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Review

Short and long-term association of exposure to ambient black carbon with all-cause and cause-specific mortality: A systematic review and meta-analysis☆

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ABSTRACT

Black carbon (BC) is a product of incomplete or inefficient combustion and may be associated with a variety of adverse effects on human health. The objective of this study was to analyze the association between various mortalities and long-/short-term exposure to BC as an independent pollutant. In this systematic review, we searched 4 databases for original research in English up to 6th October 2022, that investigated population-wide mortality due to BC exposure. We pooled mortality estimates and expressed them as relative risk (RR) per 10 μg/m^3 increase in BC. We used a random-effect model to derive the pooled RRs. Of the 3186 studies identified, 29 articles met the eligibility criteria, including 18 long-term exposure studies and 11 short-term exposure studies. In the major meta-analysis and sensitivity analysis, positive associations were found between BC and total mortality and cause-specific disease mortalities. Among them, the short-term effects of BC on total mortality, cardiovascular disease mortality, respiratory disease mortality, and the long-term effects of BC on total mortality, ischemic heart disease mortality, respiratory disease mortality and lung cancer mortality were found to be statistically significant. The heterogeneity of the meta-analysis results was much lower for short-term studies than for long-term. Few studies were at a high risk of bias in any domain. The certainty of the evidence for most of the exposure-outcome pairs was moderate. Our study showed a significantly positive association between short-/long-term BC exposure and various mortalities. We speculate that BC has a higher adverse health effect on the respiratory system than on the cardiovascular system. This is different from the effect of $PM_{2.5}$. Therefore, more studies are needed to consider BC as a separate pollutant, and not just as a component of $PM_{2.5}$.

1. Introduction

Currently, many epidemiologic studies support a strong link between ambient particulate matter (PM) mass concentrations and a range of adverse health effects (WHO, 2021). Moreover, some studies (WHO Regional Office for Europe, 2013) showed that combustion-related particles may be more harmful to health than non-combustion-generated PM. In urban areas where traffic is the main source of primary combustion particles, black carbon (BC) is the main traffic by-product, an incomplete or inefficient combustion product of various combustion sources (WHO, 2021). Although in practical applications, BC is also expressed as a mass concentration, it is converted by light reflection wavelength with a conversion factor that depends on location, season, and type of burning particles (Hoek et al., 1997). Exposure assessment for BC can be more challenging than for PM but is more informative and accurate for determining the contribution of combustion to environmental effects and health outcomes. Therefore, considering pollution sources, mass-based PM concentrations are not suitable for characterizing the health risks of air pollution near the sources of burning particles. It can be seen that it is extremely important to study the health risk of BC as a separate pollutant. The results of the BC study can help governments in areas with more combustion sources

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to develop more targeted policies than studies of PM or its components.

BC has a porous structure and a large specific surface area, which enables it to readily adsorb a wide range of chemicals. The emission of BC during combustion is always accompanied by the production of hazardous substances such as polycyclic aromatic hydrocarbons (PAHs) and heavy metals, which can be adsorbed by BC (Hussein and Abdel-Shafy, 2016; Johansson et al., 2016; Jonker and Koelmans, 2002; Stieglitz et al., 1989) and thus aggravate toxicity. Many epidemiological studies (Kathrin Wolf et al., 2021; Paunescu et al., 2019; Wang et al., 2019; Wu et al., 2021) have shown significant associations between BC and adverse health outcomes. BC is small in size and can reach the lungs through the respiratory tract and induce oxidative stress and inflammatory response (Faria et al., 2022; Niranjan and Thakur, 2017) by triggering a free radical reaction (Folinsbee LJ, 1993). And it also has a high capacity for deposition in the body (Ching and Kajino, 2018), which is more likely to cause respiratory and cardiovascular diseases (Brugge et al., 2007; Hassoun et al., 2019).

Currently, researchers are more inclined to focus on PM and its components. However, the study of BC as a stand-alone pollutant has been neglected because of this. It might be related to the imperfect monitoring facilities of BC in many regions worldwide. Although the available researches are insufficient to support the WHO to formulate the AQG (air quality guideline), the "good practice statement (GPS)" on BC has been proposed by the WHO considering the available evidence at this stage (WHO, 2021). The GPS suggests taking measures to reduce BC/EC emissions and set standards (or targets) for environmental concentrations of BC/EC where available.

Therefore, this study used meta-analysis to analyze the effects of long-term/short-term exposure to ambient BC on mortality in the general population. And hopefully, it will provide support for evidence-based legislation and policies to improve air quality, to reduce the unacceptable health burden of air pollution, especially from fossil fuel combustion.

2. Methods

2.1. Search strategy

We conducted this study following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Appendix 1) (Moher et al., 2009; Page et al., 2021). We searched articles published before 6th October 2022 in four electronic databases (i.e., PubMed, Embase, The Cochrane Library, and Web of Science). And we ensured 3 themes were searched for, they were pollutants, air pollution, and health outcomes (Definition of BC and relevant terms see Appendix 2; Search strategy see Appendix 3). And we used "BC" as a generic term for these different metrics, but refer to the study-specific metric when describing individual studies. The protocol of this review was registered on the PROSPERO (International Prospective Register of Systematic Reviews, Registration number: CRD42021249741) website.

2.2. Study selection and study eligibility criteria

Summarizing all the articles searched, we used NoteExpress (v3.5.0.9054) to automatically delete duplicate studies and then manually remove them according to the ranking of the titles. We imported reference information from NoteExpress into the web of Rayyan (https://rayyan.qcri.org/, Qatar Computer Research Institute). In the first step, two authors (ZXJ and LBQ) screened independently by the titles and abstracts on the web of Rayyan. In case of disagreement, a third author (GC) joined to make a judgment. In the second step, we needed to further assess whether the full articles generated in the first step met the eligibility criteria. If there was a dissenting opinion, a third author was also needed.

According to the Populations of interest, Exposures, Comparators, and Outcomes (PECO) statement (Morgan et al., 2018), we applied the following eligibility (inclusion and exclusion) criteria. The PECO question in this systematic review was used: "Among (P) general population, what is the effect of (E) short-term (several minutes or days)/long-term (≥30 days) BC exposure versus (C) an incremental increase in exposure on (O) mortality". The inclusion criteria for studies were as follows: 1) Observational epidemiological study, 2) published in English, 3) general human population or susceptible population, 4) exposure conditions except for occupational exposure, 5) total mortality or cause-specific disease mortalities. See Table S1 for details.

