Abstract

The long-term effects of ambient air pollution on lung cancer (LC) and chronic obstructive pulmonary disease (COPD) mortalities in the more polluted regions in the world require a comprehensive analysis. In this study, a systematic literature search and meta-analysis ~~pooled analysis~~ using the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline were conducted to examine the association between long-term exposure to ambient air pollution for the LC and COPD mortalities in China. Two databases (PubMed and Scopus) were systematically searched and a total of eight research papers were finally included in this study with the risk of bias assessed by Newcastle-Ottawa Scale (NOS). A total of 409,945 participants were included in the analysis based on four individual Chinese cohorts during the follow-up periods between 1991-2011. The pooled risk ratios for LC and COPD mortalities were 1.08 (95% CI: 1.02-1.16) and 1.12 (95% CI: 1.11-1.13), respectively, for each 10 $\mu g/m^3$ increase in the concentrations of $PM_{2.5}$. Furthermore, the results of the meta-analysis ~~pooled analysis~~ were examined using a case study in the Yangtze River Delta region in 2015. A comparison of the estimated LC and COPD mortality risks between the current study and the previous relative risk model demonstrated that the result of cohort studies could provide more accurate relative risk values and estimated mortalities for the population in China. Although only limited cohort studies have been conducted in China, they provide significant evidence of the long-term effects of ambient air pollution on LC and COPD mortalities in the population of the more polluted regions. It is also recommended to develop a more suitable relative risk model using the results of meta-analysis ~~pooled analysis~~ for the estimation of air pollution-related mortality in the more polluted regions.

Keywords

Air pollution; Lung cancer; Chronic obstructive pulmonary disease; PRISMA; Newcastle-Ottawa Scale

1. Introduction

The effects of ambient air pollution have created an alarming situation worldwide due to the rapid urbanisation and industrialisation taking place in many countries over the past few decades (Xu *et al.*, 2015; Cui *et al.*, 2019). An estimated 4.2 million premature deaths worldwide in each year is attributable to the effects of ambient air pollution (WHO, 2016). Some regions in Asia such as Bangladesh, China, and India have been known as the more polluted regions in the world. In China, it was estimated that 1.1 million premature deaths were related to the effects of ambient air pollution in 2015 (Cohen *et al.*, 2017). Although a major risk factor of lung cancer (LC) ~~LC~~ and chronic obstructive pulmonary disease (COPD) ~~COPD~~ is known to be tobacco smoke, air pollution exposure has been shown to be significantly associated with an increased risk of LC and COPD. For example, the production of reactive oxygen species (ROS) and oxidative stress caused by toxic pollutants may induce airway inflammation and DNA mutation in lung tissues (Moller *et al.*, 2008; Macnee, 2012; Rinne and Kaufman, 2012; Nana-Sinkam and Powell, 2013; Famiyeh *et al.*, 2021). Previous studies have evidently showed that long-term exposure to ambient air pollution is associated with a higher risk of mortality due to diseases such as LC ~~lung cancer (LC)~~ and COPD ~~chronic pulmonary obstructive disease (COPD)~~ (Lepeule *et al.*, 2012, Guo *et al.*, 2018).

The evidence of health burden due to air pollution exposure in China based on the result of previous cohort studies is however limited, which may affect the actual estimation process of the health burden in China. As the number of Chinese cohort studies has been increasing over the past decade, it is necessary to conduct the review study by using these recent cohort studies in China. Furthermore, this study also aims at identifying the gaps in knowledge of the disease burden attributable to long-term exposure to air pollution in China. As most of the previous review studies have only considered the cohorts from regions such as North America and Europe (Hamra *et al.*, 2014; Chen and Hoek, 2020), it is essential for the association of ambient air pollution and mortalities such as LC and COPD in the more polluted regions to be carefully explored and studied by taking China as a case study. In particular, there are no systematic reviews on the association between air pollution and mortalities such as LC and COPD in China in the previous studies. The significances of this current study are including, but not limited to (1) providing evidence of air pollution-related mortality for the risk assessment in other more polluted regions in the world; (2) drawing attention of researchers about the importance of conducting more similar cohort studies in different regions of China ~~or India~~; and (3) informing

local governments and policy makers about the associations between air pollution and disease burden such as LC and COPD.

In this study, a systematic literature search and meta-analysis ~~pooled analysis~~ were performed to provide evidence of air pollution-related LC and COPD mortalities in the more polluted regions by focusing on Chinese cohort studies. The objectives of the study are (1) to perform an extensive systematic literature search and meta-analysis ~~pooled analysis~~ on the association between long-term exposure to air pollutants ($PM_{2.5}$, PM_{10}, SO_2 and NO_2) and mortalities related to LC and COPD in China; (2) to evaluate the summary risk estimates of mortality attributable to air pollutants using the relevant Chinese cohort studies; and (3) to evaluate the results of meta-analysis ~~pooled analysis~~ by performing a case study in the Yangtze River Delta region of China.

2. Materials and methods

2.1 Systematic literature search

The systematic literature search process was conducted according to the guidelines of PRISMA 2020 statement (Page *et al.*, 2020)~~, which is reported in Table S1~~. For the purposes of analysis, relevant studies of LC and COPD mortality attributable to ambient air pollution in China were identified and retrieved in several stages, as summarised in Figure 1. Only the English-language databases PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com/) were searched during the literature review to study the LC and COPD mortalities attributable to ambient air pollution with the results restricted to cohort studies in China. The final search was performed on 8 September 2021, with the following combinations of keywords used to determine the relevant studies: (1) air pollution, particulate matter, fine particles, $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2 or O_3; (2) mortality, COPD, lung cancer, disease or cancer mortality; (3) Mainland China, Chinese, Hong Kong, Macau or Taiwan; and (4) cohort. In order to not overlook potentially relevant papers from other databases, the reference lists of all the eligible studies were manually searched to identify any additional appropriate studies.

After identifying and collecting the studies from the two databases, duplicate records which have the same information (title of paper, authors, and publication year) were detected and removed. Title and abstract screening was performed to only include the relevant studies. Furthermore, the eligibility of relevant studies was assessed by employing full-text screening. The studies excluded from the full-text screening stage were provided with justifications. For

example, the authors excluded the studies that were performed in other study designs such as ecological studies and review studies. Studies which focused on the air-pollution related mortalities other than LC and COPD were also excluded in this current study. The detail eligibility criteria used to select the studies are summarised in Table 1.

