Environmental Science and Pollution Research (2018) 25:15133–15145
https://doi.org/10.1007/s11356-018-1629-7

RESEARCH ARTICLE

Exposure to nitrogen dioxide and chronic obstructive pulmonary disease (COPD) in adults: a systematic review and meta-analysis

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Received: 21 July 2017 / Accepted: 27 February 2018 / Published online: 20 March 2018

Abstract

Exposure to nitrogen dioxide (NO_2) has long been linked to elevated mortality and morbidity from epidemiological evidences. However, questions remain unclear whether NO_2 acts directly on human health or being an indicator of other ambient pollutants. In this study, random-effect meta-analyses were performed on examining exposure to nitrogen oxide (NO_x) and its association with chronic obstructive pulmonary disease (COPD). The overall relative risk (RR) of COPD risk related to a 10 μg/m^3 increase in NO_2 exposure increased by 2.0%. The pooled effect on prevalence was 17% with an increase of 10 μg/m^3 in NO_2 concentration, and 1.3% on hospital admissions, and 2.6% on mortality. The RR of COPD cases related to NO_2 long-term exposure was 2.5 and 1.4% in short-term exposure. The COPD effect related with a 10 μg/m^3 increase in exposure to a general outdoor-sourced NO_2 was 1.7 and 17.8% to exposure to an exclusively traffic-sourced NO_2; importantly, we did observe the effect of NO_2 on COPD mortality with a large majority in lag0. Long-term traffic exerted more severe impairments on COPD prevalence than long-term or short-term outdoor effect; long-term mortality effect on COPD was serious in single model from this meta-analysis. Overall, our study reported consistent evidence of the potential positive association between NO_2 and COPD risk.

Keywords COPD · NO_2 · Relative risk · Air pollution · Exposure assessment

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is globally the fourth leading reason of death, and this has been predicted to become the third leading reason by 2030 (Mannino and Buist 2008), getting COPD as one of the pivotal health challenges worldwide (Decramer et al. 2012). Presently, 210 million people have been suffering from COPD. Without effective prevention, the COPD deaths would elevate by over 30% in the near few decades (Eisner et al. 2010). Although smoking plays a key factor in COPD, evidences agreed that other etiologies are also important to induce COPD (Eisner et al. 2010).

Air pollution has been demonstrated to be linked with potential effects on human health, weather and climate, including elevated mortality hazard, increased rates of emergency department visits and hospital admissions, exacerbated of chronic respiratory conditions (e.g., COPD and asthma), deteriorated lung function and changed climate (Samet and Krewski 2007). Ambient air pollution is a kind of complex mixture comprised of both gaseous pollutants (e.g., nitrogen dioxide, NO_2) and solid particles (e.g., Particulate Matter, PM). Recently, reports on traffic-based exposure from the American Thoracic Society (ATS) (Eisner et al.) and the Health Effects Institute (HEI) (HEI 2010) have both addressed the crucial role of air pollution to COPD development and the urgent need of an association study between ambient air pollution or local traffic-related pollution and COPD. Exploration of one or two specific pollutants which is having the largest contribution to the health effect of COPD could have pivotal implications for environmental and social policies, as well for local government in taking action to protect

Responsible editor: Philippe Garrigues

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11356-018-1629-7) contains supplementary material, which is available to authorized users.

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public health. Known as the massive anthropogenic emission, NO_2 is an alternate for traffic-sourced air pollutant and one of the most pivotal environmental pollutants (Akimoto 2003). In view of its broadly diffusion and strong oxidization, NO_2 has drawn a widely increasing public attention on health. As with the short-term effects, the association between NO_2 and health effects remains in many studies after adjusting for other pollutants (such as PM and black smoke). Even the mechanistic evidences (Wegmann et al. 2005) and one latest study (DeVries et al. 2016) both implied a causal relationship between NO_2 short-term exposure and respiratory effects. Hence, it is reasonable to infer that NO_2 may exert some direct effects on the development of these diseases. Additionally, it is much harder to evaluate the long-term effects of NO_2 separately because of its high correlations with other pollutants in those studies. Therefore, NO_2 might represent a mixture of traffic-sourced air pollutants. However, some epidemiological studies suggested a relationship of long-term NO_2 exposures with respiratory diseases that was independent of mass metrics (WHO 2013).

Given the potential crucial roles of NO_2 in multiple respiratory diseases, the role of NO_2 in the development of COPD remains largely uncertain so far, which requires further investigations. The common feature of the existing available researches was almost conducted with small sample sizes, which might limit the statistical power to uncover mild effect and/or correlation. In this circumstance, we widely reviewed and discussed the accumulated scientific evidence on the effects on COPD of NO_2 and extensive rationales for the plausible answers were also given in this study. We sought to test the hypotheses that NO_2 might have potential detrimental effects on COPD. In particular, we aimed to determine whether culture, exposure term, sources of exposure, lag periods, pollution model, etc. could influence this situation.

Methods

Literature search

Systematic searches of the literature were performed by using PubMed and ISI Web of Knowledge resources (until January 13, 2018). The keywords for the searches included nitrogen dioxide [Title/Abstract] or NO_2 [Title/Abstract] or nitrogen oxide [Title/Abstract] or NO_x [Title/Abstract] concatenated with Chronic Obstructive Pulmonary Disease [Title/Abstract] or COPD [Title/Abstract] or Chronic Bronchitis [Title/Abstract] or Emphysema [Title/Abstract] or Chronic Obstructive Airways Disease [Title/Abstract] or COAD [Title/Abstract]. First, two professional workers identified eligible articles by the abstracts available. Second, if the abstracts were consistent with the inclusion and exclusion criteria, the whole article text was obtained (included criteria published after January 1, 1997; observational studies; human studies in adults; diagnosed with COPD; effects of NO_2 or NO_x on COPD; the risk estimates included such as hazard ratio (HR), relative risk (RR), odds risk (OR), excessive risk (ER) or increased risk (IR). Excluded criteria detailed as age did not accord with, NO_2 or NO_x were not reported, inadequate detail on classifications, not on human studies, English not chose or English translation unavailable).

Study selection

Studies were included if effects on COPD were evaluated and the associations between COPD and NO_2 or NO_x ($NO+NO_2$) assessed (detailed as inclusion criteria). Articles were excluded if no original data were analyzed, or articles were on reviews, or inadequate detail on classification, and other descriptive or intervention articles (detailed as exclusion criteria). However, articles conducted on groups restricted to at-risk subjects should be included.

Data extraction

Two professional workers separately extracted the data and came to a consensus on all of the items according to inclusion and exclusion criteria. Once meeting the criteria, the following information was collected: subject group characteristics (including age of COPD patients, the sample size, lag days, statistical methods, pollution model (single or multiple)), sources of exposure, study region, year of publication, study design and study period, exposure endings, the average levels of NO_2, and the exposure metrics (such as HR, RR, OR, ER or IR).