2.3. Data extraction

When we finished screening, two authors (ZXJ and LBQ) extracted data and other authors (WYJ, GC, and LZG) did check and verify. If there were disagreements or different disputes, the authors (ZXJ, LBQ, WYJ, GC, and LZG) needed to read the original paper and made decisions. Finally, we retained these articles with complete information and a representative population. There were some references without complete data. To ensure the completeness of the data, we sent emails to the authors to obtain more data or necessary explanations. And articles were excluded if we could not obtain the effect estimates for BC and its standard error (SE) or 95% confidence interval (CI).

We extracted the following from references: title, author, published year, study period, study design, study location, study population (age and number of deaths), details on exposure (pollutant, measurement method, pollutant concentrations), human outcomes (outcomes, Official classification), details of effect size (type of effect size, effect estimate value, 95% CI), statistical method, confounding factors, etc. For the results of the association between air pollutants and outcomes, most articles reported the results of single-pollutant models or two-/multi-pollutant models, as well as adjusted results for different potential confounding factors. For the report with multiple results, we 1) prioritized the extraction of the results from the single-pollutant model, 2) prioritized the extraction of the result of adjusting confounding factors in the single-pollutant model, 3) selected the author-recommended model result (usually presented in abstract) in the adjusted model for different confounding factors. In the short-term exposure study, the lag effect is often studied. For this, we prioritized the extraction of (Atkinson et al., 2014; Mustafić et al., 2012) 1) the results of the single-day lag model, 2) the most common or the most significant results (if not significant, selecting the result with the largest value) of effect size was used to estimate the health risks of pollutants if there were multiple results of the lag model.

The following are the criteria of extraction for other conditions in the present study: 1) if there were separate results for multiple cities, we included them directly as different studies, 2) for different years in the same area, we selected the most recent results, 3) for different seasons or age groups in the same year, we used meta-analysis to summarize the results and include it.

2.4. Data synthesis

In the epidemiological study, relative risk (also named risk ratio, RR), odds ratio (OR), and hazard ratio (HR) are the intuitive and common standards (Mustafić et al., 2012). HR and OR are usually equivalent to RR when the mortality is very low (Davies et al., 1998). Therefore, we used RR as the effect measure for the associations between mortality and per 10 μg/m^3 increase in air pollutants. For the unit conversion factor of absorbance and concentration, 10^{-5}/m ≈ 0.8 μg/m^3 was used (Rich K, 2002). If the reported effect sizes were not in increments of per 10 μg/m^3, we converted the effect values to RR per 10 μg/m^3 according to the following formula:

$$RR_{(s\tan dardized)} = RR_{(original)}^{Increment(10)/Increment(original)}$$

Some studies presented the effect estimates as ER (extra risk) or ERR (extra relative risk), whereas ER or ERR can be converted to RR using the equation:

$$ER(\%) = (RR - 1) \times 100$$

In addition, we needed to obtain SE to do a meta-analysis. However, most studies only had a 95% CI. We converted it to a SE by the following equation (Higgins and Green, 2008):

$$SE = \frac{\ln(UCI) - \ln(LCI)}{2 \times 1.96}$$

UCI means upper confidence interval, and LCI means lower confidence interval.

2.5. Risk of bias

The included original references were assessed for risks of bias. Different study types required different methods of assessment. It needed to be finished independently by two authors (ZXJ and GC) and the results were reconciled until a consensus was reached.

We used the Office of Health Assessment and Translation (OHAT) tool recommended by the National Toxicology Program's Office of Health Assessment and Translation to assess the risk of bias (Rooney et al., 2014). This tool based on several bias parts (e.g., exposure, outcome, confounding, selection, incomplete outcome, selective reporting, conflict of interest, and others) assessed the risk of bias for each study (Table S2-S3) (Achilleos et al., 2017). Each part is evaluated as "low risk", "probably low risk", "probably high risk", "high risk" or "not applicable" according to the specific criteria.

2.6. Statistical analysis

2.6.1. Meta-analysis

If there were 3 or more studies of the same air pollutants and health outcomes, we performed the meta-analysis. For the pooled RRs, a random-effects (RE) model with a DerSimonian-Laird estimator (Dersimonian and Laird, 2015) was used to pool the estimates (RR and 95% CI). We used I-square (I^2) and Cochran's Q test to estimate the heterogeneity across studies; tau-squared (tau^2) was calculated to indicate the estimate of the variance in effect size. It quantifies the degree of heterogeneity and represents the proportion of the total variance in pooled estimates attributable to the heterogeneity of the true effects. 25%, 50%, and 75% of the I^2 values were taken as low, moderate, and high degrees of heterogeneity, respectively (Higgins and Thompson, 2002). In addition, an 80% prediction interval (PI) was used to assess the heterogeneity between studies (Chiolero et al., 2012). If PI is considerably wider than the CI (double the size) and overlaps with 1, we need to consider the heterogeneity (Brozek et al., 2021).

For health outcomes in the short-term exposure studies, we analyzed total mortality, cardiovascular disease mortality, and respiratory disease mortality. And for the long-term exposure studies, we analyzed total mortality and other cause-specific mortality including cardiovascular disease mortality, ischemic heart disease mortality, coronary heart disease mortality, cerebrovascular disease mortality, respiratory disease mortality, lung cancer mortality, chronic obstructive pulmonary disease mortality, which the number of articles of the same outcome has 3 or more than 3.

The R Studio program package 'meta' was used to perform the meta-analysis and produce forest plots.

2.6.2. Additional analyses

For each meta-analysis, it is necessary to examine the publication bias. Funnel plots, Begg's and Egger's tests are visual evaluation methods for identifying publication bias. The funnel plot is a more intuitive representation of bias but has some limitations. Therefore, we used contour-enhanced funnel plots (Peters et al., 2008; Sterne and Egger, 2001) and Egger's test (Egger M, 1997) to distinguish between asymmetries caused by publication bias and those due to other factors in this review. All tests were two-sided, and statistical significance was defined as $p < 0.1$. Because the number of studies with the same outcomes was less than 10, it was difficult to find the reason for asymmetry and we only analyze the publication bias for the number of studies with more than 10.

