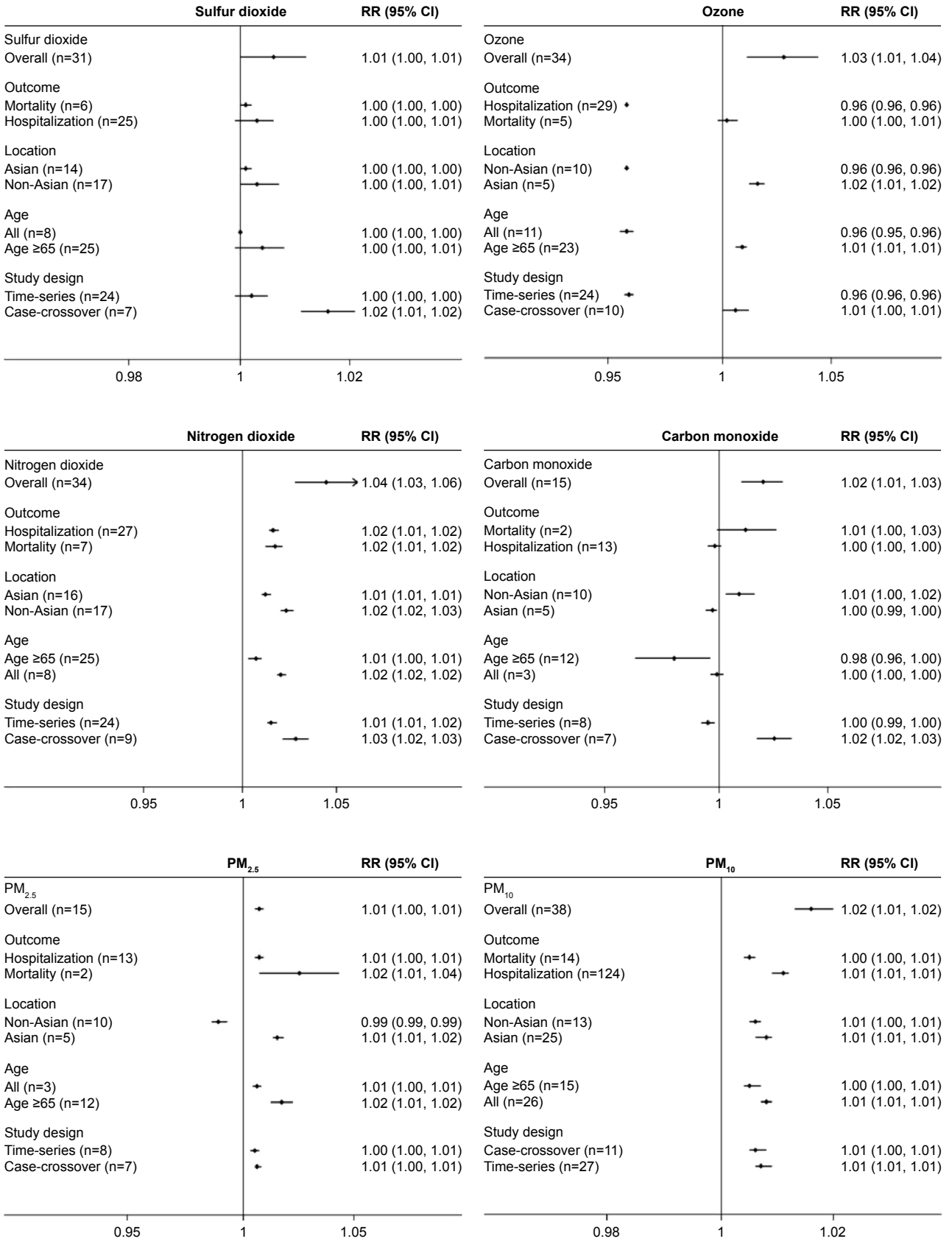

Figure 3 Subgroup analysis for all gaseous and particulate air pollutants stratified by outcome, location, age, and study design.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