Data synthesis and analysis

The effects showed as interquartile (quintile or percentile) differences, or different units were converted into effects of a 10 $\mu g/m^3$ increase of NO_2 or NO_x. For these measuring NO_2 in parts per billion, a conversion factor of 1 ppb = 1.88 $\mu g/m^3$ for both NO_2 and NO_x was employed, and this is based on ambient pressure of 1 atm and a temperature of 25 °C (Vrijheid et al. 2011). To convert the effect assessment from NO_x to NO_2 effects, multiply by a conversion factor of 0.75 before pooling data (EPA 2005). RRs were used in a random-effects model (determined by results of heterogeneity test), and therefore the risk assessment in the comprehensive analysis was independent of the work design. The risk assessment and 95% confidence intervals (CI) from most studies were showed to be adjusted for the factors the original authors thought as confounders. The effect on standard error (SE) was calculated based on the risk estimates and the 95%CI (SE = (lnRR-lnLowestlimit CI)/1.96 or SE = (lnHighestlimit CI-lnRR)/1.96). Stratified analyses were also provided by study region, sources of exposure, exposure term,

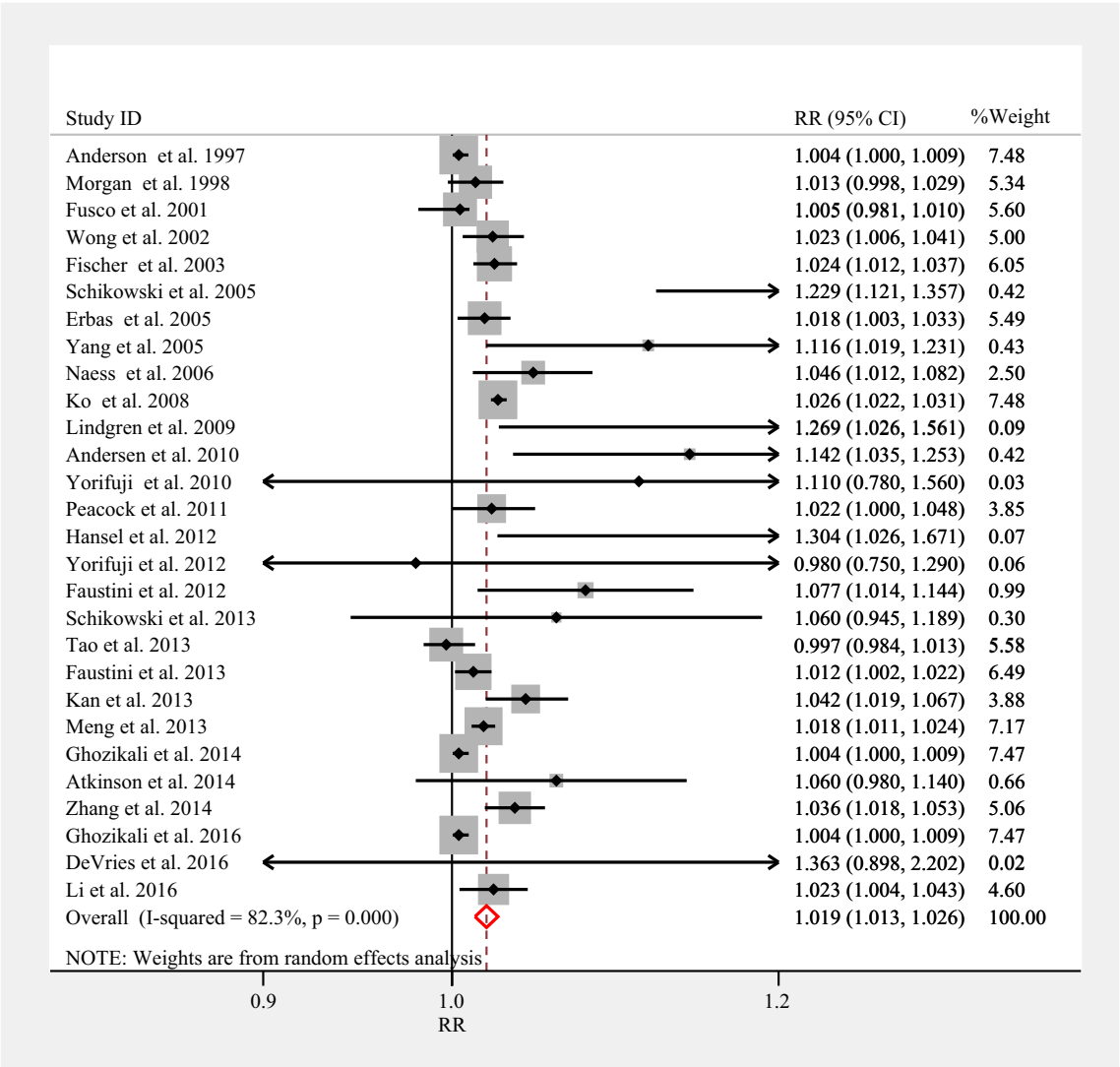

Fig. 1 Relative risks of COPD relevant to a 10 μg/m^3 increase in NO_2 exposure. The meta-estimate and weights in the forest plot estimated from random effects meta-analyses

exposure ending, and lag periods. Heterogeneity test was carried out according to the Q-test (DerSimonian and Laird 1986), and *P* values more than 0.05 suggests a lack of heterogeneity (Fig. 1). Funnel plots and Egger's linear regression test were employed to evaluate diagnosis of the possible publication bias (Egger et al. 1997) (Fig. S1). Sensitivity analysis was assessed by using Metaninf and it was robust and reliable (Fig. S2). The Stata software used to perform all analyses (Version 12.0; StataCorp LP, College Station, TX) using two-sided *P* values.