Sensitivity analyses were conducted to examine the robustness of the results according to the characteristics of the short-term exposure by: 1) removing one study at a time, 2) removing the studies with major high or probably high risks of bias (the key criteria (exposure, outcome, and confounding bias in this review) or most of the other criteria of the study were characterized as "high risk" or "probably high risk"); and examine the robustness according to the characteristics of the long-term exposure by: 1) removing one study at a time, 2) removing studies that used model predictions to measure pollutants, and used measurement of EC instead of BC in calculating pooled effect estimates.

2.7. Assessing certainty of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess the quality of evidence for each pollutant-outcome pair (Brozek et al., 2021). GRADE classifies the levels of evidence as high, moderate, low, or very low. In the field of Environ Health, most of the studies are observational epidemiological studies. Therefore, we set them initially to moderate. The final determination of the quality of evidence would be evaluated in conjunction with other factors for upgrading and downgrading. We referred to the section on evidence certainty in the WHO global air quality guidelines to clarify the factors of upgrading and downgrading (See Appendix 4 for a detailed explanation).

3. Results

3.1. Literature search

We searched 3186 articles in the 4 international databases mentioned above, and 1461 articles were removed after deduplication. 1725 records were screened by title and abstract, and the remaining 233 records were screened by full text. And then, 29 eligibility articles were included. Finally, removing the articles studying BC or EC as a component of $PM_{2.5}$, 18 eligibility articles (17 cohorts and 1 case-control) were included in the long-term studies and 11 eligibility articles (11 time-series) were included in the short-term studies. The screening process and detailed reasons for exclusion are shown in Fig. 1. In addition, we checked whether eligible articles from other meta-analysis articles could be included to ensure that no articles were missing. No eligible articles were found for inclusion through the check.

Of 41 eligible criteria studies, the detailed descriptive information is shown in Appendix 5. For the studies on short-term exposure effects, most of the studies were located in Europe, with only 3 of them in Asia. Also, all studies were in high-income economies, except for Serbia which was an upper-middle-income economy, and Iran and India which were lower-middle-income economies (Bank TW, 2022). These selected studies cover the period from 1985 to 2017. And the articles focused on total mortality (11 articles), cardiovascular disease mortality (11 articles), respiratory disease mortality (10 articles), and less consider mortalities from other cause-specific diseases. For the studies on long-term exposure effects, the majority of studies were located in Europe, with two regions in North America and one in Asia. All are high-income economies, except China, an upper-middle-income economy (Bank TW, 2022). These selected studies cover the period from 1961 to 2017. And the articles focused on total mortality (15 articles) and cause-specific disease mortalities including cardiovascular disease mortality (13 articles), respiratory disease mortality (11 articles), cardiopulmonary disease mortality (3 articles), lung cancer mortality (10 articles), ischemic heart disease mortality (6 articles), chronic

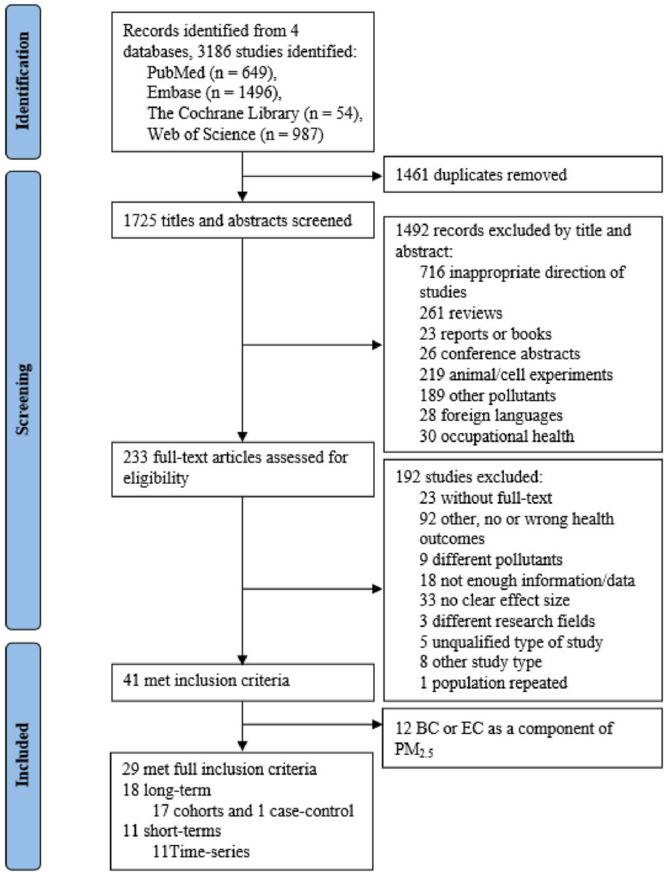

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram.

obstructive pulmonary disease mortality (3 articles), coronary heart disease mortality (3 articles), cerebrovascular disease mortality (3 articles), etc. The distribution of the areas of interest in these studies may indicate that European countries are placing greater emphasis on the link between BC and human health.

BC, BS, or absorption were measured by optical method and were highly correlated with each other (Roordaknape et al., 1998). If the direct measurement were not available for the authors, they generally used the predicted results of the model or EC concentrations instead of BC. Although thermally determined EC and optical measures of BC are also highly correlated, the quantitative relation between them varies between countries, cities, and types of locations (e.g., regions, urban, traffic) (Cyrys et al., 2003; Schaap M, 2007).

Compared to $PM_{2.5}$, the concentrations of BC (or BS) were not very high. BC was generally measured using the optical method. In many cases, if the authors couldn't obtain direct measurements, they replace BC with predicted results of the model or the EC concentrations.

3.2. *Risk of bias assessment*

The risk of bias assessment in the short-term exposure studies is shown in Table S4. Among them, there was 1 article with a probably high or high risk of confounding bias and 3 articles with probably high risks of exposure bias.