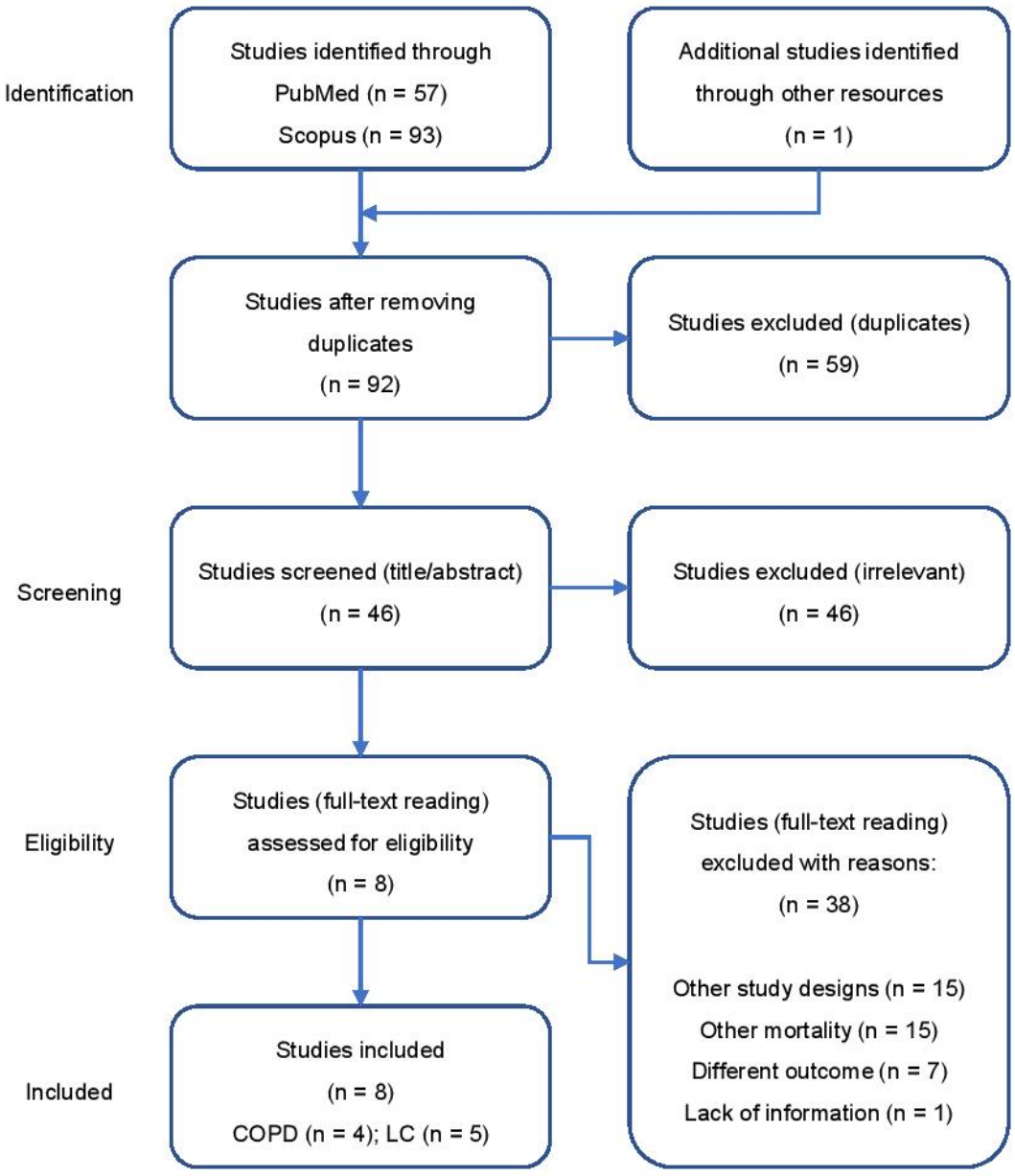

Figure 1. Flowchart of the systematic literature search process (PRISMA 2020).

Table 1. The eligibility criteria for the systematic literature search process.

No.	Studies that meet the eligibility criteria
1	Investigated the relationship between ambient air pollutant ($PM_{2.5}$, PM_{10}, CO, NO_2, SO_2 or O_3) and mortality (LC or COPD)
2	Performed cohort study in China, including China mainland, Hong Kong, Macau, and Taiwan
3	Reported the risk ratios or relative risks (RR) and their 95% confidence interval (CI) or standard error (SE)

For the research papers included, the following information were extracted and moved to a Microsoft Excel database: title of the paper, first author, publication year, study region, follow-up years, cohort size, baseline age, pollutant-mortality involved, risk estimates. All eligible cohort studies employed proportional hazards model for the analysis and reported the risk estimate as the risk ratio of mortality per 10 $\mu g/m^3$ increase in pollutant level, except for Cao *et al.* (2011) which only reported the percent increase of mortality, and Yang *et al.* (2018) which reported risk estimate per interquartile range (IQR) increase in pollutant. Therefore, a unit conversion was needed to standardise the data before performing the meta-analysis ~~pooled analysis~~. Standard error (SE) was estimated based on the reported values of risk ratio and 95% confidence intervals from the eligible studies were employed. Furthermore, a round-off error might be present when all the risk ratios were standardised and rounded to two decimal places. In this analysis, only the result of a single-pollutant model was considered in the meta-analysis ~~pooled analysis~~. All the models from the selected cohort studies were adjusted for the effects of age, sex, body mass index (BMI) and smoking status. In addition, most of the studies were further adjusted by other potentially confounding factors. The risk estimates from the most adjusted model or the most mentioned model by the original authors was extracted and summarised in this current study.

All the eligible studies were examined by a methodology quality assessment known as the Newcastle-Ottawa Scale (NOS) (Wells *et al.*, 2012). This assessment method employs a nine-point scoring system, where each point is allocated for the corresponding criterion that a study has fulfilled. NOS includes the following criteria: (1) representatives of the exposed cohort; (2) selection of the non-exposed cohort; (3) exposure assessment; (4) outcome of interest is not present at the start of the study; (5) control for the important factor and/or other factors (maximum 2 points); (6) outcome assessment; (7) a follow-up long enough for outcomes to take place; (8) adequacy of follow-up of cohorts. In this analysis, the smoking factor was taken

as the important factor in the model, in which one point was allocated for the studies that adjusted for the smoking factor. A study with a score of 6 or more was considered as a high-quality study.