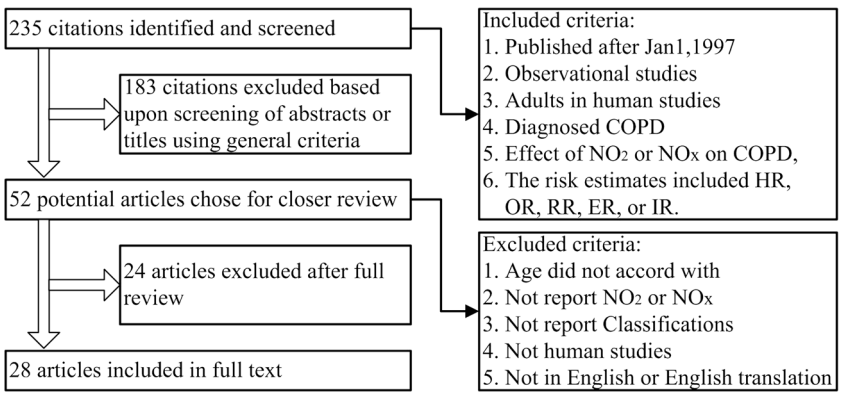

Fig. 2 Results of search for eligible studies

Table 1 Description of studies included

ID	Author	Year	Region	No. of COPD	Study design	Study period	Exposure endings	NO_2, Mean (SD)	RR	Unit, $\mu g/m^3$	Lag days	Exposure term	Sources exposed	Adjusted RR	Age
1	Anderson	1997	European	1.1[a]	RE	1977–1992	Hospitalization	52.8	1.019 (1.002, 1.047)	50	1–3	Short	Outdoor	Yes	All age
2	Morgan	1998	Australia	9.7[a]	RE	1990–1994	Hospitalization	15 (6)	1.043 (0.993, 1.096)[f]	17[c]	1	Short	Outdoor	No	65+
3	Fusco	2001	Italy	13 [a]	Cohort	1995–1997	Hospitalization	86.7 (16.2)	1.01 (0.959, 1.022)[f]	22.3	0	Long	Outdoor	Yes	All age
4	Wong	2002	China	6[a]	RE	1995–1998	Mortality	56.40 (19.24)	1.023 (1.006, 1.041)	10	0–2	Short	Outdoor	No	–
5	Fischer	2003	Netherlands	15[a]	RE	1986–1994	Mortality	32	1.05 (0.92, 1.21)	30	0–6	Long	Outdoor	Yes	45+
6	Schikowski	2005	Germany	116	–	1985–1994	Prevalence	39	1.39 (1.20, 1.63)	16	–[d]	Long	Traffic	Yes	54.4[e]
7	Erbas	2005	Australia	–	RE	1989–1992	Hospitalization	–	1.06 (1.01, 1.11)	17[c]	0	Short	Outdoor	Yes	–
8	Yang	2005	Canada	3.07 [a]	RE	1994–1998	Hospitalization	17.27 (3.77)	1.12 (1.02, 1.24)	5.5 [c]	0–6	Short	Outdoor	Yes	65+
9	Naess	2006	Norway	233	Cohort	1992–1998	Mortality	39	1.21 (1.05, 1.39)	42	–[d]	Long	Outdoor	Yes	51–70
10	Ko	2008	China	80[a]	RE	2000–2004	Hospitalization	51.2 (21.8)	1.026 (1.022, 1.031)	10	0–3	Long	Outdoor	No	–
11	Lindgren	2009	Sweden	415	CS	1980–2006	Prevalence	25.0 (6.1)[b]	1.43 (1.04, 1.95)	1	–[d]	Long	Traffic	Yes	18–77
12	Andersen	2010	Danish	1786	Cohort	1971–2006	Hospitalization	18.1 (5.6)	1.08 (1.02, 1.14)	5.8	–[d]	Long	Traffic	Yes	35+
13	Yorifuji	2010	Japan	–	Cohort	1999–2006	Mortality	–	1.11 (0.78, 1.56)	10	–[d]	Long	Traffic	Yes	65+
14	Peacock	2011	UK	94	Cohort	1995–1997	Outpatient	51.4 (15.8)	1.06 (1.0, 1.13)	14[c]	1	Short	Outdoor	Yes	40–83
15	Hansel	2012	USA	84	Cohort	2010–2011	Mortality	10.8 (10.6)	2.71 (1.1, 6.9)	20[c]	–[d]	Short	Indoor	Yes	40+
16	Yorifuji	2012	Japan	50	Cohort	2002–2009	Mortality	22 (15)	0.98 (0.75, 1.29)	10	–[d]	Long	Traffic	Yes	65–84
17	Faustini	2012	Italy	15,884	RE	2005–2009	Mortality	60.4 (16.9)	1.196 (1.035, 1.382)[f]	24	0–5	Short	Outdoor	No	35+
18	Schikowski	2013	European	150	Cohort	2008–2011	Prevalence	28.9 (15.4)	1.07 (0.91, 1.26)	1	–[d]	Long	Outdoor	Yes	43–73
19	Tao	2013	China	2.00[a]	–	2001–2005	Hospitalization	45.8 (29.3)	0.99 (0.952, 1.041)[f]	31	3	Long	Outdoor	Yes	All age
20	Faustini	2013	Italy	38,577	Cohort	2001–2005	Hospitalization	21.9	1.012 (1.002, 1.022)[f]	10	0	Long	Outdoor	Yes	35+
21	Kan	2013	China	10.7[a]	CC	2000–2001	Mortality	32.46 (14.43)	1.042 (1.019, 1.067)	10	0–1	Short	Outdoor	No	–
22	Meng	2013	China	8.05 [a]	RE	1996–2008	Mortality	6.6–12.2	1.0178 (1.011, 1.0244)[f]	10	0–1	Short	Outdoor	Yes	All age
23	Ghozikali	2014	Iran	1521	–	2008–2009	Hospitalization	33.54	1.004 (1.001, 1.009)	10	–[d]	Short	Outdoor	No	–
24	Atkinson	2014	UK	2910	Cohort	2003–2007	Hospitalization	22.5 (7.4)	1.06 (0.98, 1.14)	10	–[d]	Long	Outdoor	Yes	40–89
25	Zhang	2014	China	–	Cohort	2008–2011	Hospitalization	56	1.036 (1.019, 1.053)[f]	10	0	Long	Outdoor	Yes	All age
26	Ghozikali	2016	Iran	–	–	2011–2012	Hospitalization	29	1.0038 (1.0004, 1.0094)	10	–[d]	Short	Outdoor	No	–
27	DeVries	2016	USA	168	CC	2012–2013	Hospitalization	11 (5)	1.17 (1.09, 1.25)	1[c]	–[d]	Short	Outdoor	Yes	65+
28	Li	2016	China	10,095	–	2007–2011	Mortality	60.7 (27)	1.0235 (1.0042, 1.0432)	10	–[d]	Long	Outdoor	No	All age

CS cross-sectional, *CC* case-crossover, *RE* retrospective ecological

[a] No. of COPD is daily mean

[b] Pollutant is NO_x

[c] Unit is ppb

[d] Lag days maybe 0

[e] Mean age

[f] Converted from ER, HR, IR or their percentage increases

Results

Results of the literature search

At the beginning, 235 articles were included, of which 183 deleted according to included and discarded criteria. The rest of 52 abstracts were reviewed, and whole studies were estimated, of which 28 potentially associated articles were retained. Among the remaining articles, extra 24 articles were also excluded. Finally, we involved and focused on the remaining 28 studies that were satisfied with our inclusion and exclusion criteria (Fig. 2) (Andersen et al. 2010; Anderson et al. 1997; Atkinson et al. 2014; DeVries et al. 2016; Erbas and Hyndman 2005; Faustini et al. 2012; Faustini et al. 2013; Fischer et al. 2003; Fusco et al. 2001; Ghozikali et al. 2014, 2016; Hansel et al. 2012; Kan and Chen 2003; Ko et al. 2008; Li et al. 2016; Lindgren et al. 2009; Meng et al. 2013; Morgan et al. 1998; Naess et al. 2006; Peacock et al. 2011; Schikowski et al. 2005, 2013; Tao et al. 2013; Wong et al. 2002; Yang et al. 2005; Yorifuji et al. 2010, 2012; Zhang et al. 2014) (Table 1, Table S1, $P_{Q\text{-test}} < 0.001$). Articles excluded based on reasons such like age not in accord with standard, NO_2 or NO_x concentration degrees not shown, classifications not clearly reported, researches