The risk of bias assessment in the long-term exposure studies is shown in Table S5. Among them, there were 15 articles with a probably high or high risk of confounding bias and 4 articles with probably high risks of exposure bias.

3.3. *Short-term exposure*

3.3.1. *Meta-analysis*

In the eligible studies, there were some articles examining the association between particulate matter and its components and human health. We first conducted a meta-analysis of 17 articles with the same outcomes, which also included the articles studying BC as a component of $PM_{2.5}$ (results not shown here). However, we found considerable heterogeneity in the results for each pollutant-outcome pair. The articles with BC as a component of $PM_{2.5}$ were weighted heavily in our results and had large RRs of EC. EC is one of the important, but relatively low, components of $PM_{2.5}$. And $PM_{2.5}$ contains many toxic chemicals besides EC, the human health effects of $PM_{2.5}$ cannot be considered to come primarily from EC. It follows that the estimated RR value of EC is likely to be overestimated. Therefore, we did the meta-analysis after removing these articles.

We removed 6 articles (Cakmak et al., 2009; Michikawa et al., 2021; Mostafijur et al., 2021; Sun et al., 2019; Sun-Young and Kim, 2015; Zhou et al., 2011) studying $PM_{2.5}/PM_{10}$ and its components from the 17 eligible articles on short-term exposure (Ballester et al., 1996; Ballester, 2002; Cakmak et al., 2009; Dab et al., 1996; Fischer P, 2003; Fischer P, 2009; Michikawa et al., 2021; Mostafijur et al., 2021; Orru H, 2021; Rahmatinia et al., 2021; Singh et al., 2021; Stanković et al., 2007; Sun et al., 2019; Sunyer et al., 1996; Sun-Young and Kim, 2015; Tertre et al., 2002; Zhou et al., 2011). In the remaining 11 articles, we did a meta-analysis of total mortality, cardiovascular disease mortality, and respiratory disease mortality. Fig. 2 shows the pooled effect estimates on the various mortalities.

For the 7 studies of total mortality, all but 2 articles showed statistically significant individual RRs, and the pooled effect estimates (1.007 [1.005, 1.009], PI [1.005, 1.010], $I^2 = 42\%$, $tau^2 = 0$, Cochran's Q test = 10.29, $p = 0.11$) for total mortality also showed a significantly increased risk of mortality in the short-term exposure to BC, and it had moderate heterogeneity. For the 8 studies of cardiovascular disease mortality, all but 2 articles showed a significantly increased risk of cardiovascular disease mortality, and the pooled effect estimates (1.006 [1.003, 1.009], PI [0.998, 1.014], $I^2 = 38\%$, $tau^2 < 0.0001$, Cochran's Q test = 11.20, $p = 0.13$) showed that cardiovascular disease mortality had a significantly increased risk, although PI include 1. It also had moderate heterogeneity. For the 7 studies of respiratory disease mortality, even though RRs were not significant for 5 articles, the pooled effect estimates (1.008 [1.004, 1.013] PI, [1.001, 1.016], $I^2 = 32\%$, $tau^2 < 0.0001$, Cochran's Q test = 8.86, $p = 0.18$) for respiratory disease mortality were statistically significant with moderate heterogeneity. For these mortalities, each study has a different weight.

3.3.2. *Additional analysis*

On this basis, we analyzed sensitivity: (1) removing one study at a time (Table S6). The results showed that the pooled effect estimates for total mortality, cardiovascular disease mortality, and respiratory disease mortality and their significance had no changes no matter which article was removed. (2) removing the articles in which the major risks of bias were high or probably high (Fig. 3). RRs or 95% CIs had not many changes. Regardless of the sensitivity validation, the results didn't change significantly. This suggested that the model was robust.

3.4. *Long-term exposure*

3.4.1. *Meta-analysis*

We removed 6 articles (Chen et al., 2021; Fischer PH, 2019; Liang et al., 2022; Ostro et al., 2010; Thurston et al., 2016; Wang et al., 2022) which studied PM and its components from the 24 eligible studies (Alex Eeff et al., 2018; Bauwelinck et al., 2022; Beelen et al., 2008; Beelen et al., 2009; Chen et al., 2021; Dehbi et al., 2017; Elliott et al., 2007; Filleul et al., 2005; Fischer PH, 2019; Gan et al., 2011; Gan et al., 2013; Hansell et al., 2016; Hoek et al., 2002; Hvidtfeldt et al., 2019; Liang

