

# Cardiorespiratory health effects of particulate ambient air pollution exposure in low-income and middle-income countries: a systematic review and meta-analysis

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## Summary

**Background** Most prospective studies on the health effects of particulate ambient air pollution exposure have focused on high-income countries, which have much lower pollutant concentrations than low-income and middle-income countries (LMICs) and different sources of pollution. We aimed to investigate the cardiorespiratory health effects of particulate ambient air pollution exposure in LMICs exclusively.

**Methods** For this systematic review and meta-analysis, we searched PubMed, Web of Science, Embase, LILACS, Global Health, and Proquest for studies published between database inception and Nov 28, 2016, investigating the cardiorespiratory health effects of particulate ambient air pollution exposure in LMICs. Data were extracted from published studies by one author, and then checked and verified by all authors independently. We pooled estimates by pollutant type (particulate matter with a diameter of  $<2.5 \mu\text{m}$  [ $\text{PM}_{2.5}$ ] or  $2.5\text{--}10 \mu\text{m}$  [ $\text{PM}_{10}$ ]), lag, and outcome, and presented them as excess relative risk per  $10 \mu\text{g}/\text{m}^3$  increase in particulate ambient air pollution. We used a random-effects model to derive overall excess risk. The study protocol is registered with PROSPERO, number CRD42016051733.

**Findings** Of 1553 studies identified, 91 met the full eligibility criteria. Only four long-term exposure studies from China were identified and not included in the meta-analysis. A  $10 \mu\text{g}/\text{m}^3$  increase in same-day  $\text{PM}_{2.5}$  was associated with a 0.47% (95% CI 0.34–0.61) increase in cardiovascular mortality and a 0.57% (0.28–0.86) increase in respiratory mortality. A  $10 \mu\text{g}/\text{m}^3$  increase in same-day  $\text{PM}_{10}$  was associated with a 0.27% (0.11–0.44) increase in cardiovascular mortality and a 0.56% (0.24–0.87) increase in respiratory mortality.

**Interpretation** Short-term exposure to particulate ambient air pollution is associated with increases in cardiorespiratory morbidity and mortality in LMICs, with apparent regional-specific variations.

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## Introduction

Ambient air pollution is one of the biggest environmental threats to human health and is estimated to contribute to 2.9 million annual deaths globally,<sup>1</sup> of which more than 85% occur in low-income and middle-income countries (LMICs).<sup>2</sup> Particulate matter (PM), a heterogeneous mixture of suspended solid and liquid particles from different sources and varying in size, mass, and chemical composition, is often acknowledged as the most damaging element of ambient air pollution to human health, particularly  $\text{PM}_{2.5}$  (PM with an aerodynamic diameter of  $<2.5 \mu\text{m}$ ) with its ability to penetrate deeply into the human respiratory and circulatory systems and cause direct localised<sup>3</sup> and systemic damage.<sup>4</sup> Both short-term (days) and long-term (years) exposure to PM has been independently associated with increased risks for mortality and morbidity, particularly cardiorespiratory outcomes.<sup>5–7</sup> Additionally, unlike other environmental risk factors, PM has no observable threshold, and adverse health outcomes have been recorded at levels lower than the most stringent air quality guidelines.<sup>8</sup>

High concentrations of PM have been reported from metropolitan areas around the world, particularly LMICs, because of recent sharp economic growth.<sup>9</sup> However, research on the health effects of PM is unreflective of PM's growing ubiquity across the world, with most studies, particularly multicity studies, mainly done in North America<sup>10,11</sup> and western Europe,<sup>5,12,13</sup> despite populations in LMICs having the greater burden of PM. In an attempt to quantify global health effects of PM pollution, exposure–response functions from high-income countries are often extrapolated to LMICs. This approach is inadequate because it assumes similarities between high-income countries and LMICs in the source, characteristics, and spatial variability of PM, and in their underlying population and health-care characteristics. To accurately quantify the health burden of PM, researchers urgently need to obtain an exposure–response function that is specific to LMICs, which would minimise the spatial uncertainty introduced by extrapolation of results from high-income countries. As such, the aim of this study is to investigate the cardiorespiratory health effects of particulate ambient air pollution exclusively within LMICs.

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### Research in context

#### Evidence before this study

We searched PubMed, Web of Science, Embase, LILACS, Global Health, and Proquest for manuscripts published in English between database inception and Nov 28, 2016. Our search terms included a list of low-income and middle-income countries (LMICs) as defined by the World Bank, and terms for particulate ambient air pollution and cardiorespiratory outcomes. From this search we identified 91 studies from five World Bank regions meeting the full inclusion criteria, of which 85 were included in the meta-analysis. Although systematic reviews and meta-analyses had been done on particulate air pollution, particularly for cause-specific outcomes, these mostly applied either no spatial quantification, often with a wider global focus, or, contrastingly, concentrate exclusively on a single (often high-income) country.

#### Added value of this study

To our knowledge, this study is the first systematic review and meta-analysis investigating the cardiorespiratory health effects of particulate ambient air pollution across LMIC regions exclusively. This study both acknowledges and shows the growing importance of particulate ambient air pollution in LMICs without introducing spatially anecdotal evidence by including studies from high-income regions. In LMIC regions exclusively, we found particulate ambient air pollution to be associated with both cardiorespiratory mortality and morbidity,

with more consistent estimates found for mortality (both for cardiovascular and respiratory). We found substantial spatial variations in cardiorespiratory outcomes from the regional level down to the city level; regional variations were also apparent for cause-specific outcomes such as stroke. However, all studies used fixed-site monitoring as a surrogate for personal exposure. Consequently, the studies were unable to account for the spatial heterogeneity in the distribution of air pollution, potentially leading to exposure misclassification and biased risk estimates.

#### Implications of all the available evidence

The high number of studies identified with our search strategy initially showed a promising evidence base on the health impacts of particulate ambient air pollution in LMICs. The identified studies allowed us to show how particulate ambient air pollution is associated with both cardiovascular and respiratory mortality and morbidity in LMICs exclusively, with clear spatial variations apparent. However, the absence of studies that deploy any kind of reliable personal exposure assessment is concerning, and highlights the need to investigate the health effects with more accurate exposure assessment. Only then can results be generated that fully incorporate LMICs into the global ambient air pollution policy debate, and ultimately reduce the effect of particulate ambient air pollution on LMIC populations.