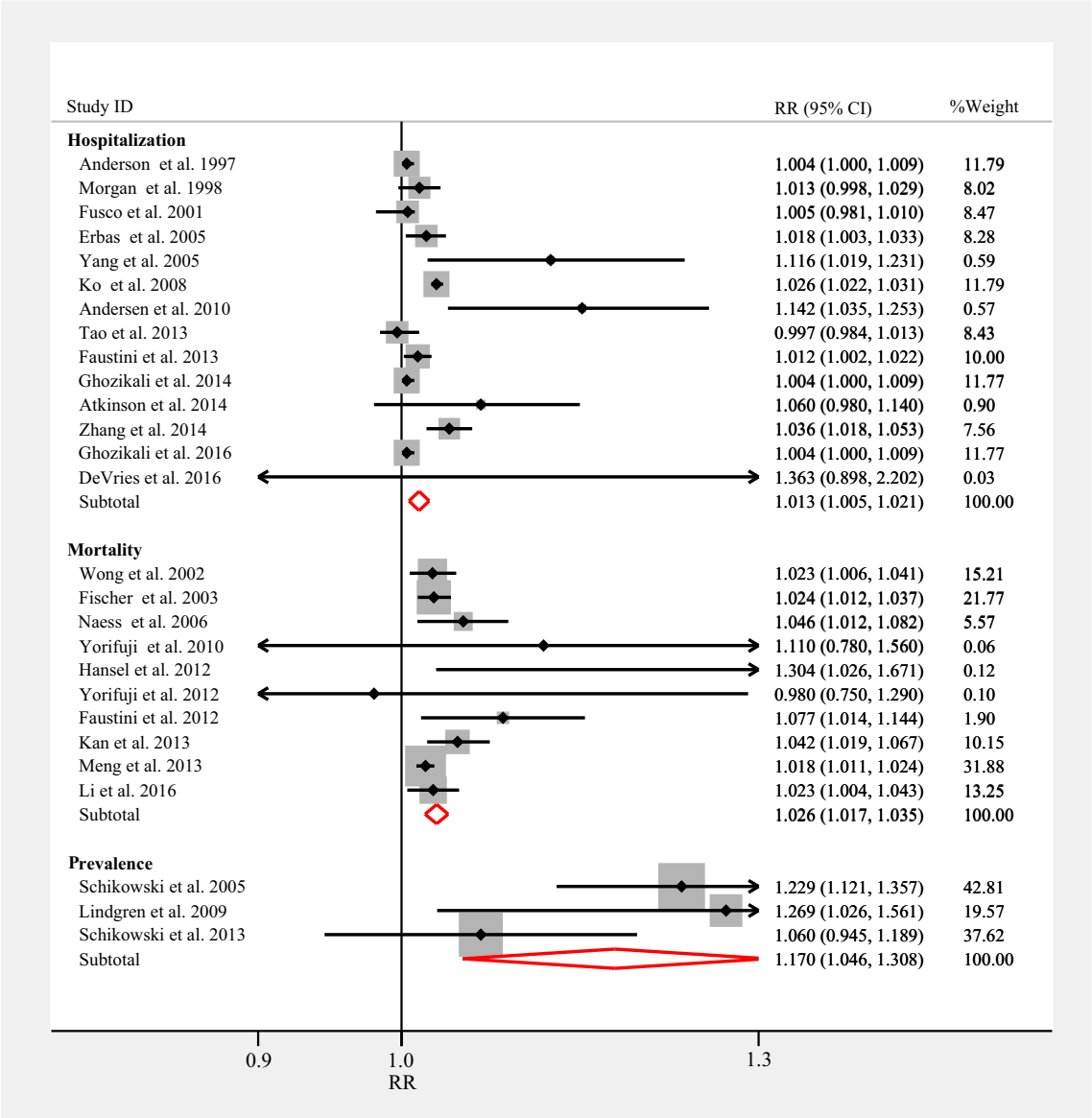

Fig. 3 Forest plot of study-specific estimates of relative risk of COPD associated with a 10 μg/m^3 increase in exposure to NO_2 stratified by exposure ending, and random effects meta-analyses employed

not focused on human, and English not chose or English translations unavailable. The included studies were all published after 1997 and were all observational studies (Table 1, Table S1). The consistent positive relationship between NO_2 and COPD was observed with adjusted or unadjusted for potential confounders classified according to original data (Fig. S3).

The effect of NO_2 on COPD stratified by prevalence, mortality, and hospital admission

Three articles reported the contributions to prevalence. The pooled prevalence risk was elevated by 17% when exposed to high-level NO_2. Ten articles studied the association between NO_2 and mortality. A 2.6% higher risk was identified for COPD death. The remaining 14 articles observed the acute effect of exposure, and the total effect assessment of hospital admissions was 1.013 with 95%CI of 1.005–1.021 (Fig. 3).

The effect of NO_2 on COPD stratified by exposure term

According to duration of exposure, 15 papers reported the effects of long-term NO_2 exposure on COPD. It was that long-term exposure led to a 2.5% increase for estimate risk. Short-term exposure effects of NO_2 on COPD have been invested by 13 articles, and these short-term exposures caused the risk elevated by 1.4% (Fig. 4). The total adverse effect of NO_2 on COPD was much higher in long-term exposure than in short-term exposure.