2.2 Meta-analysis ~~Pooled analysis~~

The heterogeneity within the studies was examined through the interpretation of Cochran's Q and I^2 statistics. The existence of heterogeneity within the individual studies was considered when the p-value of Cochran's Q was less than 0.10 ($P < 0.10$) and I^2 exceeded 50%. Larger Q values also suggest that a greater degree of heterogeneity within the studies exist (Schwarzer *et al.,* 2015). In addition, Egger's test (Egger *et al.,* 1997) and Begg's rank correlation test (Begg and Mazumdar, 1994) were applied to examine the publication bias within the studies. Funnel plots were employed to provide a visual summary of the analysis of publication bias.

The risk estimates from the research studies included in this study were extracted and combined using the inverse variance method, which employs a weighting factor of the inverse of the study variance. A fixed-effect or random-effects model with the restricted maximum likelihood (REML) estimator was applied to calculate the pooled risk ratios and their 95% confidence interval for each pair of mortality-pollutant association. If the I^2 exceeded 50% or the p-value of heterogeneity was less than 0.10, a random-effects model was used in the pool analysis, otherwise a fixed-effect model was used. Forest plots were used to illustrate the result of the combined risk estimates.

Due to a limited number of relevant cohort studies with respect to each pair of pollutant-mortality association, the meta-analysis ~~pooled analysis~~ was only performed for those pairs of association with more than 2 different cohort studies. Furthermore, the influence of individual cohort study on the pooled result was explored through a sensitivity analysis. For each sensitivity analysis, the reported risk ratio from each individual cohort study was excluded from the calculation of pooled risk ratio and the generation of forest plot. All the analyses were conducted using the meta package of the R statistical software (version 3.6.1). Results was considered as statistically significant when the measured p-value was less than 0.05 ($P < 0.05$) except for those specified.

2.3 Implication: A case study in Yangtze River Delta

A case study in Yangtze River Delta (YRD) region was performed to demonstrate potential implications of using the results of the meta-analysis ~~pooled analysis~~. Two cities of YRD region, namely Hangzhou and Ningbo, were selected and compared for the validation of result of the

meta-analysis ~~pooled analysis~~. The characteristics of the variation of pollutants and LC mortality in Ningbo during 2015 have been described in a previous study (Chung *et al.,* 2021). The summary risk estimates of meta-analysis ~~pooled analysis~~ were compared with the risk estimates of Integrated Exposure-Response (IER) model for LC and COPD mortalities attributable to ambient $PM_{2.5}$ in Hangzhou and Ningbo. As shown in Eq.1, the IER model developed by Burnett *et al.* (2014) was used to estimate the risk ratios (R_{IER})in Hangzhou and Ningbo for the current study, with the values of x_0, α, γ, and δ estimated by Jiang *et al.* (2015). The average $PM_{2.5}$ concentrations in Hangzhou and Ningbo in 2015 were used to estimate the value of x for Eq.1.

$$R_{IER}=1, \text{ for } x < x_0$$
$$R_{IER}=1+\alpha\left(1-exp\left[-\gamma(x-x_0)^{\delta}\right]\right) \text{ , for } x \geqslant x_0 \quad \text{(Eq.1)}$$

where x is the exposure to $PM_{2.5}$ ($\mu g\ m^{-3}$), x_0 is the counter-factual concentration below which we assumed there is no additional risk, and α, γ, δ represent the parameters used to describe the shape of the concentration-response curve.

Furthermore, LC and COPD mortalities attributable to $PM_{2.5}$ were evaluated and compared by using the result of risk estimate from this study and IER model. Eq.2 shows the estimation of attributable fraction (AF), which was used in many previous literatures (Jiang *et al.*, 2015; Liu *et al.*, 2016). Furthermore, the ratios of mortality attributable due to ambient particulate matter pollution and total mortality due to all risk factors in China were extracted and measured from the Global Burden of Disease (GBD) study 2015. The measured ratios from the GBD study were used as the benchmark ratios of COPD and LC mortality for the comparison of the results between the IER model and the current study.

$$AF=\frac{R_{IER}-1}{R_{IER}} \quad \text{(Eq. 2)}$$

where AF is the attributable fraction exposed to air pollution, and R_{IER} is the risk ratio estimated by Eq. 1.

3. Results

A total of 151 studies were identified in the first stage of systematic literature search, including 150 studies obtained from the databases (PubMed and Scopus) and 1 additional study identified through the reference lists of the other studies. 59 studies were excluded due to duplication. Title and abstract screening further excluded 46 irrelevant studies. During the full-

text reading process, a justification was given to all the excluded studies: 15 studies were not cohort studies, 15 studies were other mortality types, 7 studies measured different outcome, and 1 study had a lack of important data. A total of 8 eligible studies were identified after a comprehensive read of the papers. 5 studies were related to LC mortality and 4 studies were related to COPD mortality. All the eligible cohort studies were based on the exposure of air pollutant ($PM_{2.5}$, PM_{10}, SO_2, and NO_2) in the Chinese population. All the studies involved in the systematic literature search process were reported in Tables S4 and S5 ~~Table S3-4~~.

The eligible studies were published from 2011 to 2018 and involved a total of 409,945 participants from 4 individual cohorts from China during the follow-up periods between 1991-2011. The 4 Chinese cohorts include China National Hypertension Follow-up (Cao *et al.*, 2011), a cohort of 224,064 Chinese men randomly chosen from 45 districts/counties across China (Zhou *et al.*, 2014;Yin *et al.*, 2017), a cohort of 66,820 residents in Hong Kong (Wong *et al.*, 2015; Wong *et al.*, 2016; Yang *et al.*, 2018), and a cohort in four Chinese Northern cities including Tianjin, Shenyang, Taiyuan, and Rizhao (Chen *et al.*, 2016; Chen *et al.*, 2017). Table 2 summarises the characteristics of cohort studies of LC and COPD mortality in China.

Table 2. Characteristics of cohort studies in China – LC and COPD mortality.