## Methods

### Search strategy and selection criteria

For this systematic review and meta-analysis, we systematically searched PubMed, Web of Science, Embase, LILACS, Global Health, and Proquest for studies published in English between database inception and Nov 28, 2016. Search terms included “air pollution” and “particulate air pollution”, plus appropriate terms for LMICs and cardiorespiratory outcomes (appendix). We also did hand searches of the relevant scientific literature. We applied no study design restrictions to the search. This study adhered to the Preferred Reporting Items of Systematic reviews and Meta-Analysis guidelines.<sup>14</sup>

Studies included investigated the cardiorespiratory effects of PM ambient air pollution (PM<sub>2.5</sub> [PM with a diameter of <2.5 µm] and PM<sub>10</sub> [PM with a diameter of 2.5–10 µm]) within an LMIC (as defined by the World Bank classification<sup>15</sup>). We included all studies investigating mortality or morbidity, or both, by cardiorespiratory cause (International Classification of Diseases, 9th [390–459/460–519] and 10th [I00–I99/J00–J99] revisions) in adults (age ≥18 years). After the removal of duplicates, two authors (KN and CK) independently screened study titles and abstracts, with any disagreements resolved by inclusion of a third author (OK). Selected studies were then screened on the basis of the full inclusion criteria as specified in our PROSPERO protocol.

### Data analysis

Data were extracted by one investigator (KN) and stored in an Access database. Extracted data included study design, study population demographics, region, pollutant characteristics, sample size, types of cardiorespiratory events, exposure classification method, confounders addressed, analysis methods, and generated effect estimates by pollutant, outcome, and associated lag time. A second author (OK) reviewed data extraction from 10% of included studies, with no disagreements found. For the remaining studies, the other three coauthors independently checked and verified the extracted data. We calculated standardised risk estimates to show associations between cardiorespiratory morbidity and mortality per 10 µg/m<sup>3</sup> increase in particulate ambient air pollution. If alternative metrics were presented, we converted estimates using the formula shown in the appendix. If a study did not have quantifiable parameters, we contacted the authors for additional data.

We assessed each study for potential biases, including exposure assessment bias, detection bias, selection bias, and adjustment for confounders. For exposure assessment bias, we deemed that studies using less than three fixed-site monitors to assign participant PM levels had high risk of exposure assessment bias; that studies using three or more had moderate risk, and that studies using personal exposure or atmospheric modelling had low risk (see appendix for exposure classification

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assessment). We also regarded studies as having a high risk of exposure assessment bias if they were done before 1980 because insufficient technological and methodological precision in measuring and assigning PM exposure was available during that period. We deemed studies with health outcomes not based on International Classification of Diseases diagnosis codes or clinically confirmed outcomes to have a high risk of detection bias, and studies with unrepresentative study populations to have a high risk of selection bias. We also regarded studies that did not adjust for at least three of the following main confounders—long-term trends, seasonality, weather, influenza, population characteristics, and lifestyle factors (such as smoking status and alcohol consumption)—as having a high risk of bias.

Due to the expected heterogeneity in both pollutant and population characteristics resulting from differing study designs, we pooled estimates using the random-effects model, incorporating both between-study and within-study variation. We present pooled summary statistics as the excess relative risk [RR] associated with a 10  $\mu\text{g}/\text{m}^3$  increase in particulate pollutant levels (significance level 0.05). We pooled estimates by pollutant ( $\text{PM}_{2.5}$  or  $\text{PM}_{10}$ ), lagged days, and health outcome (cardiovascular and respiratory mortality or morbidity). One study estimate was included per city for the same study periods to ensure results were not biased by multiple inclusion of one city. Where duplicate cities were presented for the same study periods, we selected one estimate for meta-analysis by prioritising multicity designs because of their standardised and often higher quality methodologies, and then, if duplicates were still present, selecting the study with the lower risk of exposure assessment bias.

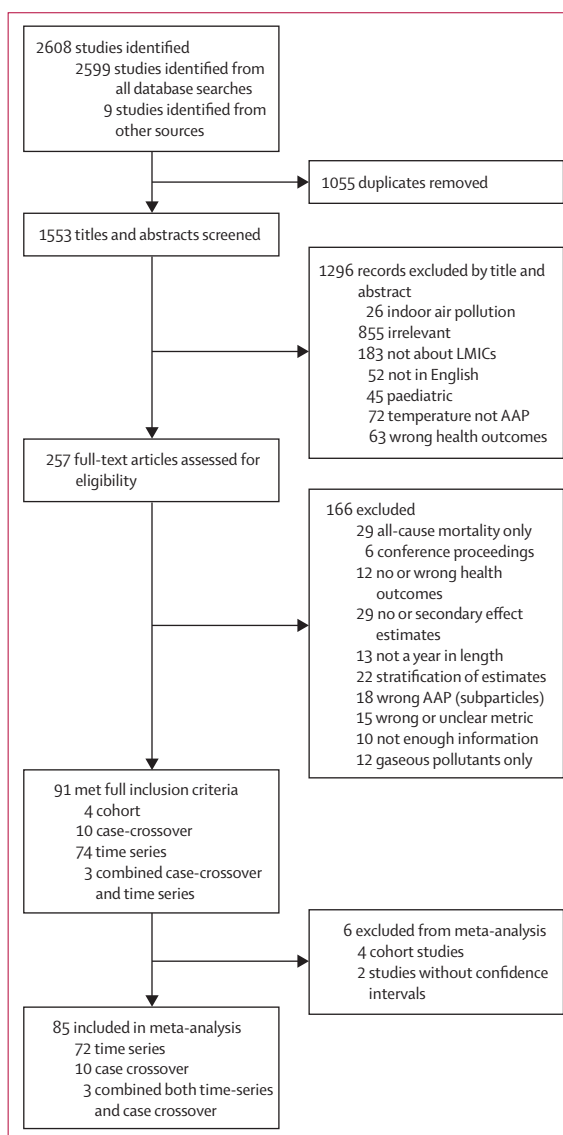
Providing study numbers were sufficient for each subgroup (>2), the subgroup analysis examined specific cardiorespiratory outcomes, adjustment for other co-pollutants, estimates with high risk of bias removed, and regional and city specific estimates. Because we anticipated fewer available effect estimates for the subgroup analysis than for the main analysis, we pooled effect estimates for lags 0–3 inclusively (apart from regional subgroups), generating sufficient numbers for meta-analysis. We assessed publication bias graphically using funnel plots with trim and fill, and estimated bias using Eggers tests. We assessed heterogeneity using the  $I^2$  statistic, with percentages higher than 75% reflective of high levels of heterogeneity.<sup>16</sup> We used meta-regression to determine sources of heterogeneity, particularly if heterogeneity persisted after the subgroup analysis. All analyses were done in R (version 3.3.2).<sup>17</sup> The study protocol is registered with PROSPERO, number CRD42016051733.