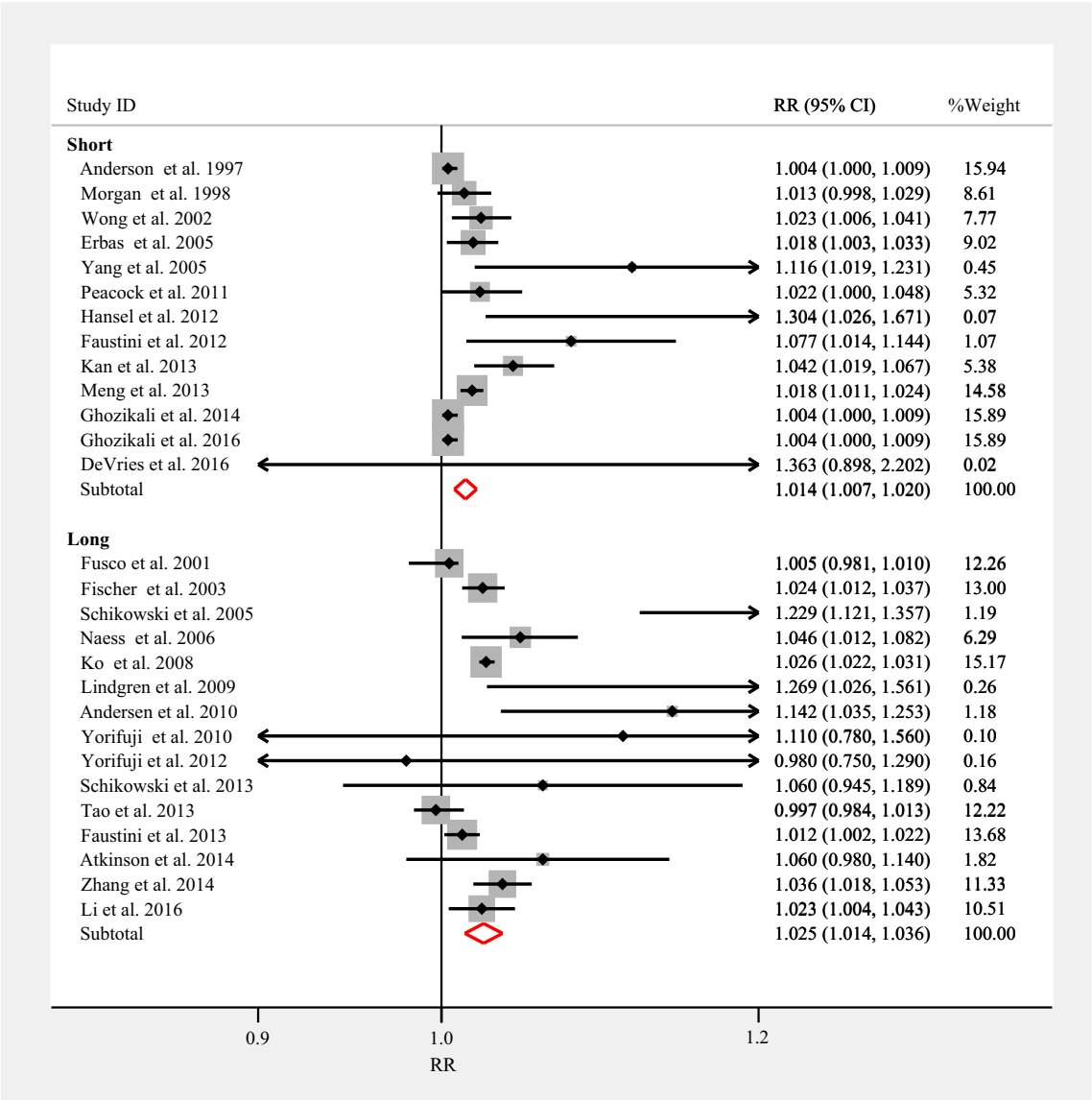

Fig. 4 Forest plot of study-specific estimates of relative risk of COPD relevant to a 10 $\mu g/m^3$ increase in NO_2 exposure stratified by exposure term, and random effects meta-analyses employed

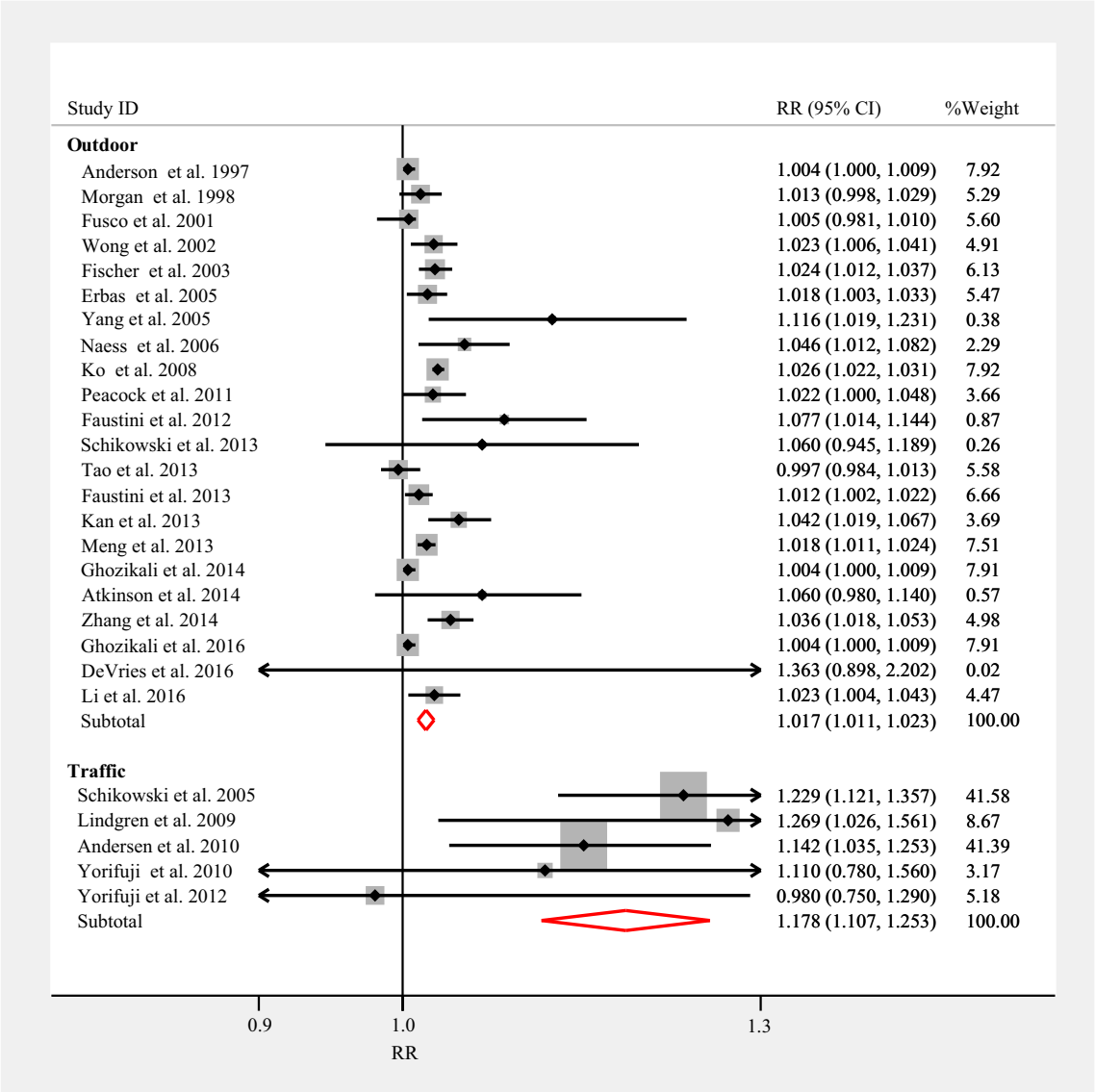

Fig. 5 Forest plot of study-specific estimates of relative risk of COPD relevant to a 10 μg/m^3 increase in exposure to NO_2 stratified by sources of exposure, and random effects meta-analyses employed

The effect of NO_2 on COPD stratified by sources of NO_2

The sources of NO_2 mainly divided into two parts in this meta-analysis: general outdoor-sourced NO_2 and traffic-sourced NO_2. From the results, 21 studies investigated the contribution of general outdoor-sourced NO_2 to COPD risk and a 1.017-fold high risk on COPD was observed. Five studies conducted the contribution of traffic-sourced NO_2 to COPD risk, and the risk increased by 17.8% (Fig. 5).