Cohort designation	**Studies**	**Sample sizes**	**Follow-up period**	**Region**	**Mortality (Code)** ~~**Outcome of interest**~~
China National Hypertension Follow-up	Cao *et al.* (2011)	70,947	1991-2000	31 cities in 16 provinces	ICD-9: LC
A cohort of 224064 Chinese men	Yin *et al.* (2017), Zhou *et al.* (2014)	224,064	1990-2006	45 district /counties	ICD-9: LC (162), COPD (490-496)
A cohort in 4 Northern Chinese cities	Chen *et al.* (2016), Chen *et al.* (2017)	48,114	1998-2009	Tianjin, Shenyang, Taiyuan, and Rizhao	ICD-10: LC (C33-34), COPD (J40-J44)
A cohort in Hong Kong	Wong *et al.* (2015), Wong *et al.* (2016), Yang *et al.* (2018)	66,820	1998-2011	Hong Kong	ICD-10: LC (C33-34), COPD (J40-44, 47)

3.1 Heterogeneity and risk of bias assessment

Table S1 ~~3~~ summarises the result of heterogeneity and publication bias in the meta-analysis ~~pooled analysis~~. For LC mortality, it was observed that high degree of heterogeneity ($I^2 > 75\%$) within studies exists in the meta-analysis ~~pooled analysis~~ since the null hypothesis that the studies are homogeneous was rejected ($P < 0.05$). However, for COPD mortality, both indicators of I^2 value and P-value for heterogeneity suggested that there was no observed heterogeneity within the studies. This effect could plausibly be contributed by two studies (Wong *et al.*, 2015; Yang *et al.*, 2018), which performed the analysis based on a similar cohort study of investigating the association between COPD and $PM_{2.5}$ exposure in Hong Kong.

Based on Egger's linear regression test and Begg's rank correlation test as shown in Table S1 ~~3~~, there was no significant evidence of publication bias in the meta-analysis ~~pooled analysis~~ of both LC and COPD mortality associated with $PM_{2.5}$ pollutant. As shown in Figure 2, the funnel plot of LC mortality did not indicate any significant asymmetrical pattern that was related to small-study effect. However, a small-study effect can be observed in the meta-analysis ~~pooled analysis~~ of COPD by interpreting the funnel plot. This unfavourable effect could plausibly be caused by the risk estimate reported by Wong *et al.* (2015), which had a wider 95% confidence interval (0.98-1.74) in the individual study. Based on the results of heterogeneity, random-effects model was used to pool the risk ratio for the association between LC and $PM_{2.5}$, whereas fixed-effect model was employed for the association of COPD-$PM_{2.5}$.

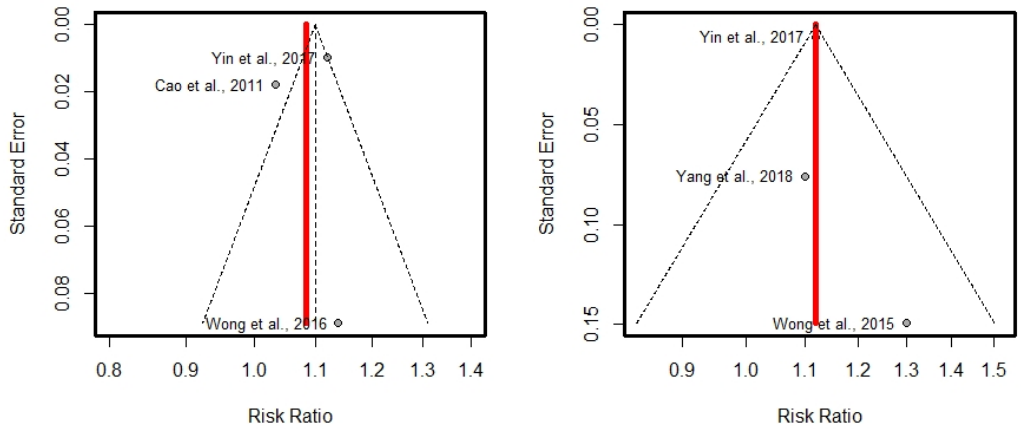

Figure 2. Funnel plots for each pair of mortality-pollutant in studies: LC-$PM_{2.5}$ (*left*), and COPD-$PM_{2.5}$ (*right*) (Red line indicates the estimate).

Tables S2 and S3 ~~Table 4 and 5~~ show the methodological quality assessment using the NOS for LC and COPD mortalities, respectively. Outcome assessment was clearly explained and

performed in all the studies. Most of the criteria were satisfied by the cohort studies. For example, all the studies adjusted for age, BMI, and smoking as covariates in the model. The following justifications were provided for the criteria in which the study did not meet the requirement. Cao *et al.* (2011) received the lowest score as the study estimated $PM_{2.5}$ exposure from the total suspended particle (TSP) measurement, which employed conversions of $PM_{2.5}/PM_{10} \approx 0.65$ and $PM_{10}/TSP \approx 0.5$. Furthermore, the follow-up process of the study by Cao *et al.* (2011) was conducted during the period of 1991 to 2000, which was less than 10 years and received less than 75% responses from the total samples due to a limited number of ambient monitoring stations in the rural regions at that time. The studies of Yin *et al.* (2017) and Zhou *et al.* (2014) only included the male population, which might contribute towards the bias of sex factor in the population. In addition, the cohort in Hong Kong (Wong *et al.*, 2015; Wong *et al.*, 2016, Yang *et al.*, 2018) only followed up with participants who were above 65 years old, which might contribute towards the bias of age factor in the population.

3.2 Lung cancer (LC) mortality

The result of the systematic literature research ~~and pooled analysis~~ of LC mortality in China is summarised in Table 3 ~~6~~. LC mortality was shown to be positively associated with each 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10} and SO_2 concentration. The pooled risk ratio of LC mortality due to each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.08 (95% CI: 1.02-1.16) in the random-effects model. Meta-analyses ~~Pooled analyses~~ were not performed on the PM_{10}, SO_2, and NO_2 pollutants due to a limited number of relevant cohort studies in China. For the effects of PM_{10} and SO_2 pollutants on LC mortality, the results of risk ratios from individual cohort studies were similar to each other, ranging from 1.01 to 1.05. However, Chen *et al.,* (2016) reported that there was no significant association between LC mortality and NO_2 exposure in the Northern Chinese cities. Forest plots of LC mortality associated with pollutant exposure are shown in Figure 3. The sensitivity analysis showed that the influence of Wong *et al.* (2016) was relatively smaller in the pooled result of LC mortality. The detail result of sensitivity analysis for the association of LC-$PM_{2.5}$ is presented in Table S6 ~~S5~~ and Figure S1.