### Role of the funding source

The study had no funder. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Of 1553 studies identified, 91 met the full eligibility criteria (figure 1). We excluded a further six studies (two did not provide CIs and four were cohort studies<sup>18–21</sup> investigating long-term health outcomes), leaving 85 studies (72 with a time-series design,<sup>7,22–93</sup> ten with a case-crossover design,<sup>94–103</sup> and three using both designs<sup>104–106</sup>) for inclusion in the meta-analysis. Two of the four papers on long-term health outcomes were derived from the same cohort study reporting different endpoints: respiratory<sup>19</sup> and cardiovascular.<sup>21</sup> The other two studies were based on populations from similar Chinese regions.<sup>18,20</sup> Because of the limited number of studies available, we opted not to include these papers in the meta-analysis, although their findings were



**Figure 1: Study selection for the cardiorespiratory effects of particulate air pollution in LMICs**

LMICs=low-income and middle-income countries. AAP=ambient air pollution.

	Cardiovascular mortality		Cardiovascular morbidity		Respiratory mortality		Respiratory morbidity	
	PM <sub>10</sub> (µg/m <sup>3</sup> )	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	PM <sub>10</sub> (µg/m <sup>3</sup> )	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	PM <sub>10</sub> (µg/m <sup>3</sup> )	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	PM <sub>10</sub> (µg/m <sup>3</sup> )	PM <sub>2.5</sub> (µg/m <sup>3</sup> )
Beijing	132.07	79.00	129.25	99.79	130.86	79.00	115.03	76.00
Shanghai	100.35	55.70	..	..	104.95	55.70	..	..
Guangzhou	68.50	55.75	..	..	70.24	..	..	..
Wuhan	128.70	..	..	..	141.8	..	..	..
Bangkok	52.10	..	..	..	67.04	..	..	..
São Paulo	43.13	..	..	..	43.75	..	..	..
Tianjin	110.10	..	..	..	..	..	..	..
Shenyang	..	79.63	..	..	..	84.50	..	..
Xian	..	179.45	..	..	..	179.45	..	..

Mean pollutant levels used in the meta-analysis providing pollutant values were given. PM<sub>10</sub>=particulate matter with a diameter of 2.5–10 µm. PM<sub>2.5</sub>=particulate matter with a diameter less than 2.5 µm.

**Table 1: Mean particulate matter levels of cities recorded within included studies in relation to risk of cardiorespiratory outcomes**

	Number of studies (%)
National or municipal centre for disease control	33 (39%)
Health insurance system	4 (5%)
Death certification by physicians	6 (7%)
Computerised hospital admission data or information system	24 (28%)
Ministry of health or public health office	16 (19%)
Death registry	2 (2%)

Percentages are based on total number of studies (n=85).

**Table 2: Outcome ascertainment method for included studies**

summarised in the results section. Most included studies were from east Asia and the Pacific region (n=63), and 16 were from Latin America and the Caribbean. Very few were from Europe and central Asia (n=2; Turkey and Serbia), the Middle East and north Africa (n=3), or sub-Saharan Africa (n=1). We extracted 989 risk estimates from these studies. The studies included around 1 million cardiorespiratory events in total (appendix). Where provided, we also extracted the mean particulate matter levels reported in the included studies at the city level (table 1).

56 studies reported on the association of PM with mortality. Of these, 39 reported on PM<sub>10</sub> only, 11 on PM<sub>2.5</sub> only, and six on both. Most of the studies (33 [39%] of 85) relied on national or municipal centres for disease control to obtain mortality and morbidity counts (table 2). A 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> or PM<sub>2.5</sub> on the concurrent day was associated with an increase in cardiovascular mortality (0.27%, 95% CI 0.11–0.44 vs 0.47%, 0.34–0.61; figure 2). Similarly, for moving average lag dimensions, 10 µg/m<sup>3</sup> increases in PM<sub>10</sub> or PM<sub>2.5</sub> across a 0–1-day lag and in PM<sub>10</sub> across a 0–3-day lag were associated with an increase in cardiovascular mortality (figure 2); however, no moving average estimates longer than 0–1 days were available for PM<sub>2.5</sub>. The excess risk for stroke mortality per 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> was greater in Latin America and the

Caribbean than in east Asia and the Pacific (figure 3).

A 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> or PM<sub>2.5</sub> on the concurrent day was associated with an increase in respiratory mortality (0.56%, 95% CI 0.24–0.87 vs 0.57%, 0.28–0.86; figure 2). For respiratory mortality, moving average measures of both PM<sub>10</sub> and PM<sub>2.5</sub> resulted in associations similar in magnitude to that of the concurrent day, with the exception of PM<sub>10</sub>, which at a lag of 0–3 days was associated with 1.12% (0.78–1.61) excess mortality; however, at a lag of 0–2 days, no significant association was seen for PM<sub>10</sub> (0.20%, –0.42 to 0.81; figure 2).

31 of the included studies examined the association between PM and morbidity, of which 26 reported on PM<sub>10</sub> whereas only nine reported on PM<sub>2.5</sub>. The associations between morbidity and PM were less consistent than those seen for mortality, particularly for cardiovascular morbidity, with no significant associations for PM<sub>10</sub> and not enough estimates available to pool for PM<sub>2.5</sub> (figure 2). However, a 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> or PM<sub>2.5</sub> on the concurrent day was associated with an increase in respiratory morbidity (figure 2).

Most studies were from east Asia and the Pacific region; as such, stratification by region was not possible for all outcome pollutant combinations. Where stratification was possible, higher excess risks per 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> were seen in respiratory mortality at lag 0 and 0–3 days in Latin America and the Caribbean than in east Asia and the Pacific region (figure 4). No similar trend was seen for cardiovascular mortality (figure 4).