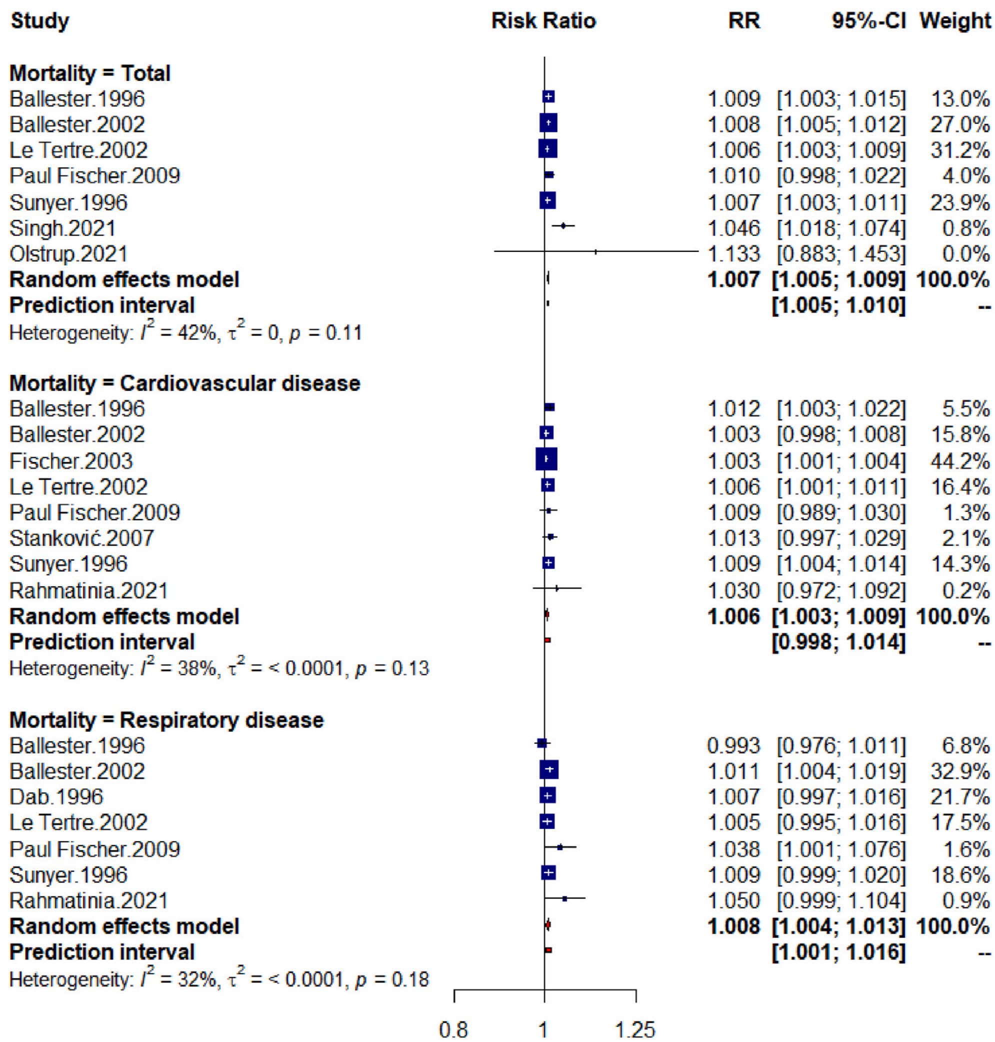

Fig. 2. Forest plot for the association between BC and various mortalities of short-term exposure in the general population, RR is for an increase of 10 μg/m^3 of BC; 95%-CI means 95% confidence interval; I^2 means the heterogeneity between effect estimates; τ^2 means the variance I^2 of between-study; the p-value is based on the Cochran's Q test.

et al., 2022; Nilsson Sommar et al., 2021; Ostro et al., 2010; Raaschou-Nielsen O, 2020; So et al., 2022; Stafoggia et al., 2022; Thurston et al., 2016; Wang et al., 2022; Yang et al., 2018; Yap et al., 2012). Fig. 4 shows the pooled effect estimates for various outcomes. In particular, ischemic heart disease (IHD) is different from coronary heart disease (CHD), but in most cases, the incidence of IHD is caused by CHD. Therefore, we added the articles with outcomes of CHD into the meta-analysis of ischemic heart disease mortality and did a separate meta-analysis for coronary heart disease mortality.

For both total mortality and cardiovascular disease mortality, there were 12 studies with 13 effect sizes available for analysis. The pooled effect estimate of total mortality was larger than 1 with high heterogeneity (1.298 [1.086, 1.550], PI [0.650, 2.590], $I^2 = 92\%$, $tau^2 = 0.090$, Cochran's Q test = 151.28, $p < 0.01$). The pooled effect estimate of cardiovascular disease mortality was not statistically significant, and PI included 1 (1.093 [0.955, 1.250], PI [0.670, 1.782], $I^2 = 83\%$, $tau^2 = 0.045$, Cochran's Q test = 72.61, $p < 0.01$). It also had high heterogeneity. For the cause-specific mortalities of cardiovascular diseases including ischemic heart disease mortality, coronary heart disease mortality, and cerebrovascular disease mortality, only the pooled effect estimate for ischemic heart disease mortality was statistically significant, and the other pooled RRs were larger than 1 but had no significance. All of them had high heterogeneity. For the 9 studies of respiratory disease mortality, they had 10 effect sizes. The pooled RR of them showed that the risk of respiratory disease mortality would be significantly increased after exposure to BC, which had high heterogeneity. For both lung cancer mortality and chronic obstructive pulmonary disease mortality of respiratory diseases, the pooled effect estimates were larger than 1 with high heterogeneity, but chronic obstructive pulmonary disease mortality is not significant. Similar to the results of short-term exposure studies, the pooled effect size of respiratory disease mortality was higher than that of cardiovascular disease mortality.

3.4.2. Additional analysis

For the results of cardiovascular disease mortality (Figure S2), the p-value of Egger's test was higher than 0.1 ($p_{CM} = 0.435$) and the funnel plots had no obvious asymmetry. Thus, they can be judged to have no publication bias. For the results of total mortality and lung cancer mortality (Figure S1, S3), their p-values of Egger's test were smaller than 0.1, while the funnel plots had obvious asymmetry. The values of Egger's test were not shown. Other outcomes were not analyzed for publication bias because of few studies.

Sensitivity analysis was carried out on the pooled results where the number of studies with the same outcomes exceeded 3 and had high heterogeneity. (1) removing one article at a time (Table S7). The results showed that the pooled effect estimates for cardiovascular disease mortality were stable no matter which article was removed. (2) removing the articles which used the model to predict BC concentration