The effect of NO_2 on COPD endings stratified by sources of NO_2 combined with exposure term and exposure endings

Exposure term included long-term and short-term exposure. COPD ending defined as mortality, hospitalization, or prevalence. According to this meta-analysis, the sources of NO_2 mainly divided into two parts: general outdoor-sourced NO_2 and traffic-sourced NO_2. Long-term traffic exerted more severe impairments on COPD prevalence than long-term and short-term

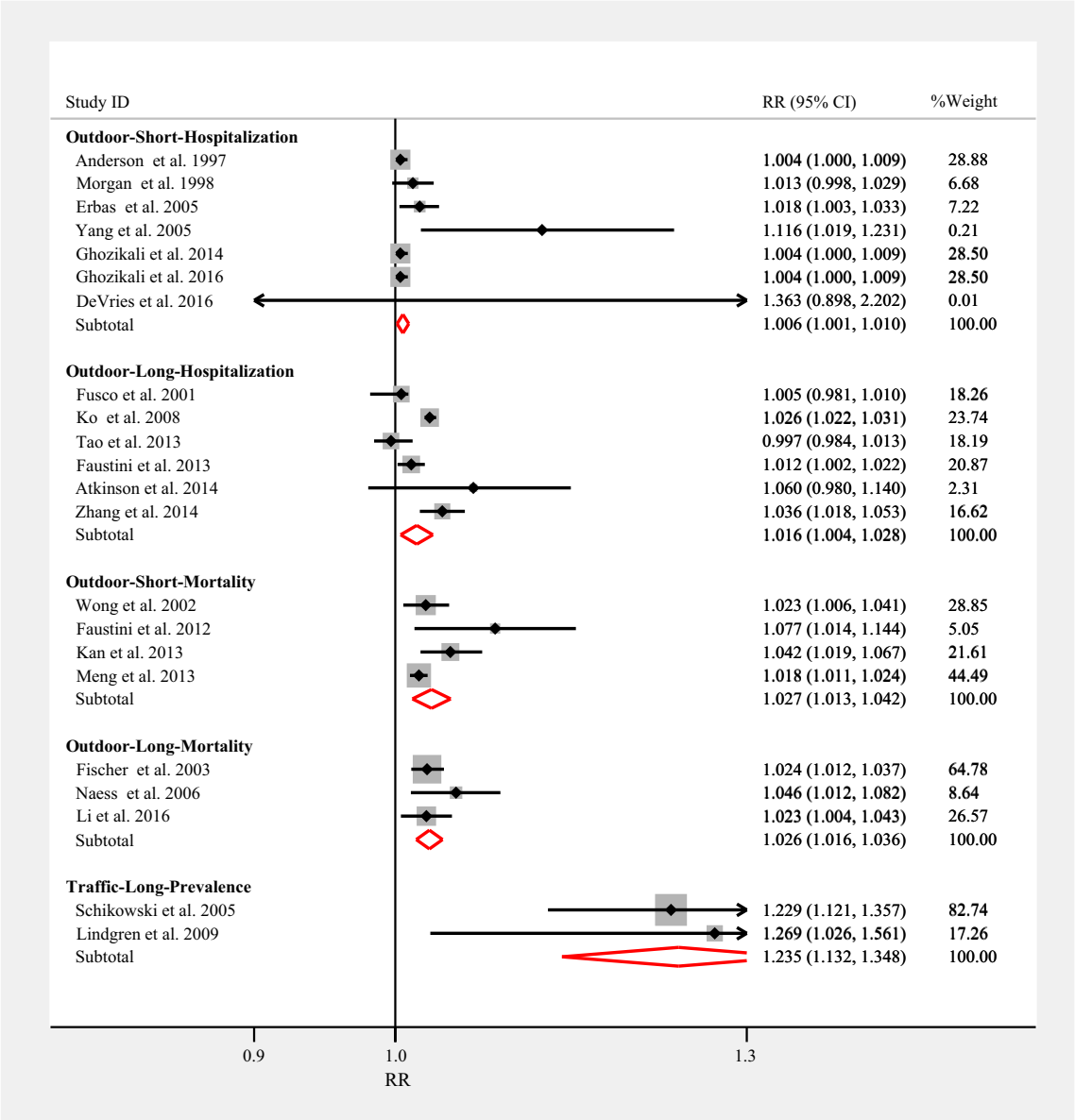

Fig. 6 Forest plot of study-specific estimates of relative risk of COPD relevant to a 10 μg/m^3 increase in exposure to NO_2 stratified by sources of exposure-exposure term-exposure ending, and random effects meta-analyses used

outdoor effects (the adverse effects were 1.235, 1.016, 1.026, 1.027, and 1.006, respectively) in Fig. 6.

The effect of NO_2 on COPD stratified by pollution model or combined with exposure term-ending

When the effect of NO_2 on COPD stratified by pollution model (multiple and single model), the effect was higher in single model than in multiple model (Fig. 7). After further stratification analysis, it has been showed that the effects of long term-mortality in single model were much higher than the others effect (Fig. 8 and Table S2).

The effect of NO_2 on COPD stratified by study region

The relative effect of NO_2 on COPD was a little higher in European (2.7%) than Asian (1.7%) stratified by study region. There are 12 qualified papers belonged to European and 11 in Asian (Fig. S4). Two original studies were performed in the USA observed a 1.17-fold high risk (DeVries et al. 2016) and a 2.71-fold high risk (Hansel et al. 2012) on COPD from NO_2 exposure, respectively; only one study conducted in Australia with a 1.06-fold high risk on COPD and one performed in Canada with a 1.12-fold high risk.