There was substantial variation in risk of cardiorespiratory health outcomes for both the PM<sub>10</sub> and PM<sub>2.5</sub> when stratified by city (figures 5, 6). Excess risk of cardiovascular mortality per 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> was greatest in Bangkok and lowest in Beijing (figure 6). Similarly, excess risk of respiratory mortality per 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> was greatest in São Paulo and lowest in Beijing. The associations between increased risk of respiratory mortality and PM<sub>10</sub> in Guangzhou were not significant. Despite low excess mortality in Beijing, the

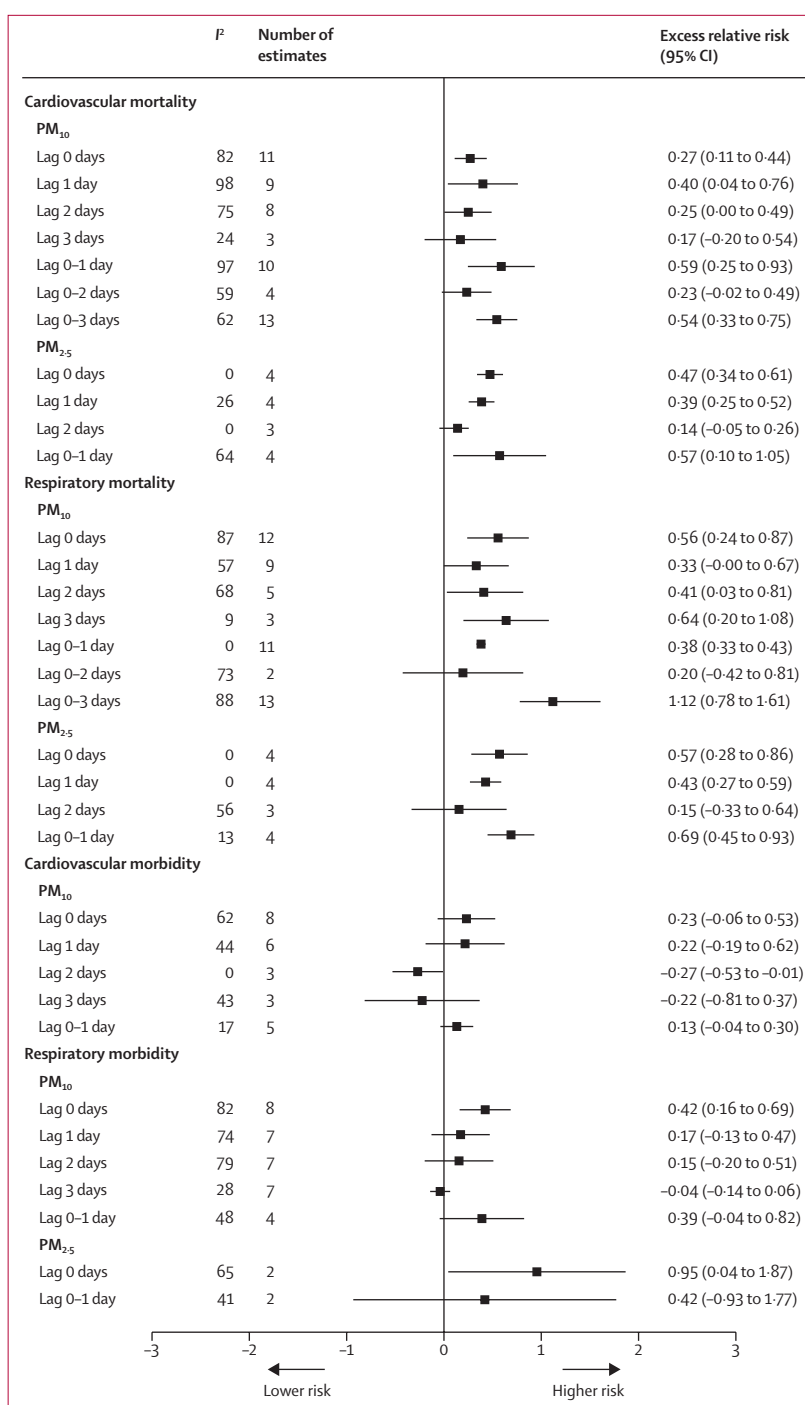
city had high respiratory morbidity in association with  $PM_{10}$  (figure 6). Among the larger Chinese cities analysed, the risk of cardiovascular mortality per  $10 \mu g/m^3$  increase in  $PM_{2.5}$  was highest in Guangzhou, followed by Shenyang and Beijing.

When the studies with estimates for  $PM_{10}$  and lag of 0–1 days were stratified, the associations of  $PM_{10}$  with both cardiovascular and respiratory mortality were attenuated after adjustment for nitrogen oxides plus sulphur dioxide (figure 7). Nitrogen oxides produced the greatest attenuation of association; however, the numbers of estimates were limited.

Publication bias was evident for  $PM_{2.5}$  and both cardiorespiratory mortality ( $p<0.0001$ ) and respiratory morbidity ( $p=0.0003$ ), but not cardiovascular morbidity ( $p=0.6281$ ); however, adjustment with the trim and fill method did not change the direction of the observed associations (appendix).  $PM_{10}$  showed evidence of publication bias for both cardiovascular and respiratory mortality and morbidity. No individual study showed substantial detection or selection bias and all studies adjusted for at least three of the main confounders; however, 36 were assigned high or unclear risk of exposure bias. We did a subgroup analysis removing these high risk estimates from the meta-analysis (figure 8). Only  $PM_{10}$  had enough estimates for this subgroup analysis. The most significant effect was seen for  $PM_{10}$  and respiratory morbidity, for which the removal of studies with high risk of bias increased the associations across all lags, with the greatest change observed for lag 2. Heterogeneity across the initial results was high, and although stratification by city and pollutant reduced some of this heterogeneity, it remained high for specific cities (Beijing, Guangzhou, and São Paulo). For Beijing, pooling of effects across 0–3 days lags contributed to higher heterogeneity ( $p<0.0001$ ), whereas pooling the effect estimates from different study periods contributed to high heterogeneity for São Paulo ( $p<0.0001$ ) and Guangzhou ( $p=0.0004$ ).