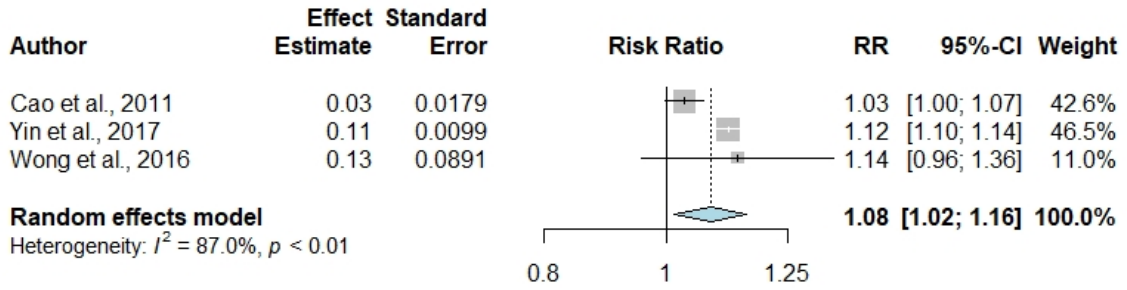

Figure 3. Forest plots for $PM_{2.5}$ pollutant combined with LC mortality.

Table 3 ~~6~~. Summary of estimated individual risk and pooled risk of LC mortality for each 10 μg/m^3 increase in pollutants from the cohort studies in China

Author, year	Exposure assessment	Exposure level - μg/m^3 (SD)	Risk ratios (95% CI)
$PM_{2.5}$			
Cao *et al.* (2011)	Air monitoring station	--	1.03 (1.00-1.07)
Yin *et al.* (2017)	Satellite-based, chemical transport model, air monitoring station	46.4 (20.2)	1.12 (1.07-1.14)
Wong *et al.* (2016)	Satellite-based, air monitoring station	33.7 (3.2)	1.14 (0.96-1.36)
PM_{10}			
Zhou *et al.* (2014)	Air monitoring station	104 (--)	1.01 (0.99-1.03)
Chen *et al.* (2016)	Air monitoring station	144.3 (3.6)	1.05 (1.03-1.06)
SO_2			
Cao *et al.*, 2011	Air monitoring station	73 (--)	1.04 (1.02-1.06)
Chen *et al.* (2016)	Air monitoring station	66.9 (3.4)	1.02 (1.01-1.03)
NO_2			
Chen *et al.* (2016)	Air monitoring station	40.7 (1.6)	0.97 (0.95-0.98)

3.3 Chronic obstructive pulmonary disease (COPD) mortality

The result~~s~~ of the systematic literature search ~~and pooled analysis~~ of COPD mortality in China is ~~are~~ summarised in Table 4 ~~7~~. Due to the limited number of relevant cohort studies in COPD mortality, the meta-analysis ~~pooled analysis~~ was only performed for the association

between COPD and $PM_{2.5}$ pollutant. For each 10 µg/m^3 increase of $PM_{2.5}$ concentration, the pooled risk ratio of COPD mortality was approximately the same as the risk estimate reported by Yin *et al.,* (2017) for fixed-effect model, which was 1.12 (95% CI: 1.11-1.13). Furthermore, Chen *et al.,* (2017) reported that risk ratios of COPD mortality per 10 µg/m^3 increase of PM_{10} and SO_2 were 1.58 (95% CI: 1.36-1.82) and 1.14 (95% CI: 1.04-1.25), respectively. Each 10 µg/m^3 increase in NO_2 was associated with risk ratio of COPD mortality of 1.01 (95% CI: 0.96-1.06) (Yang *et al.,* 2018). Forest plot of COPD mortality associated with $PM_{2.5}$ pollutant exposure is shown in Figure 4. The sensitivity analysis showed that 95% confidence interval of the pooled risk ratio became wider by extracting the study of Yin *et al.* (2017). Furthermore, the significant influence of the study from Yin *et al.* (2017) in the pooled risk estimate was also observed by comparing the results in sensitivity analysis, which is shown in Table S7 ~~S6~~ and Figure S2.

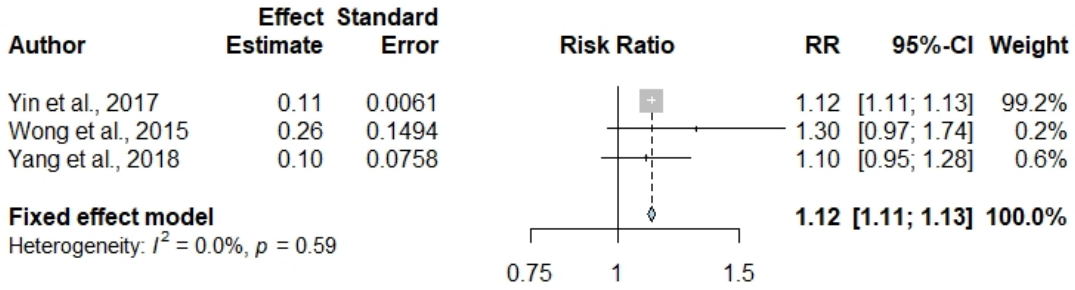

Figure 4. Forest plot for $PM_{2.5}$ pollutant combined with COPD mortality.

Table 4 ~~7~~. Summary of estimated individual risk and pooled risk of COPD mortality for each 10 µg/m^3 increase in pollutant from the cohort studies in China.

Author, year	Exposure assessment	Exposure level - µg/m^3 (SD)	Risk ratios (95% CI)
$PM_{2.5}$			
Yin *et al.* (2017)	Satellite-based, chemical transport model and air monitoring station	46.4 (20.2)	1.12 (1.10-1.13)
Wong *et al.* (2015)	Satellite-based, air monitoring station	35.3 (--)	1.30 (0.98-1.74)
Yang *et al.* (2018)	Land use regression (LUR) model, air monitoring station	42.2 (5.5)	1.10 (0.95-1.27)

PM_{10}			
Chen *et al.* (2017)	Air monitoring station	144.3 (36.3)	1.58 (1.36-1.82)
SO_2			
Chen *et al.* (2017)	Air monitoring station	66.9 (34.0)	1.14 (1.04-1.25)
NO_2			
Yang *et al.* (2018)	Land use regression (LUR) model, air monitoring station	104 (25.6)	1.01 (0.96-1.06)

3.4 Comparison of risk estimates using a case study in Yangtze River Delta

The mean concentrations (standard deviation) of $PM_{2.5}$ in Hangzhou and Ningbo in 2015 were reported to be 54.3 (30.3) μg/m^3 and 44.8 (25.3) μg/m^3, respectively. The 5th (Hangzhou: 19.2 μg/m^3; Ningbo: 17.1 μg/m^3) and 95th (Hangzhou: 113.6 μg/m^3; Ningbo: 97.3 μg/m^3) percentiles of $PM_{2.5}$ concentration were used as the exposure intervals for comparison of the risk estimates. Figures 5 and 6 show the comparison of the risk estimates for LC and COPD mortalities between current study and IER model using Hangzhou data and Ningbo data, respectively. Based on the exposure intervals of Hangzhou and Ningbo population in 2015, the risk estimates of the IER model were always lower than those of the current study for both LC and COPD mortalities. Furthermore, the difference between current study and IER model in COPD mortality was larger than that in LC mortality, which may explain that the IER model has the potential to underestimate the risk estimates in China, especially for COPD mortality. The shorter intervals of risk estimate between 5th and 95th percentiles of $PM_{2.5}$ concentration in the IER model also described that the increases of risk estimate for both LC and COPD mortality were less sensitive to the increase of $PM_{2.5}$ concentration when comparing with the current study.