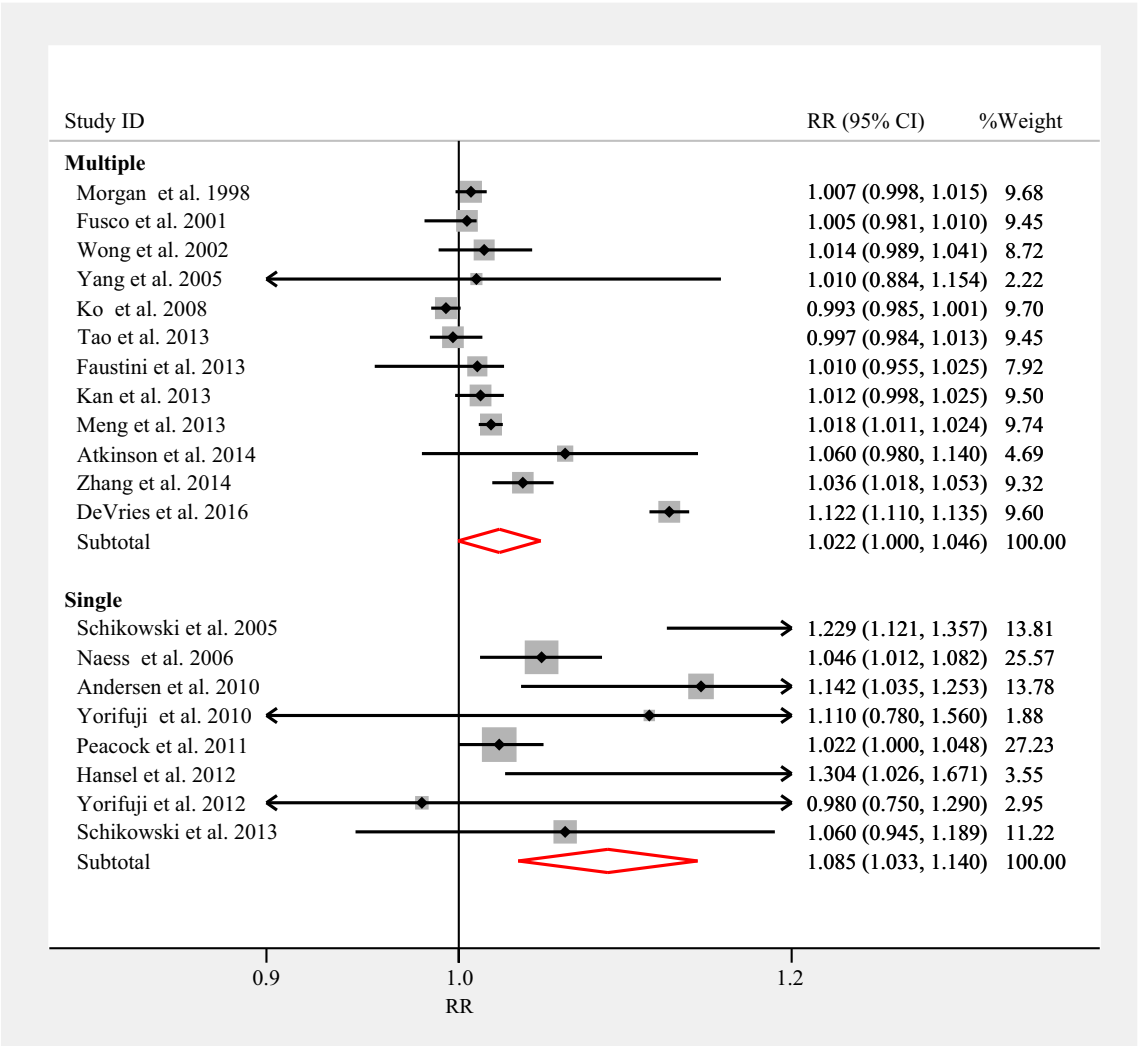

Fig. 7 Forest plot of study-specific estimates of relative risk of COPD relevant to a 10 μg/m^3 increase in exposure to NO_2 stratified by pollution model, and random effects meta-analyses employed

The effects of NO2 on COPD stratified by lag periods or combined with exposure term-ending

The effect of NO_2 on COPD was examined at different lags in time (from lag0 to lag3). Sixteen studies investigated the effect of NO_2 on COPD at lag0, and it showed that a 10 μg/m^3 increase in exposure to NO_2 was associated with COPD risk increased by 2.0% (Fig. S5). An almost similar effect was also observed at other lag periods. When stratified by lag periods-exposure ending (mortality and hospital admission), the effect was 1.035 (1.008, 1.068) on COPD mortality in lag0 (Fig. S6). After further stratification analysis, it has been showed that lag0-long-term NO_2 exposure on COPD prevalence 1.170 (1.046, 1.308) was more serious than the others effects (Fig. S7).

The effect of NO_2 on COPD stratified by exposure term-exposure ending

Exposure term was short- or long-term exposure and exposure ending defined as mortality or hospitalization. Long-term prevalence effect on COPD was more serious than long-term and short-term COPD hospitalization and mortality. The risk increased by 17% for long-term prevalence, 3% for short-term mortality, 1.8% for

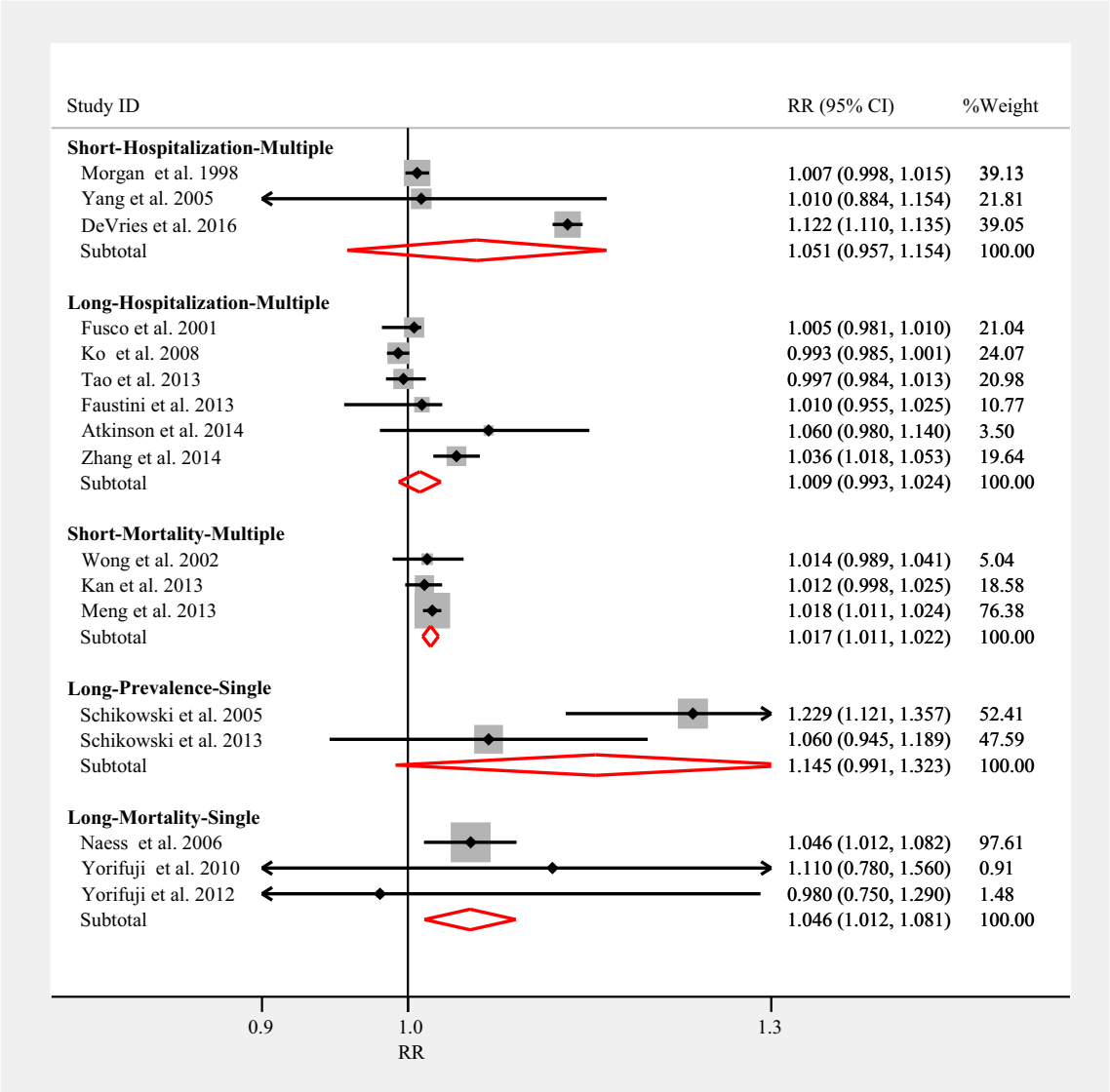

Fig. 8 Forest plot of study-specific estimates of relative risk of COPD relevant to a 10 μg/m^3 increase in exposure to NO_2 stratified by pollution model-exposure term-exposure ending, and random effects meta-analyses employed

long-term hospitalization, 2.6% for long-term mortality, and 0.6% for short-term hospitalization (Fig. S8).