## Discussion

To our knowledge, this systematic review and meta-analysis is the first to examine the cardiorespiratory health effects associated with acute exposure to ambient PM air pollution in LMICs exclusively. The 85 studies across 12 countries within LMIC regions (predominantly east Asia and the Pacific) show associations between short-term PM exposure and cardiorespiratory outcomes, with stronger risk for mortality than for morbidity. However, removal of respiratory morbidity studies with high risk of exposure assessment bias resulted in increased strength of association, which was expected because these studies were prone to measurement errors. Long-term ambient air pollution exposure also seemed to be consistently associated with increased risks for cardiovascular mortality, although the available evidence from LMICs was limited and all existing studies were from China. Although not

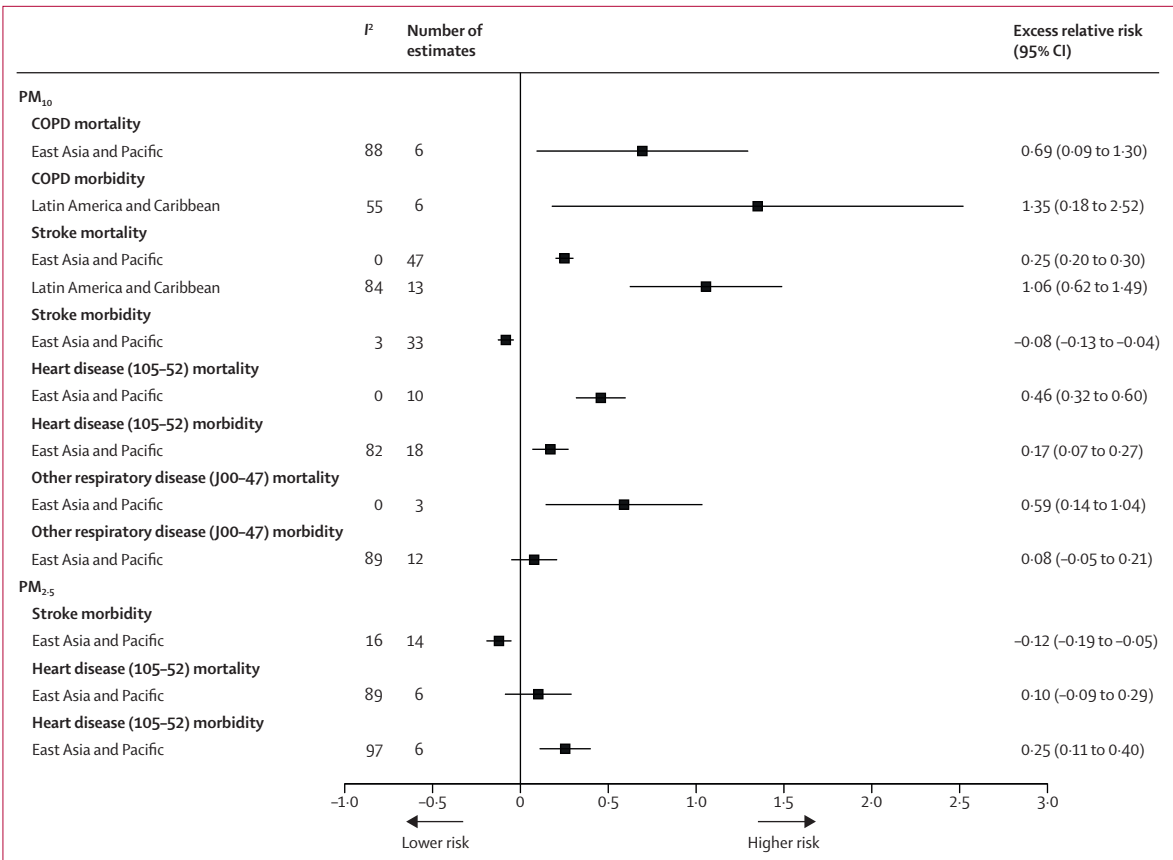


**Figure 2: Pooled associations between particulate matter and cardiorespiratory outcomes stratified by outcome and lag time**

Estimates show excess relative risk of cardiorespiratory outcomes observed for a  $10 \mu g/m^3$  increase in particulate ambient air pollution from pooled study estimates.  $PM_{10}$ =particulate matter with a diameter of 2.5– $10 \mu m$ .  $PM_{2.5}$ =particulate matter with a diameter less than 2.5  $\mu m$ .

included in the meta-analysis, the four identified cohort studies, all done in China, still contribute to the evidence base in LMICs. Estimates from studies of chronic exposure tend to be greater than estimates of acute exposure. The





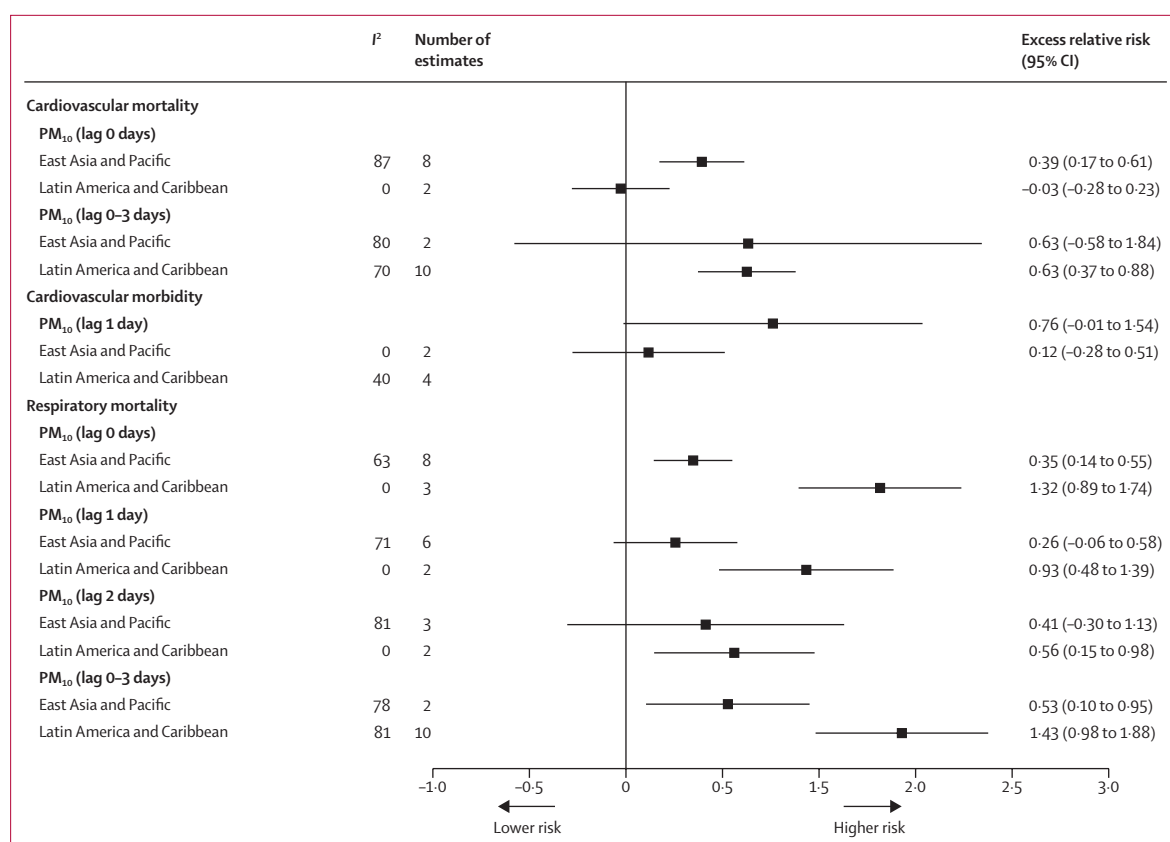
**Figure 3: Pooled associations between particulate matter and mortality and morbidity stratified by specific health outcomes**  
 Estimates show excess relative risk of cause-specific outcomes observed for a 10 µg/m<sup>3</sup> increase in particulate ambient air pollution from pooled study estimates. COPD=chronic obstructive pulmonary disease.