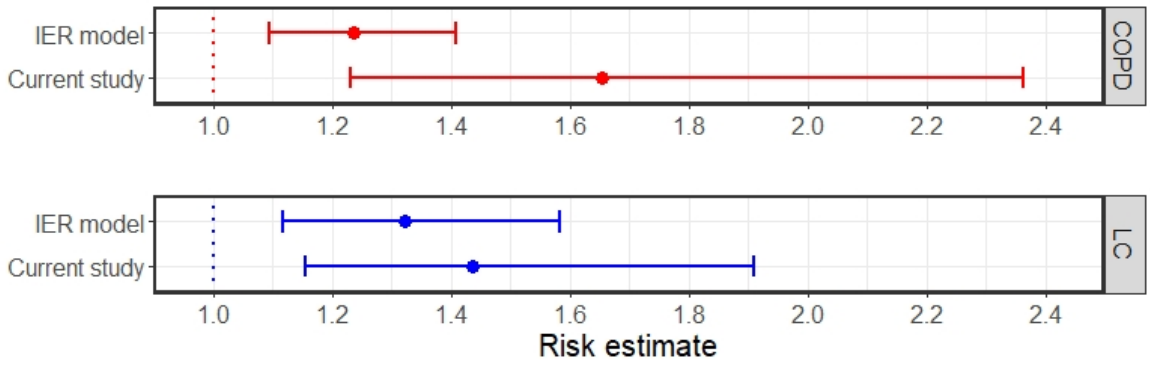

Figure 5. Comparison of risk estimates and CIs for COPD and LC mortalities using the 5th and 95th percentiles of $PM_{2.5}$ concentrations in Hangzhou in 2015.

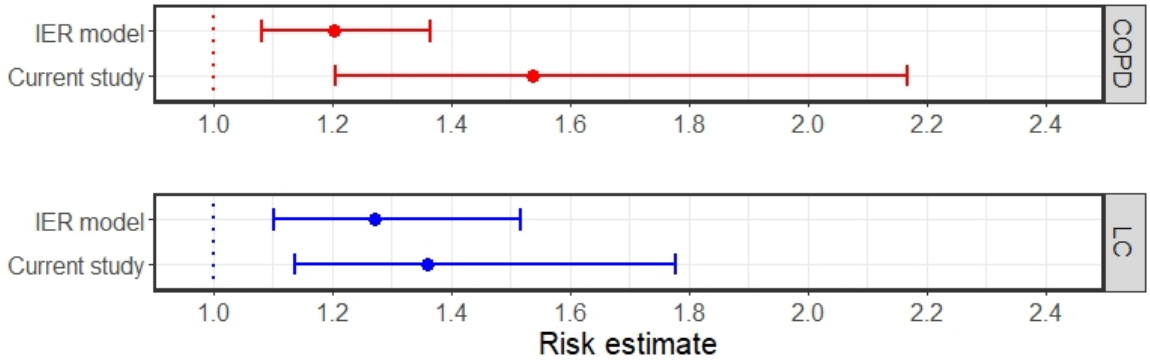

Figure 6. Comparison of risk estimates and CIs for COPD and LC mortalities using the 5th and 95th percentiles of $PM_{2.5}$ concentrations in Ningbo in 2015.

LC and COPD mortalities attributable to air pollution exposure were estimated using the result of meta-analysis ~~pooled analysis~~ and the estimated value of PAF, as shown in Eq.2. Figures 7 and 8 show the estimated ratios of LC and COPD mortality due to ambient $PM_{2.5}$ exposure and mortality due to all risk factors in Hangzhou and Ningbo, respectively. The ratios of LC and COPD mortality attributable to ambient $PM_{2.5}$ exposure and mortality due to all risk factors in China were 27.8% and 32.0% respectively in the GBD study 2015, which were used as benchmarks for the comparison of the estimated mortality ratios of LC and COPD, as shown by the dotted lines in Figure 8. The mortalities estimated by the IER model were found to be more precise than the current study, but it did not cover the benchmark value, especially for COPD mortality in both Hangzhou and Ningbo population. This might imply that the risk estimate of the IER model tends to underestimate the mortality in China or other regions with a higher level of pollution. On the other hand, the estimated ratios of LC and COPD mortalities in the current study always covered the benchmark values, indicating that the current study had the potential to provide a more accurate and realistic number of estimated mortality attributable to ambient air pollution in China.

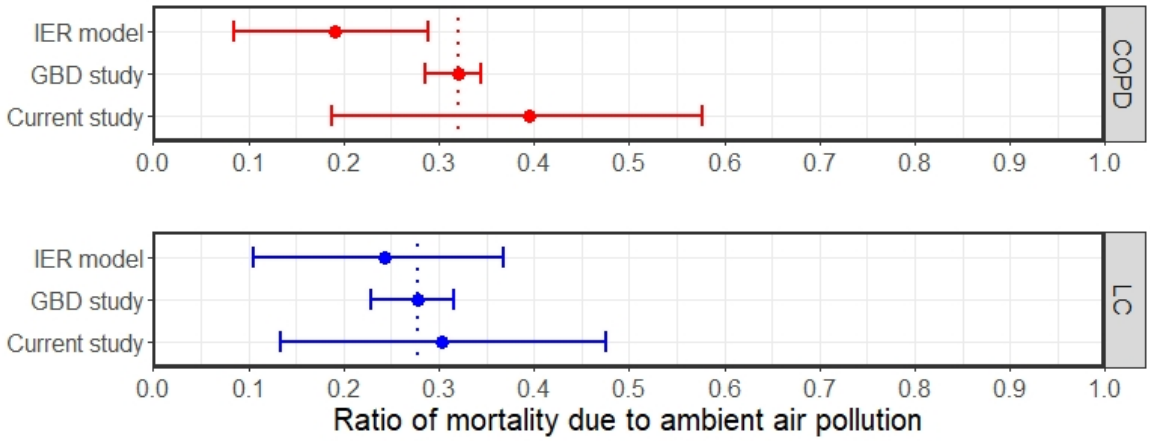

Figure 7. Comparison of estimated mortality ratio due to ambient air pollution in Hangzhou (dotted line represents the benchmark ratio obtained in GBD 2015).