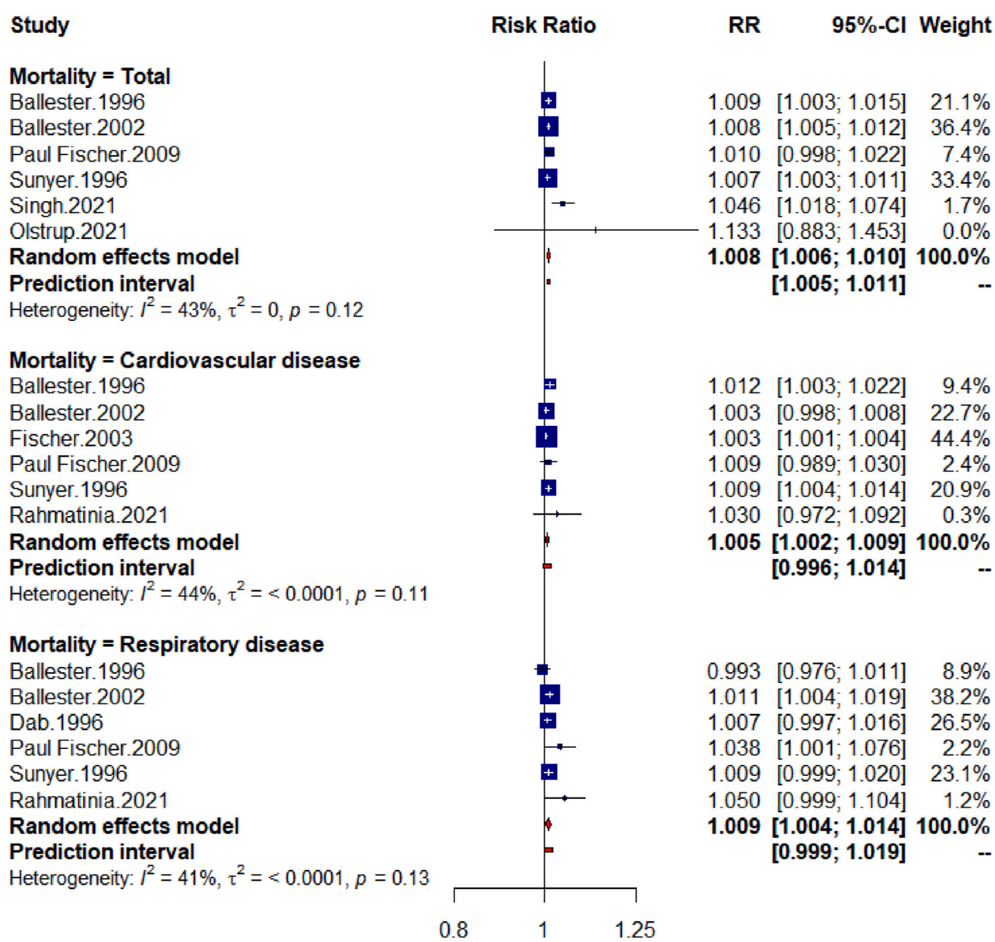

Fig. 3. Forest plot for the sensitivity analysis in the studies on short-term exposure to BC, RR is for an increase of 10 μg/m3 of BC; 95%-CI means 95% confidence interval; I2 means the heterogeneity between effect estimates; τ2 means the variance I2 of between-study; the p-value is based on the Cochran's Q test.

or use EC concentration instead of BC (Fig. 5). We did not find a single article with high weight. However, they still had high heterogeneity.

3.5. Certainty of evidence

The results of the assessment of the total mortality and cause-specific disease mortalities in the long-/short-term exposure by the GRADE tool are listed in Appendix 6. The initial levels of quality of all evidence were moderate and did not change at the final level after the assessment, except for cardiovascular disease mortality in short-term studies and lung cancer mortality in long-term studies, which were downgraded for their low certainties.

4. Discussion

To our knowledge, this is the first study to explore the association between long-/short-term exposure to BC as an independent pollutant and mortality. From the various studies published so far, the adverse health outcomes of BC exposure were mainly focused on total mortality and cardiorespiratory disease mortality. In this review, we found a significant increase in total mortality, cardiovascular disease mortality, and respiratory disease mortality in short-term exposure to BC. While in long-term exposure, total mortality, ischemic heart disease mortality, respiratory disease mortality, and lung cancer mortality were significantly increased and the pooled RRs for other cause-specific disease mortalities were higher than 1, but not significant. Furthermore, the pooled effect estimates for long-term exposure were higher than for short-term. It may be caused by cumulative damage over a long period of time. The results of sensitivity analysis showed that the results of short-term were more stable.

For total mortality, pooled RR of this study was 1.298 (1.086,1.550) in the long-term exposure, and RR was 1.223 (1.023, 1.462) after removing the articles which used the inaccurate BC measurement method. As there are not enough papers studying BC as a separate pollutant, we can only make a comparison with $PM_{2.5}$. Compared to a study on $PM_{2.5}$ in Europe (Chen and Hoek, 2020), our results of BC are in the same direction as the results of $PM_{2.5}$ (1.07 [1.03, 1.11]). However, it still needed to ensure the stability of the results by increasing the studies on the individual BC, due to the high heterogeneity and effect estimate value with a large change. In the results of short-term exposure, the result of this study (1.007 [1.005, 1.009]) had the same direction as another study (1.0065 [1.0044, 1.0086]) (Orellano et al., 2020).

For cardiovascular disease mortality, the pooled RRs for BC in this study (long-term: 1.093 [0.955, 1.250]; short-term: 1.006 [1.0033, 1.009]) were consistent with the trends of $PM_{2.5}$ in other studies (long-term: 1.11 [1.09, 1.14]; long-term: 1.14 [1.08, 1.21]; short-term: 1.0092 [1.0061, 1.0120]) (Hvidtfeldt et al., 2019; Ostro et al., 2010; Raaschou-Nielsen O, 2020). And for IHD, the pooled RR in this study for the long-term exposure (1.149 [1.024, 1.291]) also followed the trend as for $PM_{2.5}$ in other studies (1.16 [1.10, 1.21]; 1.23 [1.15, 1.31]) (Alex Eeff et al., 2021; Chen and Hoek, 2020). The pooled RRs for both coronary heart disease mortality and cerebrovascular disease mortality in the long-term exposure studies were above 1 and not significant. However, the results of them had high heterogeneity and more in-depth studies of these diseases are needed.