four identified papers are reflective of three cohort studies done in similar regions of China. In a cohort based in Shenyang, northern China, a 10 µg/m<sup>3</sup> increase in long-term PM<sub>10</sub> exposure was found to be associated with a 49% excess risk of cerebrovascular mortality (HR 1.49, 95% CI 1.45–1.53)<sup>21</sup> and a 67% excess risk of respiratory mortality (HR 1.67, 1.60–1.74).<sup>19</sup> The risk for cardiovascular death was somewhat smaller in a multicity study that also included Shenyang (RR 1.23, 95% CI 1.19–1.26;<sup>20</sup> see appendix for full descriptive results of identified cohort studies). Additionally, the explicit requirement of high resolution spatial exposure variation remains a prominent issue in all four of the identified studies with a reliance on fixed-site monitoring data only to quantify exposure. This issue remains prominent in most long-term air pollution exposure research and improvements in exposure classification are urgently needed.

Our results are similar in magnitude to those emerging from high-income countries; however, estimates for short-term PM exposure and both cardiovascular and respiratory morbidity and mortality are relatively smaller than estimates emerging from single-city and multicity studies in the USA<sup>407,108</sup> and western Europe.<sup>5,109,110</sup> A European meta-analysis<sup>111</sup> found a similar association

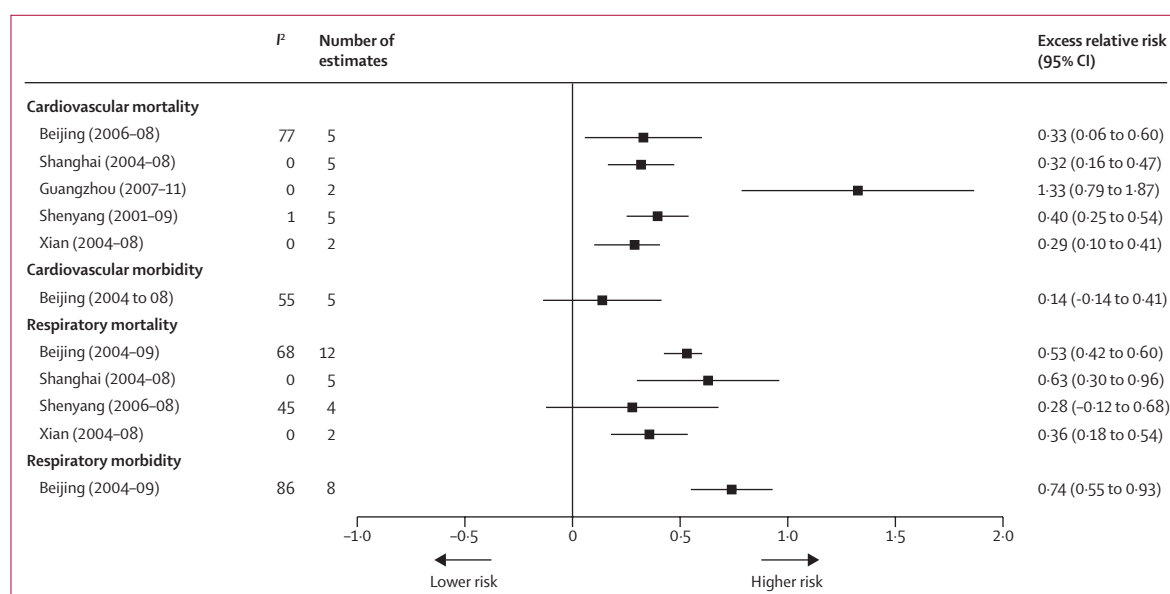
between PM<sub>10</sub> and cardiovascular mortality (0.9%) but with greater excess risk for respiratory mortality (1.3%). Unsurprisingly, our results are consistent with the few multicity studies emerging from LMIC regions;<sup>33,75</sup> however, additional multicity studies are needed to analyse morbidity. Studies from high-income Hong Kong (in southern China) produced similar results to ours for cardiorespiratory mortality,<sup>78,112</sup> but studies from Taiwan and South Korea have reported no significant associations with mortality.<sup>113–115</sup> This variability in risk of PM to cardiorespiratory outcomes might be due to variations in health-care availability and uptake between LMICs and these more developed areas, rather than pollutant or climatic factors, because the pollutant and climatic factors of Taiwan and South Korea would be similar to Chinese cities due to their close proximity.

Apart from concurrent day PM, we observed what seem to be stronger associations between PM and cardiorespiratory morbidity and mortality with longer moving average lags than with a single day lag. This temporal variability is seen across studies in both developed and developing regions,<sup>78</sup> possibly due to grouping health outcomes with varying onset times. However, our study could not address this hypothesis