Discussion

The current review and meta-analysis study provided evidences of the positive relationship between NO_2 and COPD. Moreover, stratified analyses also revealed consistent results performed by study region, sources of NO_2 (indoor, outdoor, or traffic-dominated), exposure term (long-term or short-term), exposure ending (mortality, hospital admissions, or prevalence), lag periods, lag periods-exposure ending, sources of exposure-exposure term, and exposure term-exposure ending. As far as we know, this is the first review and meta-analysis that directly linked NO_2 to COPD in adults.

To date, the air pollution problem in China has drawn extensive concern, particularly for which potential adverse effects on human health, weather, and climate. As a byproduct of economic prosperity and high socioeconomic status, NO_2 is one of the pivotal gaseous air pollutants, which continues to raise more and more attention, and except PM_{10}, it is the other one of the pollutants regulated by the European Union (Brunekreef and Holgate 2002). Therefore, we performed the current research focused on NO_x and NO_2; NO_2 is a component of NO_x, but two of them were used as markers of traffic-based exposure in epidemiological study. Evidences even identified that NO_2 characterizes the spatial variation of traffic-sourced air pollutants better than PM_{10} or $PM_{2.5}$, and also showed that health effects caused by NO_2 have extended from impaired lung function to premature respiratory death (Nafstad et al. 2004; Neuberger et al. 2002). Importantly,

evidences identified the patterns of pooled RR of mortality and hospital admission for various rubrics with the order $NO_2 > SO_2 > PM_{10} > O_3$ per unit increase in level of every pollutant (Wong et al. 2008). Our earlier studies also observed the detrimental effects of NO_2 on respiratory diseases (Zhang et al. 2014, 2015). These findings supported the efforts to reduce air pollutants and improved public health by anthropogenic intervention. Therefore, we compared this meta-analysis together with our previous study to see if there could conclude a consistent conclusion.

The relative effect of NO_2 on COPD was certainly higher in European than Asian, which might be the outcome of different exposure traits: The researches in Australia and Asian performed the effect of lower level NO_2 exposure than the researches in European and USA. The mortality effect of NO_2 on COPD cases was more serious than hospital admission for the much longer exposure term. The short-term effect of NO_2 on COPD was higher than long-term effect, suggesting that NO_2 might affect the exacerbation of COPD status, and this was also identified by the increased prevalence for COPD after NO_2 accumulated. Traffic-sourced effect was much more serious than general outdoor source that suggested that traffic indeed contributed to the increased NO_2. Additionally, in the present study, we did not find that the effect of NO_2 on COPD was robust to specific lag day; those results might show the fact that NO_2 was associated at extensive lags (from lag0 to lag3), but with a large majority in lag0, especially on COPD mortality in lag0. Notably, we identified that long-term traffic exerted more severe impairments on COPD than long-term and short-term outdoor effect; short-term mortality effect on COPD was more serious than long-term COPD effect (hospitalization and mortality) and short-term hospitalization. After further stratification analysis, long-term traffic exerted more severe impairments on COPD prevalence than long-term and short-term outdoor effect single model. The currently increasing COPD prevalence may be due to the increased long-term exposure from traffic pollution. It has been showed that the effects of long term-mortality in single model were much higher than the others effect.

It should be pointed out that adult was the main population we did focus on in order to avoid statistical bias resulting from gender differences in NO_2 effects in this study.

Oxidative stress and system inflammation have been considered as result of air pollution exposure. It was reported that both pulmonary and systemic effects have been identified and those pathways were potential contributors to the mechanisms linked to COPD pathogenesis. Evidences indicated continuous systemic inflammation in COPD. Even among non-current smokers, there were evidences for low-level systemic inflammation reaction in those with chronic airflow limitation. They also suggested that, once COPD develops, cessation of smoking might not fully attenuate the inflammatory process related with this condition. Therefore, they concluded that COPD was responsible for the systemic inflammation. NO_2 was a ubiquitous atmospheric gaseous pollutant that made a huge contribution to respiratory inflammation, infections, and symptoms (Rajarathnam et al. 2011). NO_2 inhalation exerted deleterious effects on pulmonary tissue. Unlike most water-soluble, irritant gases which have their strongest effects at earliest point of contact with the mucous membranes, NO_2 hydrolyzes more slowly and is quite capable of getting to the bronchioles and alveoli. At these locations, NO_2 undergoes almost complete hydrolysis to nitrous and nitric acids, resulting in a profound chemical pneumonitis and pulmonary edema. Earlier studies also described that immune modulatory effects of NO_2 could be responsible for these dampening effects (Brunekreef and Holgate 2002; Garn et al. 2003; Kienast et al. 1996). The exposure of NO_2 could cause impaired function of macrophages and epithelial cells leading to elevated susceptibility to infections and development of alternatively activated macrophages. For instance, one study observed that NO_2 exposure reduced LPS-induced pro-inflammatory cytokine production by alveolar macrophages in vitro, while baseline cytokine levels caused by non-stimulated macrophages were not affected by NO_2 (Kienast et al. 1996). Perhaps, macrophage and epithelial cell function was impaired after sub-chronic NO_2 exposure leading to reduced pro-inflammatory cytokine production. By decreasing the immune response to infections, NO_2 exposure might also result in increased susceptibility to exacerbations in COPD, since the majority of exacerbations were linked with viral or bacterial infections (Papi et al. 2006). This was in consistent with data indicating relationship between hospital admissions for COPD exacerbations and NO_2 (Anderson et al. 1997).

Despite of the strengths and biologic rationality of the linking showed in the present work, inherited biases in our study might have led to spurious outcomes. Firstly, information regarding this possibility was generally missing in the individual study, which might be adverse factors for COPD, and lacking of these original data confined our further estimate of underlying interactions, secondly, not every country was included (e.g., America could be not represented greatly in the present study), and thirdly, the high correlation between NO_2 and others pollutants implied the conceivability that the NO_2 effects might be due partly to confounding from other pollutants. Lastly, caution still remained in the final conclusion for NO_2 on COPD, since their association with COPD was not strong to lag specific days. The findings might also show the fact that NO_2 was related at extensive lags. It is better to integrate exposure, toxicology, and human studies to the response to the causality issue, rather than unique from the epidemiological researches.

In summary, our meta-analysis suggested an effect of NO_2 as an aggravating cause of COPD in adults. We did observe that the pooled effect on COPD prevalence was higher than hospital admissions and mortality. The effects of NO_2 on COPD mortality with a large majority were in lag0,

long-term traffic exerted more severe impairments on COPD prevalence than long-term or short-term outdoor effect, and long-term mortality effect on COPD was serious in single model from this meta-analysis. Overall, our study reported consistent evidence of the potential positive association between NO_2 and COPD risk. We believe that our study provides a pooled effect assessment for the need for air quality improvement and could also contribute to the scientific debate on this field.

Funding sources This work was supported by grants from National Natural Science Foundation of China (81520108001, 81700043), the 973 Key Scheme of China (2015CB553406), Guangzhou Department of Education for Innovative Team (13C08) and Guangdong Natural Science Foundation (2016A030313593), state Key Laboratory of Respiratory Diseases (SKLRD), and Guangzhou Institute of Respiratory Health (SKLRD- QN-201719). The funding sponsors had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, and in the decision to publish the results.

Compliance with ethical standards

Conflict of interest The authors declared that no competing interests have existed

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