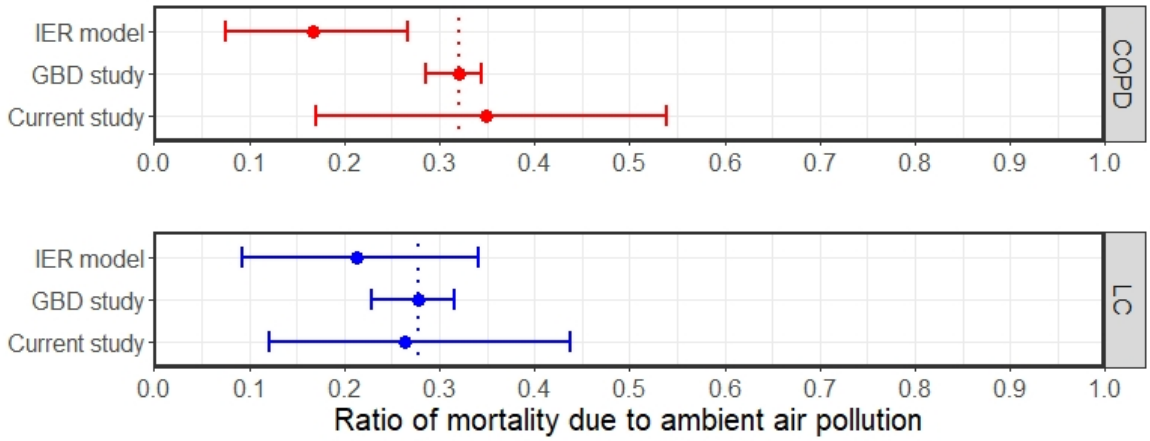

Figure 8. Comparison of estimated mortality ratio due to ambient air pollution in Ningbo (dotted line represents the benchmark ratio obtained in GBD 2015).

4. Discussion

In this study, a systematic literature search and meta-analysis ~~pooled analysis~~ were performed to investigate the association between long-term exposure of air pollution and cause-specific mortality such as lung cancer (LC) and chronic obstructive pulmonary disease (COPD) using the 8 cohort studies conducted in China. The results showed that long-term exposure to $PM_{2.5}$ pollutant was significantly associated with both LC and COPD mortalities in China. The meta-analysis ~~pooled analysis~~ showed that the combined risk ratios of LC and COPD mortalities per 10 μg/m^3 increase in $PM_{2.5}$ were 1.08 (95% CI: 1.02-1.16) and 1.12 (95% CI: 1.11-1.13), respectively. To the best of our knowledge, this study is the first systematic literature search and meta-analysis ~~pooled analysis~~ of LC and COPD mortality attributable to air pollution in the more polluted regions by considering only the Chinese cohort studies. This

study helps to identify ~~identifying~~ the more accurate effects of LC or COPD mortality with long-term exposure of air pollution in other more polluted regions in the world such as India, Bangladesh or Pakistan.

In the meta-analysis ~~pooled analysis~~ of the current study, COPD mortality showed a less convincing ~~promising~~ result than LC mortality, in terms of the heterogeneity within the studies. As shown in Table S1 ~~3~~, both the results of I^2 and the p-value for heterogeneity indicated a lack of heterogeneity in the meta-analysis ~~pooled analysis~~ of COPD mortality attributable to $PM_{2.5}$ exposure. Of the three individual cohort studies that reported COPD-$PM_{2.5}$ association, two studies were based on the same cohort, which was a cohort of 66,820 residents in Hong Kong. Both the results of Wong *et al.* (2015) and Yang *et al.* (2018) showed a wider 95% confidence intervals for risk ratio of COPD mortality, which provided little information about the effect of air pollution on COPD mortality. In Wong *et al.* (2015), the positive association of COPD with the increase in $PM_{2.5}$ exposure did not show a statistically significant result. However, they reported a risk ratio of 2.30 (95% CI: 1.15-4.63) during the follow-up period of first 2-4 years. The study conducted by Yang *et al.* (2018) focused more on other mortalities such as cardiovascular disease (CVD) and respiratory disease mortality attributable to pollutants and reported less information related to the COPD outcome. The risk ratio of COPD-$PM_{2.5}$ association was reported to be 1.12 (95% CI: 1.10-1.13) in Yin *et al.* (2017), which was found to be a more promising result among the other relevant cohort studies in China, as it employed a more accurate estimate of $PM_{2.5}$ exposure by combining the estimates of satellite-derived, chemical transport model, and local surface data.

Table 5 ~~8~~ shows the comparison of the current study with previous meta-analyses conducted in other regions. All the previous meta-analysis of LC and COPD mortality attributable to ambient air pollution mainly applied the cohort studies which were conducted in North America and European countries. Although there were typically higher pollutant exposure levels in China as compared to other regions, the result of this current study was consistent with the findings of the previous studies such as the risk ratio of LC attributable to $PM_{2.5}$ exposure in both fixed and random effects models. The result of Cao *et al.* (2011) was often used as a representative study of China region in many previous meta-analysis (Hamra *et al.*, 2014; Yang *et al.*, 2016; Huang *et al.,* 2017), because it was one of the early cohort studies conducted in China. Furthermore, Yin *et al.* (2017) and Yang *et al.* (2018) were included in Chen and Hoek (2020), which provided the evidence of cause-specific mortality related to ambient air pollution exposure using the studies from North America, Europe, and Asia.

Table 5 ~~8~~. Comparison of current study with previous studies conducted in other regions: hazard ratios per 10 μg/m^3 (* per 10ppb) increase in pollutant level.