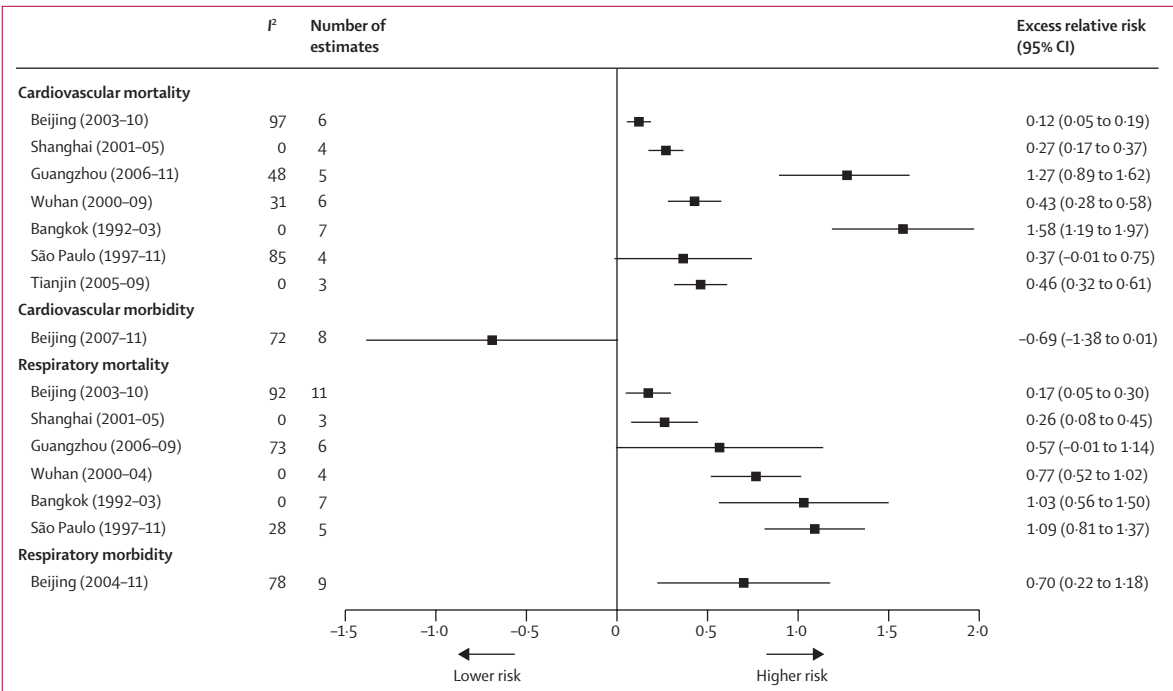
**Figure 4: Pooled association between PM<sub>10</sub> and mortality and morbidity stratified by region**

Estimates show excess relative risk of cardiorespiratory outcomes observed for a 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> across pooled study estimates stratified by region (east Asia and Pacific vs Latin America and Caribbean). PM<sub>10</sub>=particulate matter with a diameter of 2.5-10 µm.

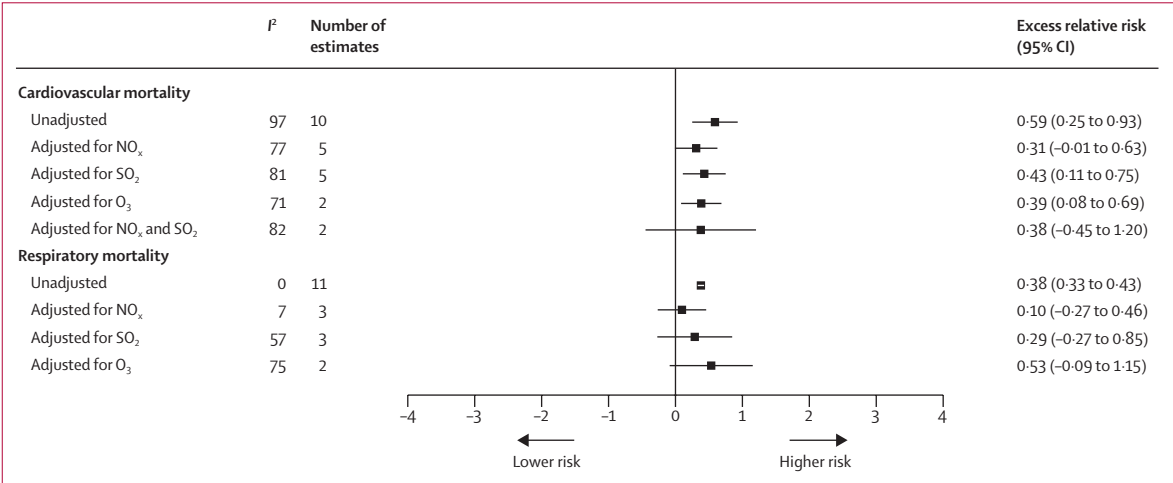


**Figure 5: Pooled association between PM<sub>2.5</sub> and mortality and morbidity stratified by city**

Estimates show excess relative risk of cardiorespiratory outcomes observed for a 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> across pooled study estimates stratified by city. The study periods of the included studies are also listed inclusively. All included cities are in east Asia and the Pacific region. PM<sub>2.5</sub>=particulate matter with a diameter less than 2.5 µm.



**Figure 6: Pooled associations between PM<sub>10</sub> and cardiorespiratory mortality and morbidity stratified by city**  
 Estimates show excess relative risk of cardiorespiratory outcomes observed for a 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> across pooled study estimates stratified by city. The study periods of the included studies are also listed inclusively. All included cities are in the east Asia and the Pacific region, except São Paulo, which is in the Latin America and Caribbean region. PM<sub>10</sub>=particulate matter with a diameter of 2.5–10 µm.



**Figure 7: Pooled association between PM<sub>10</sub> (lag 0–1 days) and cardiorespiratory outcomes adjusted for additional pollutants**  
 Estimates show excess relative risk of cardiorespiratory outcomes observed for a 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> (across a lag time of 0–1 days). Additional pollutant covariates are adjusted for in the provided estimates used in the meta-analysis. PM<sub>10</sub>=particulate matter with a diameter of 2.5–10 µm.

because it did not provide enough estimates to analyse cause-specific outcomes by lag time, warranting further research.

For cause-specific outcomes, PM<sub>10</sub> had the largest associations with chronic obstructive pulmonary disease (COPD) morbidity, which is unsurprising in view of the substantial evidence base showing associations of PM with COPD (both development<sup>116,117</sup> and exacerbation<sup>118</sup>), with exposure to PM associated