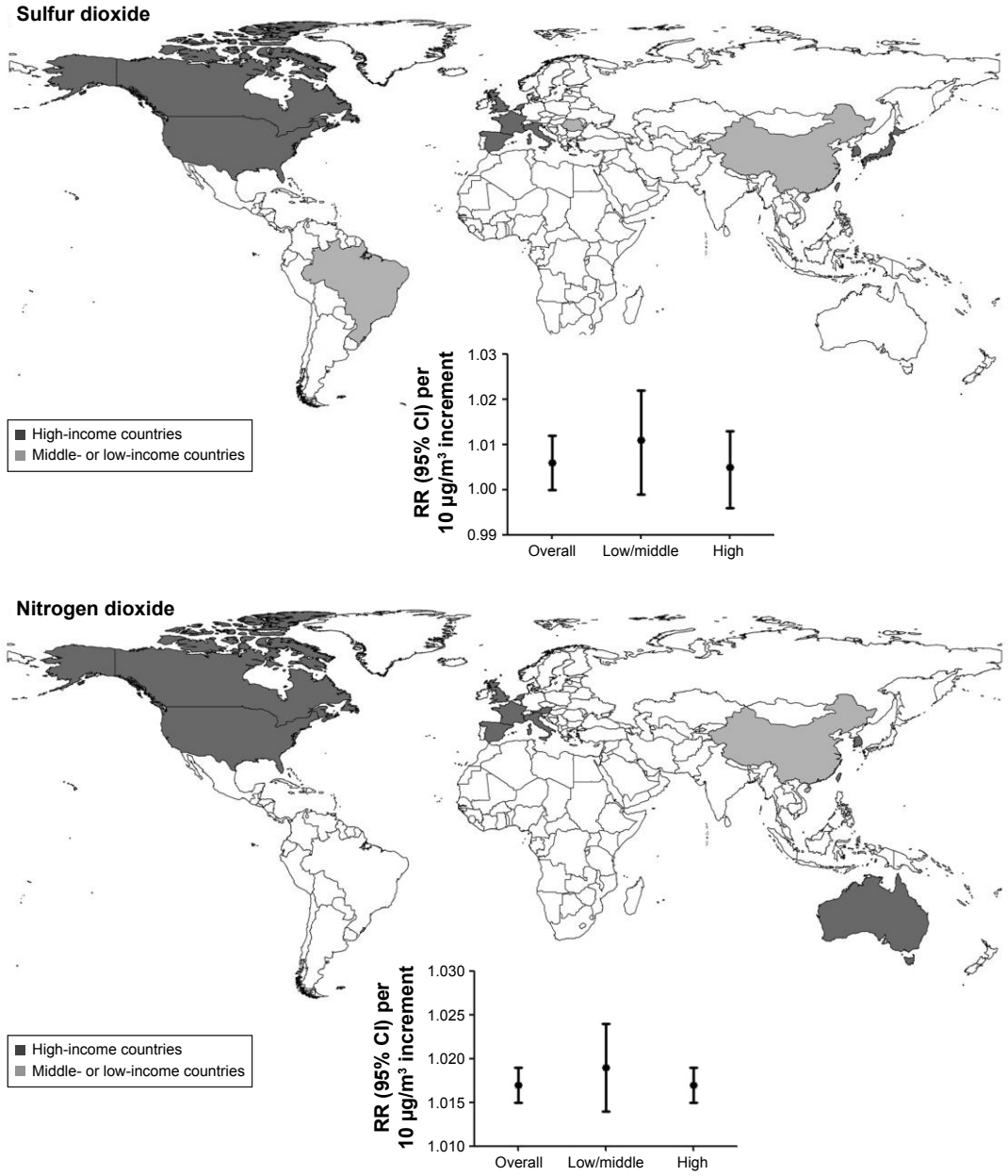

Figure 4 Cartogram identifying associations between sulfur dioxide and nitrogen dioxide short-term exposure and COPD risk stratified by countries of high- and low-/middle-income levels.

associations in low-/middle-income countries than in high-income countries.

Potential mechanisms

There were plenty of in vivo and in vitro studies to explain the plausible biomedical mechanisms for the relationship between short-term air pollution exposure and adverse outcome of COPD.[26,27] One of the main mechanisms was oxidative-mediated.[28] Air pollution could absorb chemical substances from the environment, which participated in the production process of reactive oxygen species.[29] Oxidative stress could cause an injury in the epithelium of the airway, making the airways of COPD patients more sensitive to further damage, and impair the resistance ability of the immune system.[2] Another pathogenesis mechanism is that air pollutants can cause inflammation in the lungs and can further impair the reduced pulmonary function in COPD patients.[30] However, the COPD exacerbation-relevant determinants are still largely unknown. As most research studies have focused on smoking and pneumonia risk for COPD exacerbation,[4,31,32]

further studies considering the significant roles of environmental pollution are required.

Interpretation

In the present analysis, all the air pollutants showed acute disadvantageous effects on COPD patients, especially NO_2 and O_3. Both of these two gaseous pollutants caused an increased risk of COPD significantly (RR, 95% CI): 1.04, (1.03, 1.06); and 1.03, (1.01, 1.04). One study reported that every 10 μg/m^3 increase of O_3 and NO_2 would result in 0.58% and 0.38% increment in the COPD risk, respectively.[33] In addition, exposure to SO_2 and CO showed weaker associations with COPD in the present study, which was consistent with a previous study. Fusco et al found that no effects were identified for SO_2, and only weak associations was found for CO (2.8% increase per interquartile range (IQR), 1.5 mg/m^3).[34] NO_2 and O_3 played important roles in acute respiratory attack, whereas CO seemed to be strongly associated with seasonality, especially in warmer seasons. In combination studies, it was difficult to separate all the estimates of CO by the adjustment of seasonality.[34,35] For the different effects of O_3 compared to other pollutants, the most important factor is the properties of O_3. It is the component of photochemical reaction and shows obvious seasonality fluctuation that could affect the exacerbation rate of COPD patients.[15] Moreover, it is relatively more complex to form O_3 in the ambient air, depending closely on solar radiation and brightness.[36] As for the adjustment of temperature, different methods adopted cause RR estimates to vary, and in the pooled analysis, it is hard to just limit the pollutants to a certain period.[37]