For respiratory disease mortality, in the studies of long-term

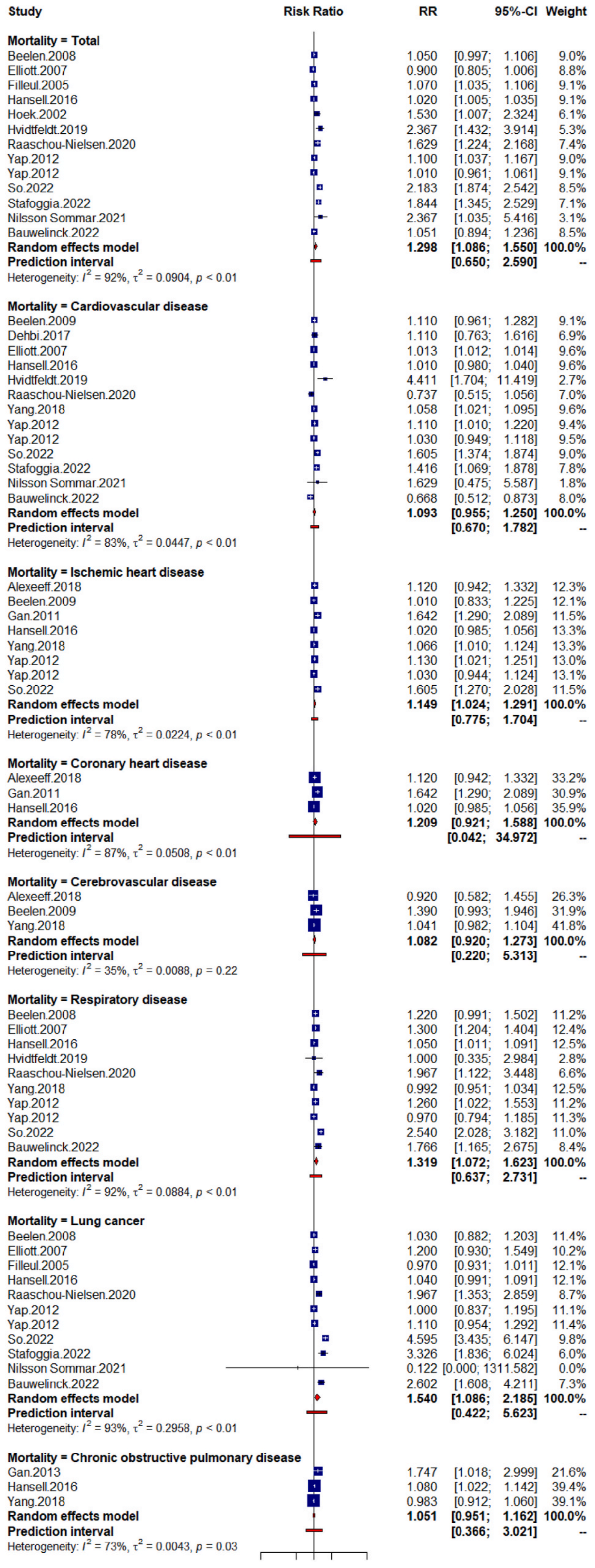

Fig. 4. Forest plot for the association between BC and various mortalities of long-term exposure in the general population, RR is for an increase of 10 μg/m^3 of BC; 95%-CI means 95% confidence interval; I^2 means the heterogeneity between effect estimates; τ^2 means the variance I^2 of between-study; the p-value is based on the Cochran's Q test.

exposure to BC, the pooled RR in this study (1.319 [1.072, 1.623]) was statistically significant. The direction of RR in the short-term exposure in this study (1.008 [1.004, 1.013]) was consistent with that of $PM_{2.5}$ (1.0073 [1.0029, 1.0116]) (Orellano et al., 2020). For the cause-specific disease mortality, the pooled RRs were higher than 1 and had high heterogeneity.

BC comes primarily from combustion sources and, unlike ambient $PM_{2.5}$, it can adsorb large amounts of combustion by-products, and is used as an indicator of primary particles. BC was considered as a separate pollutant in this study rather than a major component of $PM_{2.5}$, and we only calculated the pooled estimates from articles that studied BC as an individual pollutant. In general, the levels of BC are less than $PM_{2.5}$ in ambient air, and the spatiality and sources of BC and $PM_{2.5}$ are different, so it is difficult to simply determine whether BC has a greater impact on the respiratory system than $PM_{2.5}$. Therefore, it is important not to limit the analysis to BC as a component of $PM_{2.5}$, but to take it as an individual important pollutant.

Meanwhile, for both long-term and short-term exposure, the pooled RRs of respiratory disease mortality caused by BC exposure were higher than the results of cardiovascular disease mortality in this study. In two studies of meta-analysis on $PM_{2.5}$ (Chen and Hoek, 2020; Orellano et al., 2020), they found slightly higher outcomes for cardiovascular disease mortalities than for respiratory disease mortalities. It may show that the health effects of BC do differ from $PM_{2.5}$, and BC may have a greater adverse impact on the respiratory system than the cardiovascular system, although the pooled RR of respiratory disease mortality had a high degree of heterogeneity in the long-term exposure studies. These findings suggest that we need to strengthen our research on the adverse respiratory system effects of long-term exposure to verify whether the speculation is tenable. The size of BC is typically between 0.1 and 1 μm, which makes it easy to deposit through the respiratory tract into the lungs, resulting in respiratory diseases. The substances adsorbed by BC may have great toxicity, and it is also an important cause of adverse effects. The types of these substances are more determined by the emission sources and are also different from $PM_{2.5}$ (Long et al., 2013; Morawska and Zhang, 2002). In addition, the physicochemical properties of BC and the toxic substances adsorbed by BC are greatly affected by combustion conditions (Goldberg E D, 1985). For animal experiments, we also searched the literature. It showed that diesel exhaust particle (DEP) with high content of BC was taken as the exposure condition rather than the pure BC. The particles would deposit in the lungs of mice and cause inflammation, DNA damage, reactive oxygen species (ROS) generation, etc. (Bendtsen et al., 2020; Jeong et al., 2021; Jung et al., 2021; Kim et al., 2020). And a study showed that DEP with a greater proportion of particles was more toxic (Bendtsen et al., 2020).

Although the adverse health effects of BC are obvious now, only developed countries in Europe have paid more attention to it. In developing countries or middle-/low-income economies, little is known about the local BC emission characteristics and emission levels. Meanwhile, the characteristics of BC are highly spatially heterogeneous (Turner and Allen, 2008), and it is not possible to draw directly on existing research findings from other regions. Therefore, developing countries or middle-/low-income economies should increase monitoring and research on BC to strengthen the control of BC, and further reduce the adverse health effects of BC.

In the present study, there is something worth mentioning. Firstly, great efforts were made in many aspects for better conducting our research, including searching for all terms similar to BC, searching for potentially relevant eligible studies in the published literature of meta-analysis, and sending emails to the authors whose data in the article was incomplete. Secondly, this study summarized all observational epidemiological studies on BC since the establishment of four international databases.