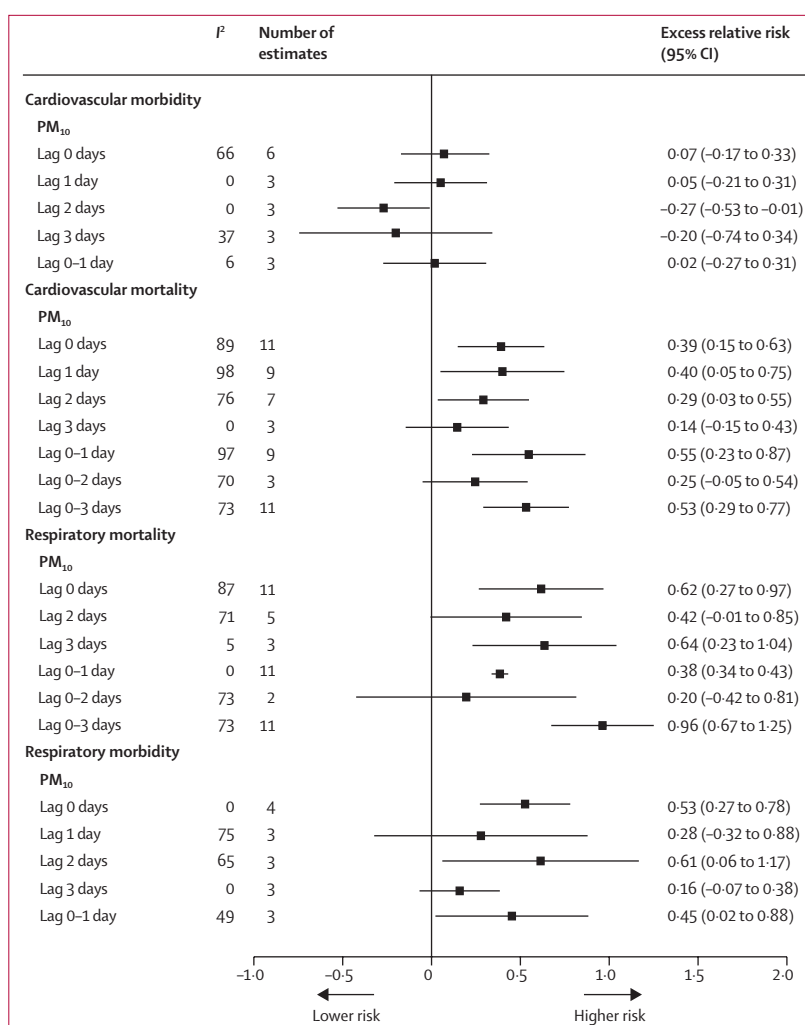
with increased production of reactive oxygen species, oxidative stress induction,<sup>119,120</sup> and pulmonary inflammation.<sup>121</sup> Although coarse particles (PM<sub>10</sub>) could be filtered out by the body's defence mechanisms and are too large to cross alveolar epithelial cells, their capacity to induce both pulmonary and systemic inflammatory responses and alter autonomic cardiac function<sup>122</sup> could account for some of the associations of PM<sub>10</sub> with cardiovascular cause-specific outcomes.



Fewer estimates were available for  $PM_{2.5}$  and the scarcity of significant associations between  $PM_{2.5}$  and cause-specific outcomes contradicts the growing evidence base of the more prominent role of  $PM_{2.5}$  in cardiorespiratory morbidity and mortality among the PM fractions.<sup>123</sup> The scarcity of observed associations between  $PM_{2.5}$  and stroke morbidity could be the result of fewer individuals surviving stroke in LMICs than in high-income countries, PM particle numbers being more important in terms of health effects than mass concentration, or the elemental composition of PM having a greater health effect than particle diameter.

The between-city differences in cardiorespiratory mortality and morbidity is probably reflective of the spatial heterogeneity of cities included. Reported measured concentrations of PM varied substantially across the included cities (table 1). When analysing city-specific results by pollutant level, we found that some cities such as Guangzhou with lower concentrations of PM showed greater associations with cardiorespiratory mortality than cities such as Beijing with higher concentrations of PM, with higher concentrations indicative of a flattening of the exposure–response curve at higher levels, an effect supported by the scientific literature.<sup>124,125</sup> However, other factors might partly account for the smaller effect sizes in very large (Chinese) cities such as Beijing, where a high quality health-care infrastructure and insurance system is available for permanent residents but not migrant workers. As such, a combination of a healthier population of permanent residents and under-reporting of adverse health among migrant workers might have resulted in smaller effect sizes.

Our systematic review and meta-analysis is the first to analyse the cardiorespiratory effects of both short-term and long-term exposure of PM in LMICs exclusively. However, several limitations should be noted. First, we were only able to identify four studies on long-term ambient air pollution exposure and most studies are from east Asia, specifically China; there remains a need for research in other regions, particularly Africa, the Middle East, and south Asia, to fully assess the effect of PM, particularly its long-term exposure, on cardiorespiratory health across all LMICs. A further limitation was the use of fixed-site monitoring (and in small numbers) as the standard surrogate for personal exposure throughout the included studies, which is less likely to represent true personal exposures than other forms of exposure assessment such as land-use regression, chemical transport models, and satellite remote sensing, particularly in large cities. Substantial heterogeneity was seen for several estimates, which was assessed with meta-regression when possible; however, often too few individual estimates were available to fully explore this heterogeneity. All included studies used clinically confirmed outcome ascertainment (table 2); however, variability in documentation procedures and



**Figure 8: Pooled associations between  $PM_{10}$  and cardiorespiratory outcomes with studies with high risk of bias removed**

Estimates show excess relative risk of cardiorespiratory outcomes observed for a  $10 \mu g/m^3$  increase in  $PM_{10}$  with estimates from studies assigned a high risk of exposure assessment bias removed from the meta-analysis.  $PM_{10}$ =particulate matter with a diameter of 2.5–10  $\mu m$ .

associated quality of the routine health-care data is a likely source of heterogeneity and a potential limitation of our study, with reliance on accurate recording of health outcomes crucial to this study. However, substantial systematic differences are unlikely to be present between whole LMIC regions and, as such, we estimate the introduction of systematic error to be minimal. However, for estimates across smaller spatial resolutions, such as our city-specific estimates, such variability in health data collection could be more exaggerated and reflected as part of the observed heterogeneity between cities. Finally, because the examined time lags between PM exposure and event onset were small, mortality displacement cannot be excluded as accounting for at least a portion of the associations observed.

The health effects of particulate ambient air pollution

in LMICs are of increasing importance. LMIC populations now consistently have a greater burden of PM than populations in high-income countries, with the growth in anthropogenic PM resulting in its widespread distribution. This systematic review and meta-analysis has reported the variation in cardiorespiratory health effects of particulate ambient air pollution from the regional level down to the city level. Further studies with improved exposure classification, done in specific LMIC areas exclusively, are needed to effectively provide information on the health effects of PM. Improved exposure classification is particularly needed in studies of long-term exposure, which remains particularly under-researched across LMICs. These recommendations are vital to accurately inform policy makers and ultimately reduce the burden of particulate ambient air pollution in LMICs.

#### Contributors

All authors were involved in study design, data interpretation, and write up. KN was responsible for searching the scientific literature, figure generation, and data collection. KN and CK were responsible for data screening. KN, CK, and OPK were responsible for data analysis.

#### Declaration of interests

We declare no competing interests.

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