Mortality-exposure	Risk ratios (95% CI) – fixed (F) or random (R) effects models	I^2 (%)	P-value for heterogeneity	Study design of individual studies	Study regions of individual studies
Cui *et al.* (2015)					
LC-$PM_{2.5}$	F: 1.09 (1.06-1.11)	18.3	0.26	Cohort	North America, Europe, others
LC-PM_{10}	F: 1.05 (1.03-1.07)	41.9	0.11		
Chen and Hoek (2020)					
LC-$PM_{2.5}$	F: 1.12 (1.07-1.16)	39.4	0.06	Cohort and case control	North America, Europe, Asia
LC-PM_{10}	F: 1.08 (1.04-1.13)	92.4	<0.01		
COPD-$PM_{2.5}$	F: 1.11 (1.05-1.17)	49.6	0.03		
COPD-PM_{10}	F: 1.19 (0.95-1.49)	85.4	<0.01		
Hamra *et al.* (2014)					
LC-$PM_{2.5}$	R: 1.09 (1.04-1.14)	53.0	0.01	Cohort and case control	North America, Europe, others
LC-PM_{10}	R: 1.08 (1.00-1.17)	74.6	0.00		
Yang *et al.* (2016)					
LC-$PM_{2.5}$	R: 1.07 (1.01-1.13)	81.6	<0.01	Cohort	North America, Europe, others
LC-PM_{10}	R: 1.10 (0.99-1.26)	66.3	<0.01		
LC-NO_2	R: 1.13 (1.06-1.21) *	68.7	<0.01		
LC-SO_2	R: 1.15 (1.01-1.30) *	86.4	<0.01		
Huang *et al.* (2017)					
LC-$PM_{2.5}$	R: 1.11 (1.05-1.18)	63.2	0.005	Cohort and case control	North America, Europe, Asia
This study					
LC-$PM_{2.5}$	R: 1.08 (1.02-1.16)	87.0	< 0.01	Cohort	China

The result of meta-analysis ~~pooled analysis~~ employed in the current study was further investigated by performing an estimation of premature mortality in Hangzhou and Ningbo during 2015, which was in line with the findings obtained in the GBD study 2015 in terms of the estimated ratio of mortality attributable to ambient $PM_{2.5}$ and mortality due to all risk factors. As shown in Figure 5-8, the comparison of the result with the IER model indicated that the IER

model tends to underestimate the risk estimate and mortality due to air pollution exposure in China regions, which was also discussed by other studies (Yin *et al.*, 2017, Maji *et al.*, 2018). The development of the IER model was described in Burnett *et al.* (2014), and the model was widely used to estimate the premature mortality such as cerebrovascular disease (stroke), IHD, COPD, and LC in most of previous studies (Apte *et al.*, 2015; Cohen *et al.*, 2017; Huang *et al.*, 2018). Furthermore, other than ambient air pollution exposure, the model is also applicable to several types of exposure such as second-hand smoking, household air pollution, and active smoking. The wide application of the IER model was mainly because it relied on different types of source type-specific risk ratio of mortality from the relevant published cohort studies. However, with respect to the effect of air pollution exposure, only 3 out of 15 risk ratio estimates for COPD mortality, and 4 out of 59 risk ratio estimates for LC mortality were considered in the initial development of the IER model. Therefore, the limited number of relevant studies that reports the effects of air pollution exposure on LC and COPD mortalities could result in a less accurate estimation of mortality for the IER model, especially in the regions with a relatively high concentration level of pollutants such as China and India.

The current study has several strengths. Firstly, the systematic literature search and meta-analysis ~~pooled analysis~~ were only restricted to cohort studies in order to provide a more conclusive finding of the effect of ambient air pollution on LC and COPD mortalities in the more polluted region in the world. As most of the previous studies mainly focused on the other study regions such as North America and Europe in which the pollutant concentrations were relatively low, they delivered limited significant information of risk estimate on the regions with higher pollutant concentration. Secondly, the processes of systematic literature search and meta-analysis ~~pooled analysis~~ were performed according to the PRISMA 2020 guidelines, and the included cohort studies were further evaluated by measures of heterogeneity and publication bias, and a quality scoring system called the Newcastle-Ottawa Scale (NOS). Thirdly, the study provided the evidence that addresses the need of a more suitable relative risk model for estimating the LC and COPD mortality attributable to ambient air pollution in China.

Furthermore, the finding of the current study also helps to provide the information for the health impact assessment of ambient air pollution in the more polluted regions in the world such as China. The air pollution-related mathematical model such as the AirQ+ model has been widely employed to quantify the health impact of air pollution, including the mortalities of LC and COPD. For example, the application of the AirQ+ model developed by the WHO estimates the impact of air pollution on the health burden in a population by utilising the regional

information of air quality data, health data, etc. Previous studies employed the AirQ+ model to estimate the air pollution-related mortality in different countries such as Portugal (Brito *et al.*, 2022) and Iran (Fallahizadeh *et al.*, 2021). The meta-analysis in the current study provides the updated information of the impact of ambient air pollution on LC and COPD mortalities in China using the result of cohort studies, which aims to estimate the health impact of air pollution more accurately in the application of the air pollution-related mathematical model such as AirQ+ model.

Nevertheless, the current study has some limitations, as well as recommendations of future works. Firstly, the number of existing Chinese cohort studies for the effect of air pollution on both LC and COPD mortalities was limited in this study, which may increase the likelihood of bias towards a particular cohort. It is suggested that more cohort studies in other more polluted regions be conducted in order to improve the accuracy of the findings. Furthermore, other sources from different databases should be explored and searched in the future work, which may not necessarily be restricted to studies written in English. The result of the meta-analysis in the current study is subject to update by incorporating the most recent studies or the studies identified from other databases, including those published in Chinese.

5. Conclusions

In this study, it employed a systematic literature search and a meta-analysis ~~pooled analysis~~ of LC and COPD mortalities attributable to long-term effect of ambient air pollution in the more polluted regions using the evidence of Chinese cohort studies. The results evidently showed that long-term exposure to pollutants such as $PM_{2.5}$, PM_{10}, SO_2, and NO_2 were significantly associated with both LC and COPD mortalities. The pooled risk ratios of LC and COPD mortalities per 10 $\mu g/m^3$ increase in $PM_{2.5}$ were 1.08 (95% CI: 1.02-1.16) and 1.12 (95% CI: 1.11-1.13), respectively. In addition, the development of a more suitable relative risk model using the results of cohort studies in the more polluted regions is required to improve the accuracy of the estimated effects of air pollution on the LC and COPD mortalities in those regions.

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Abbreviations

CI	Confidence interval
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
ICD	International Classification of Diseases
IER	Integrated exposure response
GBD	Global Burden of Disease
LC	Lung cancer
NO_2	Nitrogen dioxide
NOS	Newcastle-Ottawa Scale
O_3	Ozone
PM	Particle matter
$PM_{2.5}$	Particles with an aerodynamic diameter of equal to or less than 2.5 μm
PM_{10}	Particles with an aerodynamic diameter of equal to or less than 10 μm
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
REML	Restricted maximum likelihood
SD	Standard deviation
SE	Standard error
SO_2	Sulphur dioxide
WHO	World Health Organization

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