On the other hand, this study still has some limitations. Firstly, in order to make our study traceable and better understood, it is indeed a pity that we were not able to analyze articles in all languages other than

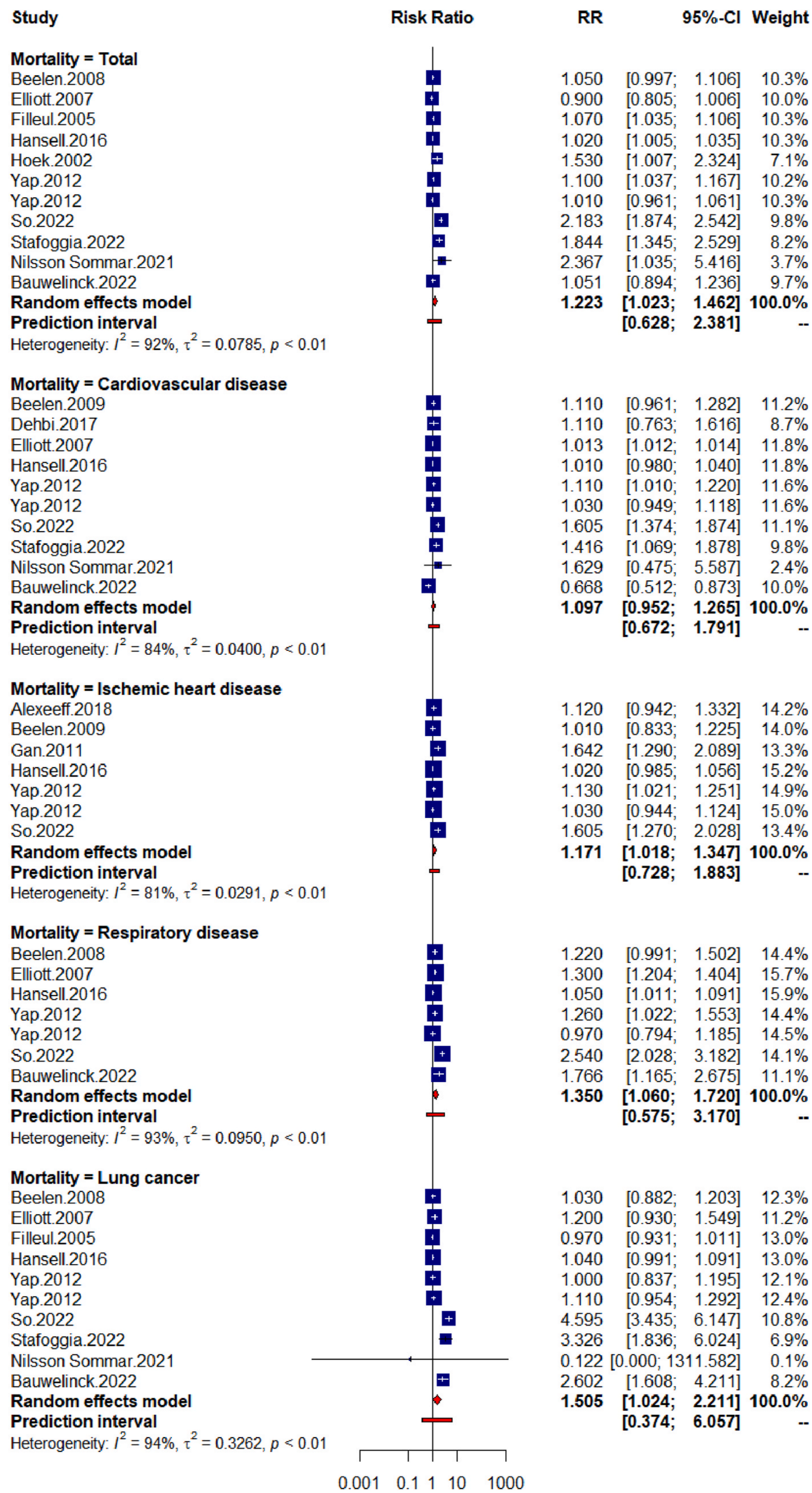

Fig. 5. Further sensitive analysis of mortality to remove studies with inaccurate BC measurement in the long-term exposure studies, RR is for an increase of 10 μg/m^3 of BC; 95%-CI means 95% confidence interval; I^2 means the heterogeneity between effect estimates; τ^2 means the variance I^2 of between-study; the p-value is based on the Cochran's Q test.

English. Secondly, not many studies have taken BC as a separate pollutant; next, most of the studies came from Europe or high-income economies. Of 29 eligible studies, there are only 3 studies from the middle-income economy, which made this review couldn't be directly extended to the world. However, this is not caused by the subjective choice of authors but is inevitable. Fourthly, when we extracted data from the articles, some studies had only graphs and no values. It would be a pity if they were removed. For this reason, we sent emails to the authors of these studies to obtain information, but we only received replies from some of them. Finally, we were unable to perform a valid subgroup analysis due to relatively few studies of BC as a single pollutant. There is, therefore, in this review, a great deal of heterogeneity in the results of long-term exposure for which we could find no explanation, and this requires further investigation.

5. Conclusion

In the present study, we found that short-term exposure to BC had significant adverse health effects. Long-term exposure exacerbated the effects, probably due to long-term cumulative damage. The adverse effects of respiratory diseases caused by BC might be more serious than cardiovascular diseases, which are different from those of $PM_{2.5}$. However, the results of long-term exposure to BC had large heterogeneity and low stability. Therefore, increased research on BC as an independent pollutant is needed, especially in other regions outside Europe. Enhanced monitoring and research on BC can help to understand and distinguish the toxicity of BC from that of BC as a component of $PM_{2.5}$, and it can provide information for future regulatory activities and benefit assessments. The emission reduction measures of BC can effectively reduce the emission of hazardous air pollutants, to reduce the health risk of these pollutants.

Author contributions statement

ZXJ and WYJ conceptualised the study and designed the methodology. ZXJ and LBQ conducted the literature searches, extracted the data, and conducted a preliminary analysis of the data. ZXJ, LBQ, WYJ, GC, LZG, GMM, and ZXY verified the literature searches, data extraction, and all data analysis. ZXJ and WYJ wrote the initial draft of the paper. All authors reviewed and edited the final draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2023.121086.

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