Particulate pollutants have always been considered to be responsible for the most adverse cardiovascular and respiratory diseases, and some adverse impacts induced by $PM_{2.5}$ might be aggravated by PM_{10}.[19] In the present study, particulate pollutants showed significant adverse impact on COPD patients, which further confirmed that elevated levels of particulate matters in polluted environments could promote the exacerbation of COPD. A study in New Zealand reported an 3.37% increase for each 14.8 mcg/m^3 increase in PM_{10}, and an Australian study also showed a 4% increase in admissions for every 10 μg/m^3 increase of PM_{10}.[38] However, there were still limited studies about PM_{10} in developing countries. In an Asian time-series study, per 10 μg/m^3 increase in PM_{10} indicated an 0.36% increase in respiratory mortality.[39] Because of a disproportional burden of COPD exacerbation in these middle-/lower-income counties, more studies on PM_{10} are required to explore the combined effects of particulate pollutants.

The heterogeneities of the air pollutants CO, NO_2, and O_3 were more significant than that of SO_2. For particulate pollutants, the heterogeneity of $PM_{2.5}$ was greater than that of PM_{10}. Subgroup analysis indicated that lag exposure and age >65 years contributed heterogeneities more significantly. In individual studies, they measured daily variations of each pollutant in limited areas for the time period from 0 to 7 days and adjusted different kinds of confounders.[27] Therefore, lag exposure for them would be a source of heterogeneity. Subgroup of mortality and age >65 years were also the origins for heterogeneity because COPD showed signs between the ages of 35 and 40 years primarily and it then developed very fast after 65 years. Once exposed to risk factors, COPD patients would exacerbate quickly, and mortality rate increased.[40] A high quality study with higher score tends to have the higher methodological quality.[41]

The current analysis also indicated that the association between SO_2 and NO_2 short-term exposure and COPD acute risk seemed to be more pronounced in low-/middle-income countries than in high-income countries, and only 20% of the included studies were from low-/middle-income countries, and more than half of them originated from the People's Republic of China (Figure 4). This finding was of great importance because urban cities in some developing countries were in a rapid industrialization process and under the threat of severe environmental problems.[42] Moreover, data from these countries were scarce, resulting from a lack of cohesive air quality policies, inadequate environmental monitoring, and a paucity of disease surveillance data.[19] More monitoring information is in great demand for developing countries in order to investigate the health impacts of air pollutants. Considering the severe air pollution and disproportionate burden of COPD acute risk in the developing countries, this highlighted issue needs more attention.

Practical implications

The findings of the present study have provided evidence for the association between short-term air pollution exposure and the risk of COPD exacerbations. This called for improvement and implementation of regulations on the air quality that will provide measurable benefits to public health. More policies should be implemented to reduce major air pollutants, such as adoption the absorbers of noxious gases before release, utilization of environmentally-friendly fuels, and adoption of advanced technologies.[43] Our results urge future research studies on the relationship between concentration of air pollutants and the risk estimation and also for more cooperative actions to issue alerts to high-risk populations in order to facilitate substantial public health benefits.

Limitations

It was acknowledged that several limitations should be considered. First, the lag selection in methodologies was controversial. Exclusion of any lag from lag0 to lag7 might miss considerable information for pooled analysis. In this analysis, all the methodologies used had been reviewed. Therefore, the "priori lag" method was chosen based on the most commonly used approach. Besides, there were still potential sources of bias in the present study: the estimates included were from each publication, and whether multiple hospitalizations might occur for the same patients was not identified. Moreover, the concentration–response relationships are really fundamental references in air quality standards, but lack of details to construct the dose–response functions may limit the ability for setting criteria. Finally, for the air pollutants under the single-pollutant model, underlying interactive effects might exist.[44] There was no clearly stated selection of models in combined analysis, and most of the parameters preferred the idea that multiple models for air pollutions in meta-analysis were still imperfect;[45] therefore, the single-air pollutant model was used in the present study for estimations.

Conclusion

This systematic review and meta-analysis confirmed that short-term exposure to major air pollutants could significantly increase the risk for COPD exacerbations. Environmental and public health policies that can decrease the concentrations of air pollution might reduce the exacerbation burden of COPD.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (41272180).

Disclosure

The authors report no conflicts of interest in this work.

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